Vaxzevria: Periodic safety update report assessment

29th June 2022 to 28th December 2022

This document consists of:

1. The PRAC assessment report of the Vaxzevria periodic safety update report (PSUR) covering the period 29 June 2022 to 28 December 2022, and;

2. The Vaxzevria PSUR itself.

The PSUR is a pharmacovigilance document intended to provide an evaluation of the risk-benefit balance of the medicinal product during the reference period mentioned above.

The objective of the PSUR is to present a comprehensive and critical analysis of the risk-benefit balance of the product, taking into account new or emerging safety information in the context of cumulative information on risk and benefits. The marketing authorisation holder is legally required to submit PSURs at defined time points after the authorisation of a medicinal product.

EMA's safety committee, the PRAC, assesses information in the PSUR to determine if there are new risks identified for a medicine and/or if its risk-benefit balance has changed. The outcome of this assessment is summarised in the PRAC assessment report of the PSUR.

The PSUR and the PRAC assessment report of the PSUR include information about **suspected** side effects, i.e. medical events that have been observed following the use of the vaccine, but which are not necessarily related to or caused by the vaccine itself. Information on suspected side effects should not be interpreted as meaning that the vaccine or the active substance causes the observed event or is unsafe to use.

Only a detailed evaluation and scientific assessment of all available data, as described in the PRAC assessment report of the PSUR, can determine the impact of new data on the benefits and risks of a medicine.

Further information on the safety of COVID-19 vaccines and on PSUR submission and assessment is available on the EMA website.

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EMA/PRAC/291334/2023
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC PSUR assessment report

Procedure no.: EMEA/H/C/PSUSA/00010912/202212

Active substance(s): COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria)

Period covered by the PSUR: 29/06/2022 To: 28/12/2022

Centrally authorised Medicinal product(s): For presentations: See Annex A	Marketing Authorisation Holder
Vaxzevria	AstraZeneca AB

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure:	9 March 2023	9 March 2023
☐	PRAC Rapporteur's preliminary assessment report (AR)	8 May 2023	8 May 2023
☐	MS/PRAC members and MAH comments	7 June 2023	7 June 2023
☐	PRAC Rapporteur's updated assessment report following comments	22 June 2023	22 June 2023
☐	PRAC Rapporteur's 2nd updated assessment report	n/a	30 June 2023
☐	PRAC recommendation	6 July 2023	6 July 2023

Procedure resources	
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1. Background information on the procedure

This is the assessment of PSUR(s) submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) for COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria).

2. Assessment conclusions and actions

This is the **fourth Periodic Benefit-Risk Evaluation Report (PBRER)** for Vaxzevria (AZD1222/Vaxzevria). It summarises safety and efficacy/effectiveness data for the period **from 29 June 2022 to 28 December 2022**, and places it in the context of the cumulative data and the overall benefit risk profile.

Vaxzevria is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS CoV-2. Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralizing antibody and cellular immune responses.

Vaxzevria is indicated for active immunization of individuals ≥18 years old for the prevention of COVID-19. The Vaxzevria primary vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks after the first dose. A booster dose (third dose) of 0.5 ml may be given to individuals who completed the primary vaccination course with Vaxzevria or another authorised COVID-19 vaccine at least 3-months after completing the primary vaccination course. The approval and dosing interval of booster dose for Vaxzevria may vary according to the countries of authorisation.

Vaxzevria is supplied as a vial containing either 8 doses or 10 doses per vial, 0.5 mL per dose for intramuscular (IM) injection.

Vaxzevria was first authorised for emergency use in the United Kingdom on 29 December 2021. The vaccine received conditional marketing authorization in the EU on 29 January 2021. The conditional marketing authorisation was switched to a **standard marketing authorisation on 31 October 2022**. As of 28 December 2022, Vaxzevria has been granted either full marketing authorisation, conditional marketing authorisation or emergency use authorisation in more than 90 countries managed by AstraZeneca and its partners – Serum Institute of India (SII), R-pharm and Fiocruz.

During the period under review:

- There were no actions taken for safety reasons.
- The EU-SmPC Section 4.8 was updated to include '**Tinnitus'** (uncommon), and '**Cutaneous vasculitis**' (not known) was included in the list of ADRs.

After the DLP, based on the final pooled analysis of COV001/2/3/5 studies, the MAH proposed to update the EU-SmPC section 4.8 to update frequency categories for 'Dizziness' and 'Abdominal pain'. This is currently under discussion within the variation II/0089. Additional discussion regarding the frequency of pyrexia and the inclusion of deep vein thrombosis (as well as subclavian vein thrombosis) in the list of ADRs has been also raised in the variation.

Exposure

The estimated **cumulative exposure of clinical trial subjects** is approximately **35,942 healthy volunteers** who have received Vaxzevria and 1,523 who have received AZD2816.

The estimated **cumulative exposure from post approval experience** is over 3.02 billion doses distributed globally and over **2.35 billion doses administered worldwide**. **In the EU,** there were approximately **69 million doses administered** (i.e. **~39 million Dose 1**, **~30 million Dose 2**, and ~32,000 Booster dose).

The MAH clarified that there are no remaining batches in the EU/EEA markets, and the MAH has no current plans for placing Vaxzevria in EU/EEA markets.

Signals

During the period under review, **3 validated signals were closed and classified as identified risks not categorised as important by the MAH**:

- *Immune thrombocytopenia (ITP):* was already listed in section 4.8 of the EU-SmPC
- *Cutaneous vasculitis*: was included in section 4.8 of the EU-SmPC
- *Tinnitus*: classified was included in section 4.8 of the EU-SmPC

There was **1 signal** (*Feeling hot*) that was **closed and rejected** shortly after the reporting interval by the MAH: 'Feeling hot' is adequately covered with the listed ADR of Feverishness and Fever.

There was **1 ongoing signal** (*Decreased appetite*) **classified as an identified risk not categorised as important** by the MAH: Decreased appetite (uncommon) is already listed in section 4.8 of the EU-SmPC.

After the DLP, the PRAC:

- **Closed a signal of *Pemphigus*** (EPITT 19858): the current evidence is insufficient to establish a causal relationship between Vaxzevria and pemphigus or pemphigoid. These topics should continue to be monitored in the PSURs.
- **Confirmed a signal of *Myositis*** (EPITT 19882), which was assessed within the current PSUR: the current evidence is not sufficient to confirm a causal association between Vaxzevria and myositis overall. However, a stronger signal is confirmed for dermatomyositis (DM). The review of data from the cumulative review of cases of DM and updated O/E analysis did not provide sufficient information to confirm or rule out a causal association. DM should continue to be monitored in PSUR and in the PASS (Responses to RSI - section 6).

New safety information

During the reporting period, **no new safety concerns** were identified by the MAH.

However, **new information** became available regarding **Venous thromboembolism (VTE)**. A re-assessment of the observational studies reporting VTE, focusing on the studies including a large number of Vaxzevria vaccinees was conducted. Using a variety of study designs, this demonstrates a consistent increase in VTE among the younger age-groups. In addition, observed expected analysis performed by EMA found a significative imbalance both for deep vein thrombosis (DVT) without thrombocytopenia and for Pulmonary embolism in the younger age-groups. Overall, the PRAC considers that there is sufficient evidence to conclude there is a reasonable possibility that Vaxzevria is causally related to VTE. An update of the EU-PI is thus requested (see below Section – Recommendations).

The safety concerns have changed:

- Thrombosis is now considered as an important identified risk. The RMP should be updated at the next regulatory opportunity.
- The MAH proposed to remove the important potential risk VAED/VAERD and the missing information 'Interaction with other vaccines' and 'Long-term safety' from the safety concerns. This is not

supported as these topics will be assessed through the PASS using EU/UK databases (see variation II/0084/G).

Several safety topics (**Health Authority Requests** and **Other identified risks not categorised as important**) were under close monitoring during the reporting period. Following the assessment of these issues, the PRAC concluded:

- To **close the monitoring** of Glomerulonephritis and nephrotic syndrome including IgA nephropathy, New daily persistent headache and Histiocytic necrotizing lymphadenitis.
- To **continue the monitoring** of Menstrual disorders, Hearing loss, Corneal graft rejection, Fatal cases, Severe cutaneous adverse reactions, Dermatomyositis.

  These events will continue to be monitored as part of the MAH's ongoing surveillance activities. Events of Hearing loss and Corneal graft rejection do not need to be further discussed through PBRERs unless significant new safety information is identified. Fatal cases and SCARS, in particular erythema multiforme should continue to be discussed in the next PBRER, as well as literature on menstrual disorders.

Late breaking information:

Immunocompromise study D8111C00010 was discontinued due to recruitment challenges. This was agreed by the PRAC and CHMP (see variation II/0084/G).

The MAH was requested to submit in depth analyses of myocarditis and pericarditis through a LEG procedure by the end of May 2023. This was triggered by the identification of an increased risk of myocarditis and pericarditis with another adenovirus vector vaccine (Jcovden) in the US.

New benefit information

New immunogenicity and effectiveness data support a positive effect of prime vaccination and homologous boost vaccination with Vaxzevria against variants, including Omicron B4.5.

New information on the benefit of Vaxzevria does not modify the conclusions of previous assessments.

Benefit/risk balance

New information on the benefit of Vaxzevria does not modify the conclusions of previous assessments.

On 14 April 2023, the MAH was requested to submit as a legally binding measure (LEG) further information regarding Vaxzevria and myocarditis (LEG 115). The MAH was also requested to critically discuss the implications on the benefit-risk of Vaxzevria. Based on the available data, no safety concern was identified for myocarditis. On 26 May 2023, the MAH clarified within this procedure that a quantitative benefit-risk assessment for Vaxzevria was undertaken as the context of management and prevention of the COVID-19 evolves with the emergence of the new variants (e.g., currently Omicron XBB.1.5). Results of the analysis were not available at that time and were planned to be submitted by the end of August. The MAH was thus requested to submit a quantitative B/R analysis by the 31 August 2023 in a new separate LEG (outcome of the LEG 115 procedure; July 2023).

Overall, the PRAC considers that based on the benefit and risk information collected during the period under review, the benefit risk balance of the vaccine does not substantially change. However, the following points are noted:

1. the vaccine is based on the original Wuhan strain,
2. the epidemiology of the virus, the available possibilities for prevention and treatment of a SARS-CoV-2 infection, and the current risks for serious outcomes of the disease have evolved,

3. the well-established safety profile of this vaccine includes serious adverse drug reactions (ADRs) that have been identified post marketing, such as TTS (frequency very rare), VTE (frequency unknown), Guillain Barré syndrome (GBS) (frequency very rare), transverse myelitis (frequency not known), capillary leak syndrome (CLS) (frequency not known), cerebrovascular venous and sinus thrombosis (frequency not known) and cutaneous vasculitis (frequency not known).

Nevertheless, assessment of the data within the current PSUR led to the conclusion that overall, in the absence of new data changing the established benefit risk balance, it remains unchanged. This conclusion is without prejudice to the further review and outcome of the quantitative benefit risk assessment in the LEG procedure to be submitted by the end of August 2023.

3. Recommendations

Based on the PRAC review of data on safety and efficacy, the PRAC considers that the risk-benefit balance of medicinal products containing COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria) remains unchanged but recommends that the terms of the marketing authorisation(s) should be varied as follows:

Scientific conclusions and grounds for variation to the terms of the marketing authorisations

In view of available data on **Venous Thromboembolism** from the literature and spontaneous reports, the PRAC considers a causal relationship between COVID-19 Vaccine (ChAdOx1-S [recombinant]) and Venous Thromboembolism is at least a reasonable possibility. The PRAC concluded that the product information of products containing COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria) should be amended accordingly.

Precise scope:

Update of sections 4.4 and 4.8 of the SmPC to add the adverse reaction Venous Thromboembolism with a frequency 'not known' and a warning/precaution as stated below. The Package leaflet is updated accordingly.

The following changes to the product information of medicinal products containing COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria) are recommended (new text **underlined and in bold**, deleted text ~~strike through~~):

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows:

Coagulation disorders: [Text to be added following the paragraph on Cerebrovascular venous and sinus thrombosis]

Venous thromboembolism: Venous thromboembolism (VTE) has been observed following vaccination with Vaxzevria and should be considered for individuals at increased risk for VTE.

Risk of **severe adverse** ~~***very rare***~~ *events after a booster dose*

The risk of **severe adverse** ~~**very rare**~~ events (such as coagulation disorders including thrombosis with thrombocytopenia syndrome, **VTE**, CLS, GBS and TM) after a booster dose of Vaxzevria has not yet been characterised.

- Section 4.8

The following adverse reaction(s) should be added under the SOC Vascular disorders with a frequency 'not known':

Venous thromboembolism[b]

[b] Cases have been reported post-marketing (see also section 4.4).

Package Leaflet

- Section 2

Warnings and precautions

Talk to your doctor, pharmacist or nurse before you are given Vaxzevria:

- **If you have risk factors for blood clots in your veins (venous thromboembolism (VTE))**

Blood disorders

Blood clots in veins (venous thromboembolism (VTE)) have been observed following vaccination with Vaxzevria.

Risk of **severe adverse** ~~***very rare***~~ *events after a booster dose*

The risk of **severe adverse** ~~**very rare**~~ events (such as blood disorders including thrombosis with thrombocytopenia syndrome, **VTE**, CLS, GBS, TM) after a booster dose of Vaxzevria is unknown.

- Section 4

Not known (cannot be estimated from the available data)

- **blood clots in veins (venous thromboembolism (VTE))**

This recommendation is without prejudice to the further review and outcome of the quantitative B/R LEG procedure to be submitted by the end of August.

4. Issues to be addressed in the next PSUR

The MAH should also address the following issues in the next PSUR:

1. **Exposure**

   The MAH is requested to provide estimated exposure data for other countries such as African countries, if available.

2. **Thrombosis with thrombocytopenia syndrome'**

   The MAH should update the cumulative review on TTS after booster dose and discuss the need to update the SmPC Section 4.4, paragraph on 'Thrombosis with thrombocytopenia syndrome' and paragraph on 'Risk of very rare events after a booster dose'.

3. **SCARs, in particular erythema multiforme**

   a. SCAR cases: The MAH is requested to review and discuss all available literature cases (i.e. cases that might have been discussed in the previous PSUR together with any new literature cases)
   b. Erythema multiforme cases: The MAH is requested to present:

- a cumulative review of erythema multiforme (at PT level) based on data from all available sources;
- a causality assessment of the cases (using the WHO-UMC causality assessment) and discuss the cases assessed as WHO Possible, Probable or Certain;
- relevant literature data;
- a discussion on the need for updating product information and/or risk management plan, and submit proposal as required.

4. **Safety concerns**

The MAH is requested to update the safety concerns of the PSUR and RMP as follows:

- To Re-classify the important potential risk of 'Thrombosis' as an important identified risk at the next regulatory opportunity
- To maintain 'Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)' in the important potential risks
- To maintain 'Interactions with other vaccines ' and 'Long-term safety' in the missing information.

5. **Dermatomyositis**

The MAH is requested to present new cases of dermatomyositis (DM) and as well as new data from the literature.

5. PSUR frequency

☒No changes to the PSUR frequency

The current **1-year** frequency for the submission of PSURs should remain unchanged.

Annex: preliminary PRAC Rapporteur assessment comments on PSUR

1. PSUR Data

1.1. Introduction

This Periodic Benefit Risk Evaluation Report (PBRER) for COVID-19 Vaccine (ChAdOx1-S [recombinant]) (Vaxzevria) covers the period **from 29 June 2022 and 28 December 2022**.

The International Birth Date (**IBD**) **is 29 December 2020**.

VAXZEVRIA is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of the Severe Acute Respiratory Coronavirus 2 (SARS CoV-2). Following administration, the S glycoprotein of SARS CoV-2 is expressed locally stimulating neutralizing antibody and cellular immune responses.

VAXZEVRIA is indicated for active immunisation of individuals ≥18 years for the prevention of COVID-19.

VAXZEVRIA is supplied as a vial containing either 8 doses or 10 doses per vial, 0.5 mL per dose for intramuscular (IM) injection. VAXZEVRIA vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks after the first dose. It is recommended that individuals who receive a first dose of VAXZEVRIA complete the vaccination course with VAXZEVRIA. A booster dose (third dose) of 0.5 ml may be given to individuals who completed the primary vaccination course with VAXZEVRIA or another authorised COVID 19 vaccine. The third dose should be administered at least 3 months after completing the primary vaccination course. The status of approval and the recommendation in national prescribing information (PI) documents relating to the booster dose vary.

The MAH does not propose any update of the product information as part of the submission of this PBRER.

1.2. Worldwide marketing authorisation status

VAXZEVRIA was first approved for active immunisation in individuals 18 years of age and older for the prevention of COVID-19 in United Kingdom (UK) on 29 December 2020. It received conditional marketing authorisation in the EU on 29 January 2021.

VAXZEVRIA has been approved either as Marketing Authorisation (MA), Conditional Marketing Authorisation (CMA), or emergency use authorisation in more than 90 countries managed by AstraZeneca and its partners – Serum Institute of India (SII), R-pharm and Fiocruz.

Rapporteur assessment comment:

The MAH provided a summary of the worldwide MA status applicable to VAXZEVRIA (see Table 1 in PSUR#4). Compared to the previous PSUR period, Costa Rica, Ecuador, Taiwan, and Uruguay are not included anymore in the list of countries with an MA, CMA or EUA.

Of note, the conditional MA was switched to a standard MA on 31 October 2022.

1.3. Overview of exposure and safety data

1.3.1. Actions taken in the reporting interval for safety reasons

No significant actions related to safety were taken or proposed during the reporting period.

1.3.2. Changes to reference safety information

The reference safety information is the Core Data Sheet (CDS).

The VAXZEVRIA CDS in effect at the beginning of the reporting period was dated 11 May 2022 (version 18.0). During this reporting period, the VAXZEVRIA CDS was updated to include the changes summarised in Table 1.

For the purpose of this PBRER, the **CDS dated 08 November 2022 (version 21.0)**, is the reference for both the benefit and risk sections.

Table 1 - Summary of safety-related changes to the VAXZEVRIA CDS during the reporting period

CDS version date	**CDS Section Number – CDS Section Title** **Detail of the safety-related change**
01 July 2022	**CDS Section 4.8 – Undesirable effects** Addition of tinnitus under "ear and labyrinth disorders" with the frequency "uncommon"
31 August 2022	**CDS Section 4.8 – Undesirable effects** Addition of cutaneous vasculitis with the frequency "not known".
08 November 2022	**CDS Section 4.4 – Special warnings and special precautions for use** Addition of text pertaining to Thrombocytopenia including immune thrombocytopenia. Re-organised the content under medical concept of Coagulation disorders with the following sub-topics: - Thromboembolism in combination with thrombocytopenia - Cerebrovascular venous and sinus thrombosis without thrombocytopenia - Thrombocytopenia **CDS Section 4.8 – Undesirable effects** Addition of immune thrombocytopenia in summary of post-authorisation data, with the frequency "not known".

Post the DLP of PBRER, it was decided to update the CDS to include "**Decreased appetite**" as an ADR and Number and percentage of solicited and unsolicited events were updated based on the final pooled analysis from COV studies (COV001, 002, 003 and 005: 31 December 2021). See section 2.2.

Rapporteur assessment comment:

The reference safety information for this PSUR is the CDS version 21.0, dated of 11 November 2022. It is noted that the latest changes to the CDS are in line with the current EU-PI (dated of 20 March 2023):

- Update of the section 4.8 to include tinnitus (uncommon), cutaneous vasculitis (not known), immune thrombocytopenia (not known) and decreased appetite (uncommon)
- Update of the section 4.4 to re-organise the warnings and special precautions regarding the coagulations disorders (i.e. TTS, CVST without thrombosis, and thrombocytopenia).

1.3.3. Estimated exposure and use patterns

1.3.3.1. Cumulative subject exposure in clinical trials

Estimates of overall cumulative subject exposure are provided in Table 2, based on actual enrolment/randomisation schemes for ongoing trials.

Table 2 - Estimated cumulative subject exposure from clinical trials

Treatment	Number of subjects
VAXZEVRIA	35942
AZD2816[a]	1523
MenACWY	10960
Rabies vaccine	200
Placebo	11972

Cumulative numbers from initiation of the first clinical trials up to 28 Dec 2022. Participants rolled over from COV001 and COV002 into COV009, no additional dosing in COV009. COV009 excluded to avoid double-reporting.
[a]AZD2816 is a discontinued vaccine developed from AZD1222 targeting Beta variant of SARS-CoV-2.

Rapporteur assessment comment:

As of 28 December 2022, a total of 60,597 subjects were enrolled in completed and ongoing clinical trials. These include **35,942 subjects who were exposed to VAXZEVRIA** and 1,523 subjects who were exposed to AZD2816 (targeting Beta variant of SARS-CoV-2).

1.3.3.2 Cumulative and interval patient exposure from marketing experience

1.3.3.2.1 Cumulative doses distributed

Table 3 - VAXZEVRIA exposure, based on doses distributed, by Region

Region[b]	Exposure by doses distributed		Percentage (%)	
	Interval (01 July 2022 to 31 December 2022)	Cumulative (Up to 31 December 2022)	Interval	Cumulative
Europe	0	248,197,720	0	8.22
International	36,646,740	680,370,580	20.14	22.52
North America	14,178,700	33,267,900	7.79	1.10
Japan	57,600	62,720,740	0.03	2.08
SSI[a]	109,067,400	1,745,773,940	59.95	57.79
Fiocruz[a]	21,971,750	209,957,440	12.08	6.95
R-Pharm[a]	0	10,358,700	0	0.34
BKT[a]	0	30,000,000	0	0.99
Total	**181,922,190**	**3,020,647,020**	**100**	**100**

[a]Data from Serum Institute of India (SSI), Biokangtai (BKT), and R-Pharm is as of 30 June 2022 and from Fiocruz is as of 31 Dec 2022.
[b]Where AstraZeneca is the MAH, dose volumes cited represent doses dispatched from AZ manufacturing sites and contracted manufacturing sites. The destinations noted 'Region' represent what is known at the time of dispatch. Country to country donations may or may not be reflected dependent on the timing and type of donation.

A more detailed breakdown of doses distributed across the countries within the EU can be found in Appendix 6 of PSUR#4.

PRAC Rapporteur's comment:

As of 31 December 2022 (DLP), a total of **~3 billion doses of VAXZEVRIA have been distributed**, including ~181 million doses during the reporting interval, which is ~51% less doses than during the previous reporting period (~374 million doses in previous PSUR).

1.3.3.2.2 Cumulative doses administered

Exposure data by doses administered has either been provided to AstraZeneca directly from Government bodies or has been sourced from country specific websites. Administration data from the licence partners (Serum Institute of India, Fiocruz and R Pharm) have not been provided to AstraZeneca directly.

Please note that administration in other markets where the VAXZEVRIA is authorised has not yet been made available to AstraZeneca. As such, the doses administered presented in this report is less than the doses distributed. The cumulative global post-marketing patient exposure (by doses administered) to VAXZEVRIA, since launch to 31 December 2022, have been estimated to be over 2.35 billion doses.

The vaccine administration data is provided by the health departments only in cumulative manner. Therefore, the interval data is calculated by subtracting the previous cumulative from the current cumulative data across all the countries. The weekly administered data is subject to change every week, based on the reconciliation and update provided by the individual markets. Hence, the negative values are due to a greater cumulative value from previous report in comparison to current report.

Table 4 - VAXZEVRIA interval and cumulative exposure based on doses administered, by Region/Country

Region	Interval			Cumulative			Percentage (%)	
	Dose 1	Dose 2	Dose 3/ Dose 4/ Booster	Dose 1	Dose 2	Dose 3/ Dose 4/ Booster	Interval	Cumulative
European Union	**22,490**	**14,334**	**10,179**	**38,935,859**	**29,830,777**	**31,951**	0.025	2.922
United Kingdom	**-7,439**	**-7,973**	**831**	**24,725,401**	**24,141,350**	**59,155**	-0.008	2.078
Afghanistan		0			975338		0.000	0.041
Australia	**-188,227**	**-170,548**	**386,772**	**6,710,682**	**6,644,072**	**479,167**	0.015	0.588
Philippines		284777			22135134		0.149	0.940
India		165833251			1745211297		86.67	74.12
Canada	1654	1083	204	2236627	577088	1788	0.002	0.120
Argentina	7256	11021	61373	10181628	9944079	6643766	0.042	1.137
Bangladesh	220251	371169	5248251	20769391	19503709	15968643	3.052	2.389
Colombia	453211	513600	456393	5761263	3886086	2039794	0.744	0.496
Ecuador	25295	50994	1172435	1764549	1470105	5039008	0.653	0.351
Iran	5006	6213	238149	5601073	5045996	3779468	0.130	0.613
Japan	-18	341	0	58689	59160	0	0.000	0.005
Brazil	**35,844**	**-988,002**	**15,505,290**	**62,269,829**	**56,441,002**	**32,863,466**	7.606	6.437
Chile	4	14	1130	410045	139643	2656600	0.001	0.136
Guatemala	4751	5213	18633	2038088	1612254	837482	0.015	0.191
Ghana		448113			10545038		0.234	0.448
Lebanon		2,077			722870		0.001	0.031
Iraq		0			717233		0.000	0.030
Mexico		0			49783383		0.000	2.114
Malaysia	1378	1729	12452	2047982	2027704	1631803	0.008	0.242
Nepal	131436	190873	676894	5506364	4789110	4703764	0.522	0.637
Peru	3547	10929	138128	2244579	2110451	3747778	0.080	0.344
Saint Lucia	0	0	0	37850	34810	0	0.000	0.003
Taiwan	471	1944	1070	8072530	7164623	60558	0.002	0.650
Thailand	20407	21384	53437	14098645	28682204	5923245	0.050	2.068
New Zealand	3	27	191	3317	3646	2076	0.000	0.000
South Korea		27 539			20348873		0.014	0.864
Uruguay	3	0	0	46687	44454	179	0.000	0.004
Grand Total		**191,349,237**			**2,354,582,258**		**100**	**100**

Data cut off may vary for several countries. Detailed information on data cut off is available in Section 5.2.1.2 of the PSUR.

A more detailed presentation of doses administered by country/states as well as vaccine administration by dose number, age and/or gender where provided for specified countries can be found in Appendix 6 of

PSUR#4. A summary of the post-marketing patient exposure by age and gender (as currently available) is presented in Table 10 and Table 11 of the PSUR#4, respectively.

Exposure by doses administered is used as part of Observed versus Expected (O/E) Analyses, refer to Appendix 8 of PSUR#4 for further details.

PRAC Rapporteur's comment:

As of 31 December 2022, a total of ~38 million first doses, ~29 million second doses and ~31,000 booster doses have been administered cumulatively in the EU; and a total of **~2.3 billion doses have been administered worldwide**. This may be underestimated as administration data from some markets where Vaxzevria is authorised has not yet been made available to the MAH.

During the reporting interval, in the EU, 22,490 first doses and 14,334 second doses were administered. However, interval administration data are estimated by subtracting the previous cumulative from the current cumulative data across all the countries. These data are subject to regular update of weekly administered data from Government bodies or has been sourced from country specific websites.

Data per gender is still not available for EU countries. The MAH claimed that since ECDC does not include gender breakdown at country level, this cannot be provided. However, it commits to continue its efforts to collect exposure data by country, age, and gender for all EU countries as it has been already requested.

Overall conclusion on exposure data

1. European market

During the **interval period**, **0 doses were distributed** and an estimated 47,003 doses were administered (based on subtraction of cumulative data between periods).

ECDC vaccine tracker provides more accurate **interval administration data**. An search[1] in the database identified **1126 doses administered** in the EU/EEA during the period under review. Of note, since 2023 week 01, less than 15 doses have been administered per week. This may correspond to the vaccination of people who are not eligible and/or do not want another vaccine, or to errors in the coding of the vaccine names in the databases.

Cumulatively, 165 million doses were distributed and **68,8 million doses administered** (i.e., 38,9 mo Dose 1; 29,8 mo Dose 2; and 32,000 Booster dose).

Finally, as provided in the **Marketing status** reporting (annex to cover letter):

- the pack size "08 multidose vials" (initially marketed in 6 countries) was not on the EU/EEA market at the time of the DLP (last date of cessation of marketing: 01.04.2022)

- the pack size "10 multidose vials" (initially marketed in 28 countries) was not on the EU/EEA market at the time of the DLP (last date of cessation of marketing: 31.07.2022 in Romania; cessation date of 01.04.2022 or earlier in all other countries)

According to the EU-PI, the shelf-life of unopened vial is 9 months when stored in a refrigerator (2°C – 8°C). Taking all this information into account, the PRAC Rapporteur understands that the last batch distributed in the EU/EEA market should have now been expired.

The MAH is requested to provide clarification regarding any remaining batches in the EU/EEA market (how many, in which countries) and their expiry dates. The MAH should also clarify his plans regarding the marketing of Vaxzevria in EU/EEA. [RSI]

[1] Search performed on 04.05.2023

2. <u>UK market</u>

Exposure data based on distribution were not available.

During the interval period, the estimated number of **administered doses was negative**. The MHRA weekly update states that for the Autumn 2022 COVID-19 vaccination booster campaign, the bivalent mRNA vaccines (Pfizer/BioNTech and Moderna) were mainly used while Nuvaxovid was recommended for those who cannot receive an mRNA vaccine. The exposure to Vaxzevria is therefore expected to be zero in the reporting period.

Cumulatively, **48,9 million doses were administered** (i.e., 24,7 mo Dose 1; 24,1 mo Dose 2; and 59.000 Booster dose).

3. <u>Global market</u>

Globally, the regions covered by the Serum Institute of India have the highest exposure, with 1,75 billion doses distributed cumulatively, including 109 million doses for the interval period.

During the reporting period, the exposure based on administered doses remained high in India (166 mo doses), Brazil (32 mo doses), Bangladesh (17 mo doses), and to a lesser extend Colombia, Ecuador, Nepal, Peru, Philippines, and Thailand (3-6 mo doses, each).

However, information regarding exposure in other countries in the world, such as African countries, was not available in the PSUR. ***The MAH is requested to provide estimated exposure data for other countries such as African countries, if available [request for the next PBRER].***

Finally, it is noted that from Monday 20 March 2023 Vaxzevria is no longer available as an approved COVID-19 vaccine in Australia[2].

1.3.4. Data in summary tabulations

Cumulative summary tabulations of serious adverse events from clinical trials

A cumulative summary tabulation of serious adverse events (SAEs) from AstraZeneca-sponsored and license partner sponsored interventional clinical trials that have been reported during the Vaxzevria clinical development programme, from the Development International Birth Date (DIBD) to the data lock point (28 December 2022), organised by SOC, is presented in Appendix 2 of PBRER.

There is an increase in Clinical trial SAEs/ cases in the current PBRER interval compared to the previous PBRER interval, this is because the COV Studies (001, 002, 003 and 005) were unblinded and the cases were edited to add the treatment allocation. There is no new safety concern identified from these events.

Cumulative and interval summary tabulations from post-marketing data sources

Cumulative and interval summary tabulations of adverse reactions (ie, AEs considered as "a reasonable possibility of a causal relationship between the medicinal product and the event") that have been reported from marketed experience with Vaxzevria, from the IBD to the data lock point, organised by SOC, are presented in Appendix 2 of PBRER.

Compared to the previous interval, there is a decrease in the case and event count for the current reporting interval. This is due to decreased update in many regions, compared to the previous intervals.

Rapporteur assessment comment:

A cumulative total of 2,216 cases representing 4,614 serious adverse events have been reported from

[2] https://www.health.gov.au/our-work/covid-19-vaccines/our-vaccines/astrazeneca

AstraZeneca-sponsored and license partner **interventional clinical trials**. The vast majority of these case reports were still blinded as they contained only expected Suspected Serious Adverse Reactions.

A cumulative total of 3,049,929 adverse events, originating from 808,019 cases, have been spontaneously reported from **post-marketing exposure**, of which 244,927 adverse events, from 59,926 cases, were reported during the interval period. The majority of the AEs reported during the interval and cumulative period were from the SOCs 'General disorders and administration site conditions', 'Nervous system disorders', 'Musculoskeletal and connective tissue disorders' and 'Gastrointestinal disorders'.

Cumulatively, most commonly spontaneously reported adverse events were Headache, Pyrexia, Chills, Fatigue and Myalgia. Most commonly spontaneously reported serious AEs were Headache, Pyrexia, Fatigue, Chills and Nausea.

During the period under review, most commonly spontaneously reported serious AEs were COVID-19, Vaccination failure, Headache, Fatigue and Pyrexia.

Based on the number of spontaneously reported adverse events and the estimated number of doses administered (191,349,237 doses), approximately 1.28 adverse events/1,000 doses occurred during the period under review, which is in line with the previous interval period (0.98/1,000 doses). For the overall period from launch up to the DLP of this PBRER, the occurrence of adverse events was estimated at 1.30/1,000 doses.

No new important safety information is identified from the data in summary tabulations. The distribution of events over the different SOCs and the most commonly reported PTs are in line with the known safety profile of Vaxzevria.

1.3.5. Findings from clinical trials and other sources

1.3.5.1. Completed and ongoing clinical trials

During the reporting period, no clinical trials were completed.

There were 11 (COV001, COV002, COV003, COV004, COV005, COV006, COV008, COV009, D8110C00001, D8110C00010 and D7220C00001) ongoing clinical trials during the reporting period.

There was no clinically important information that arose from ongoing clinical trials during the reporting period. The clinical trials described below have completed recruitment but final Clinical Study Reports (CSRs) had not yet been published by the end of the reporting period and therefore are not considered as completed.

Rapporteur assessment comment:

The MAH detailed in this section there were no clinical trials completed during the reporting period. For the 11 ongoing clinical trials, recruitment is completed, but final Clinical Study Reports had not yet been published. One out of these 11 clinical trials (D8111C00010) will be discontinued due to recruitment challenges.

There were 11 ongoing clinical trials during the reporting period:

COV001 – PhI/II – UK –1077 healthy adults 18 to 55 years - single IM dose or a 2- dose IM regimen of the low dose (LD) (~2.5 x10^{10} vp) and/or the standard dose (SD) (~5x10^{10} vp) of COVID-19 VACCINE ASTRAZENECA or the comparator, meningococcal vaccine (MenACWY).

COV002 – PII/III – UK- 10,812 participants ≥ 18 years of age (in addition 60 HIV-infected) - single IM

dose or a 2-dose IM regimen of the LD and/or the SD or the comparator, MenACWY.

COV003 – Ph III – Brazil – 10,416 participants ≥ 18 years of age - 2-dose IM regimen of the SD or, MenACWY or the MenACWY as the prime dose and saline placebo as boost dose. An optional fourth dose of ChAdOx1 nCov-19 vaccine was offered to a subgroup of 350 (+/- 10%) participants who previously received three doses of ChAdOx1 nCov-19 within the trial, randomly selected, and regardless of interval after the third dose. Participants in this booster sub-study were followed for 6 months from the booster vaccination.

COV004 – Ph Ib/II- Kenya - ~400 healthy adults ≥ 18 years – Ib (~40 participants): 1 IM SD dose or rabies vaccine as control – II (~360 participants): 2-dose SD or rabies vaccine.

COV005 – Ph I/II – South Africa - 2130 participants with and without HIV aged 18-65 years - 2-dose IM regimen of the SD or saline placebo. Ph I (HIV-uninfected; n=70 and HIV-infected n=100). Ph II with 1900 HIV uninfected.

COV006 – Ph II – UK - ~300 healthy children and adolescents 6-17 year - SD dose (4 or 12 weeks apart) or active control (licensed Meningococcal B vaccine) IM.

COV008 – Ph I – UK – 54 healthy adults 18-40 years – 1 or 2 doses of intranasal ChAdOx1 nCOV-19 ($5x10^9$ vp, $2x10^{10}$ vp or $5x10^{10}$ vp).

COV009 – Post-approval follow-up for COV001 and 002 trials – long term safety and immunogenicity. Up to 1,077 participants will be eligible for enrolment for the COV001 cohort and up to 10,812 participants for the COV002 cohort. No treatment given. Duration 12 months.

D8110C00001 – Ph III - US, Chile, Peru- 32,451 participants ≥ 18 years of age - 2 IM doses of either SD or saline placebo 4 weeks apart. At least 25% of participants ≥ 65 years. All participants will remain on study for 2 years following administration of first dose of study intervention (Day 730).

D7220C00001 – Ph II/III – multi-country - ~2590 participants ≥18 years to study AZD2816 (for prevention of COVID-19 caused by variant strains). Goal: 1300 previously vaccinated participants receiving single-dose vaccination and 1290 unvaccinated participants receiving 2-dose primary vaccination. Participants will receive COVID-19 VACCINE ASTRAZENECA (5×10^{10} vp) or AZD2816 (5×10^{10} vp). Dosing intervals will be 4 weeks (for COVID-19 VACCINE ASTRAZENECA and AZD2816) or 12 weeks (AZD2816 only).

D8111C00010– Ph IV – multi-country - ~360 participants ≥ 18 years of age. Previously unvaccinated immunocompromised adults will receive 3 IM doses of AZD1222. As of 28 June 2022 there have been 34 participants enrolled in the study.

Main Findings:

For COV001, COV002, COV003 and COV005: There was no significant change in the safety profile during the reporting period.

For COV006: A manuscript is in preparation for submission to peer reviewed scientific publication and a summary was provided. No new safety signal was identified.

For D8110C00001: No new information has become available during the reporting period.

For D7220C00001: No emergent safety issues were identified. There were no clinically meaningful differences between the safety profiles of booster doses of AZD1222 and AZD2816. Analyses of data through to data cut-off, up to a maximum of 107 days after booster dose, did not identify any emergent safety issues.

Overall, based on review of the data for the ongoing clinical trials (11), no new safety signal was

identified during the reporting period.

Final analyses for AZD2816 programme were conducted at the end of year 2022. The final results will be included in next PBRER when the CSRs will have been completed. There were no safety concerns identified and the lack of efficacy against omicron following primary immunization in a naïve population while maintenance of immune response in a previously vaccinated population was confirmed as already described in a previous PBRER.

1.3.5.2. Vaccination errors

Please note that Vaccination errors data is not reproduced here (see Section 9.2 of PBRER)

Rapporteur assessment comment:

Interval review: A total of 2900 case reports, including 2963 vaccination error AEs have been identified during the reporting period. This is less than compared to 7728 case reports and 8104 vaccination error AEs as reported during the previous reporting interval. The frequently reported (>50%) vaccination errors were Expired product administered (938) followed by Interchange of vaccine products (681) and Wrong product administered (525). **Interval case reports represent 13.92% of cumulative cases (20820)**.

Of the 2900 case reports, 396 were reported as serious (191 case reports were medically confirmed and 205 were consumer reports). In 2280 (78.62%) cases no associated AEs were reported in connection with the vaccination error. Other AEs were co-reported in the remaining 620 (21.37%) case reports, of which 343 (55.32 %) cases were serious including 19 case reports with a fatal outcome.

Cumulative review: A total of 20820 case reports, including 22292 vaccination error AEs, have been identified during the cumulative period. Of those 20820 case reports, 1950 were considered serious (592 case reports were medically confirmed and 1358 were consumer reports). In 15159 (72.8%) cases no other AEs were reported in connection with the vaccination error. Other AEs were co-reported in the remaining 5661 (27.2%) case reports, of which 1822 (32.2%) cases were serious, including 75 case reports with a fatal outcome.

Notably, there were 19 case reports with fatal outcome during reporting interval which is ~29% less than 27 fatal case reports as reported in previous PSUR#3.

Interchange of vaccine products (n=12) and off label use (n=11) were the most frequently reported vaccination error events.

Most frequently reported AEs (≥2) in these reports were: COVID-19 (3), Death (3), Sudden death (3), Constipation (2), COVID-19 pneumonia (2) and Pulmonary embolism (2).

Reported causes of death in these cases were Death (3), Sudden death (3), COVID-19 pneumonia (2), Pulmonary embolism (2), Adverse drug reaction (1), Asthma (1), Cerebral haemorrhage (1), Cerebral venous thrombosis (CVT) (1), Cerebrovascular accident (1), COVID-19 (1), Cystic fibrosis (1), Deep vein thrombosis (1), End stage renal disease (1), Lung transplant (1), Lymphoma (1), Malignant neoplasm progression (1), Pneumonia (1), Product dose omission issue (1), Pulmonary thrombosis (1), Renal disorder (1), Respiratory failure (1), Somnolence (1), Thrombocytopenia (TCP) (1) and Thrombosis with thrombocytopenia syndrome (TTS) (1).

The MAH concluded that the review of these fatal cases did not identify safety issues in relation to type of vaccination errors.

In conclusion, some medication errors are expected to occur despite written instructions and

educational activities for HCPs administering the vaccine. The number of cases, the type and seriousness of the reported medication errors are comparable to the previous PSUR#3. These cases do not indicate any trends of systemic substantial errors or a need for additional risk mitigation activity.

The MAH's conclusion is accepted that at the moment no new relevant patterns of (potential) vaccination errors were identified.

Taking into consideration the review of the risk [vaccination errors], no further action is considered warranted at this stage.

1.3.5.3. Literature

Relevant literature articles containing new and significant safety findings relevant to VAXZEVRIA published during the review period were retrieved. Articles of interest related to event reviews completed as part of Health Authority requests, Important identified and Potential risks or Missing information have been included within the review of those safety concerns throughout section 2.3. Other articles containing new and significant safety findings are summarized below.

- **Graves' disease following vaccination against SARS-CoV-2** (**Triantafyllidis et al 2022**) [**systematic cumulative literature review** of Graves' disease following COVID-19 vaccination; 21 eligible articles]: of the 57 patients with Graves' disease following COVID-19 vaccination, 9 received VAXZEVRIA. Of the 9 patients with VAXZEVRIA, 6 were females and 3 were males, age ranged between 30 and 70 years, 7 developed new onset Graves' disease, 1 exacerbation and in 1 case previous history of Graves' disease was not reported. The latency in the 9 patients ranged from 1 to 14 days. Treatment was reported in 7 out of the 9 patients, outcome was reported for 3 patients, in 1 patient improvement was achieved after 3 months and in 1 after 30 days. The authors discussed various potential mechanisms for such association, although none was supported with confirmatory data. The authors concluded that Graves' disease is possibly a condition, physicians and other healthcare professionals (HCP) may expect to see in patients receiving COVID-19 vaccines. MAH's comment: The publication identified fewer number of cases of Graves' disease following COVID-19 vaccination, particularly involving VAXZEVRIA. Furthermore, the authors indicated low quality of case reports and could not exclude selection bias, and hence causality in the reported cases could not be inferred. Overall, this article does not provide sufficient evidence of an increased risk of Graves' disease in vaccinees who received VAXZEVRIA.
- **Cutaneous symptoms of connective tissue disease after COVID-19 vaccination** (**Nguyen et al 2022 [A]**) [**systematic review of literature** on cutaneous symptoms of connective tissue diseases (including lupus, systemic sclerosis, scleroderma, sclerotic skin, dermatomyositis (DM), morphea) after COVID-19 vaccination; 30 articles selected]: the selected articles include 22 single case reports, 3 case series, 2 cohort studies, 2 cross-sectional studies, and 1 clinical trial, encompassing 2020 patients, of whom 93 patients developed post-vaccine cutaneous symptoms of connective tissue diseases, such as skin thickening, and ulceration, erythematous macules, and papules, Raynaud's phenomenon. The majority of affected patients had pre-existing autoimmune disease, 72/93 (77.4%); new diagnosis of connective tissue disease after COVID-19 vaccination was established in 21/93 (22.6%) patients. The most common vaccines administered were Pfizer - 60.5%, Sinovac - 19.6% and Moderna - 10.8%; AstraZeneca COVID-19 vaccine was administered in 9.1% of patients. The authors concluded that only a small percentage of patients developed autoimmunity after COVID-19 vaccination, and suggested that autoimmunity may occur in genetically predisposed patients. The authors also suggested that the mechanisms could involve development of autoantibodies due to cross-reactivity of SARS-CoV-2 proteins and tissue antigens, or that mRNA-containing lipid nanoparticles (LNPs) may trigger autoimmunity by upregulating production of pro-

inflammatory cytokines and chemokines, no new data was presented to substantiate the mechanisms. MAH's comment: The referenced evidence is based on diverse sources, mostly involving mRNA vaccines, with AstraZeneca COVID-19 vaccine amounting to less than 10% of included patients, it was not reported how many of them developed cutaneous symptoms of connective tissue diseases after the vaccination. No new mechanistic data was presented, while one of the suggested mechanisms is not relevant for AstraZeneca COVID-19 vaccine.

Rapporteur assessment comment:

The MAH's review of literature does not suggest any new safety issue.

1.3.6. Lack of efficacy in controlled clinical trials

Rapporteur assessment comment:

There were no new clinical trial efficacy data available during the reporting period

1.3.7. Late-breaking information

Immunocompromise study (D8111C00010): a Type II Variation for removal of IC study was submitted to EMA. The Committee For Medicinal Products For Human Use (CHMP) opinion (received on 10 February 2023) and supported discontinuation of the category 1 study D8111C00010 and the removal from the Annex II (conditions or restrictions with regard to the safe and effective use of the medicinal product) of EU Product Information.

After the data lock point of the PBRER (28 December 2022), following the review of the safety data (solicited and unsolicited events) from the final pooled analysis (DCO3:31 December 2021) COV001, COV002, COV003, COV005 and the relevant post-market data; AstraZeneca decided update the CDS to include Decreased appetite as an ADR in Section 4.8 with a frequency of "Uncommon" along with some minor changes to frequency categories for other adverse events (Dizziness and Abdominal pain in the VAXZEVRIA group; Vomiting, Pain extremity and Urticaria in the Control group).

Rapporteur assessment comment:

Following the approbation of the variation II/0084/G, the immunocompromised study was discontinued and removed from the RMP. The final report from the study D8111R00020 (systematic literature review) is currently under assessment (variation II/0091) to address the missing information 'Use in immunocompromised patients'.

The final results and pooled analysis for studies COV001-COV005 are currently under review (variation II/0089). The frequency of the ADRs Dizziness and Abdominal pain is proposed to be updated from uncommon to common in the EU-PI. Decreased appetite is already listed with a frequency uncommon in the section 4.8 of the EU-PI.

After the DLP of this PSUR, an increased risk of myocarditis and pericarditis has been suggested for another adenovirus vector vaccine (Jcovden)[3]. This triggered a request to submit in depth analyses of myocarditis and pericarditis for both Jcovden and Vaxzevria at EU level. For Vaxzevria, analyses will be submitted by the end of May 2023 through a LEG procedure.

[3] https://www.fda.gov/news-events/press-announcements/fda-roundup-march-14-2023

2. Signal and risk evaluation

2.1. Summary of safety concerns

Table 5 presents a summary of the safety concerns included in the Core RMP for VAXZEVRIA (Version 7.0, dated 22 February 2022) and the EU RMP for VAXZEVRIA (Version 5.0 succession 1, dated 25 May 2022) that were in effect at the beginning of the reporting period.

Table 5 - Summary of safety concerns at the beginning of the reporting period [from Appendix R3 of the PBRER]

Risk Category	Core Risk Management Plan (V7)	EU Risk Management Plan (V5 S1)
Important identified risk	Thrombosis in combination with Thrombocytopenia	Thrombosis with thrombocytopenia Syndrome
		Thrombocytopenia, including immune thrombocytopenia
		Guillain-Barré syndrome
Important potential risk	Cerebrovascular venous sinus thrombosis without thrombocytopenia	Thrombosis
	Immune-mediated neurological conditions	Nervous system disorders, including immune-mediated neurological conditions
	Vaccine-associated enhanced disease (VAED)	Vaccine-associated enhanced disease (VAED), including vaccine associated enhanced respiratory disease (VAERD)
Missing information	Use of VAXZEVRIA in pregnant and breastfeeding women	Use during pregnancy and while breastfeeding
	Use of VAXZEVRIA in subjects with severe immunodeficiency	Use in immunocompromised patients
	Use of VAXZEVRIA in subjects with severe and/or uncontrolled underlyingdisease	Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)
	Use of VAXZEVRIA with other vaccines	Use in patients with autoimmune or inflammatory disorders
		Interactions with other vaccines
		Long-term safety

2.2. Signal evaluation

There were five validated signals that were either ongoing or closed during the reporting period (see Tabular overview in next page).

Three validated signals were closed during the reporting period, immune thrombocytopenia (ITP) cutaneous vasculitis and Tinnitus. One signal of feeling hot was closed after the DLP. One signal of decreased appetite was ongoing.

Rapporteur assessment comment:

The signal of '**Cutaneous vasculitis**' was closed by the MAH. Cutaneous vasculitis is classified as an identified risk not categorised as important. The signal was review in the previous PSUR procedure. Cutaneous vasculitis (frequency not known) was listed as an ADR in the EU-PI as an outcome of the PSUR03. No new information was provided in this PSUR.

The signal of '**Immune thrombocytopenia**' was closed and it was considered by the MAH that there is a reasonable possibility of a causal association between VAXZEVRIA and Immune thrombocytopenia. CDS was updated accordingly. At the EU level, ITP was already listed in sections 4.4 and 4.8 of the SmPC and classified as an important identified risk in the EU-RMP. No new information was provided in this PSUR.

The signals of '**Feeling hot**' and '**Decreased appetite**' were triggered by the final pooled analysis of COV studies. After the DLP of this PSUR, the MAH:

- Closed and rejected the signal of 'Feeling hot'. The MAH considered that 'Feeling hot' is adequately covered in the VAXZEVRIA CDS with the listed events of Feverishness and Fever, and need not be specifically included as an ADR.
- Classified the signal of 'Decreased appetite' as an identified risk not categorised as important. The MAH was in the progress to update the CDS to include Decreased appetite as ADR in Section 4.8 with frequency of 'uncommon'.

The final Clinical Study Reports and pooled analysis for the COV studies are currently under assessment within the type II variation EMEA/H/C/005675/II/0089 procedure. Of note, 'Decreased appetite' (uncommon) is already included in the EU-SmPC.

After the DLP of this PSUR:

- The MAH closed the signal of '**Tinnitus**' as an identified risk not categorised as important. Tinnitus was already listed as an ADR in the EU-PI. No new information was provided in this PSUR.
- The PRAC closed a signal of pemphigus (EPITT 19858): it was concluded that the current evidence is insufficient to establish a causal relationship between Vaxzevria and pemphigus or pemphigoid. However these topics should continue to be monitored in the PSURs.
- The PRAC confirmed that the signal of myositis (EPITT 19882) requires further evaluation. This topic is discussed below in section 2.3.22.

- Tabular overview of signals: new, ongoing or closed during the reporting interval 29.06.2022 to 28.12.2022.

Signal term	Date detected	Status (new, ongoing or closed)	Date closed (for closed signals)	Source or trigger of signal	Reason summary	Method of signal evaluation	Outcome, if closed
Cutaneous vasculitis	25.04.2022	Closed	31.08.2022	Literature Article, Regulatory Authority	Regulatory Authority Enquiry or Request. GSP or SSaMT Leader consider signal requires evaluation.	Quantitative Signal Detection System (Observed versus expected analysis), External Quantitative Signal Detection System (EVDAS), Literature review. Qualitative data analysis (Individual Case Safety Report or Case Series)	Change to Reference Safety Information and Product Labelling. Summary: CDS Section 4.8 (undesirable effects) was updated to include cutaneous vasculitis as an ADR (frequency: not known)
Immune thrombocytopenia	06.07.2022	Closed	08.11.2022	Qualitative data analysis (Individual Case Safety Report or Case Series), Literature cases	GSP or SSaMT Leader consider signal requires evaluation based on new well-documented spontaneous case reports and also published literature	Quantitative Signal Detection System (Observed versus expected analyses), Literature review, Preclinical review, Clinical review, Qualitative data analysis (Individual Case Safety Report or Case Series), Epidemiology analyses	Change to Reference Safety Information and Product Labelling Summary: Update to 4.4 Special warnings and special precautions for use. Addition of ITP to 4.8 in summary of post-authorization data
Feeling hot	22.12.2022	Closed	17.01.2023 (after DLP)	AZ clinical trial	GSP or SSaMT Leader consider signal requires evaluation	Qualitative data analysis (Individual Case Safety report or Case Series) Literature Quantitative Signal detection system	No signal
Decreased appetite	22.12.2022	Ongoing	na	AZ clinical trial	GSP or SSaMT Leader consider signal requires evaluation	Qualitative data analysis (Individual Case Safety report or Case Series) Literature Quantitative Signal detection system	Change to Reference Safety Information and Product Labelling: CDS Section 4.8 (Undesirable effects) to be updated to include Decreased appetite as an ADR (frequency: uncommon)

2.3. Evaluation of risks and safety topics under monitoring

2.3.1. Important Identified Risk – Thrombosis in combination with thrombocytopenia/Thrombosis with thrombocytopenia syndrome

Please note that TTS data is not reproduced here (see Section 16.3.2.1 of the PBRER).

MAH's Summary

The analysis of thrombosis in combination with thrombocytopenia following the second dose of VAXZEVRIA showed that the rate of events was extremely low and lower than after administration of the first dose. The majority of the vaccinees who experienced TTS events post Dose 2 were male (59% vs 42%) and were older (Median age was 65.5 years vs. 45 years) compared to first dose recipients. The median time to onset of second dose cases was 14 days compared to 12 days for the cases with first dose. Of the 644 CVST cases, 64% were in females, 35% occurred in males, and in 1% gender was unknown.

Overall, the most common events were Cerebral venous sinus thrombosis, Deep vein thrombosis, Pulmonary embolism, and Thrombosis.

Overall, there were more fatal reports for TTO within 14 and 21 days. Seventy-four (74%) percent of the fatal reports occurred with 14 days compare to 64% for all cases and 88% of the fatal report occurred with 21 days compare to 80% for all cases. The highest number of fatal reports occurred due to HLT of Cerebrovascular venous and sinus thrombosis. Cerebral haemorrhage was the most common bleeding event associated with fatal event.

The arterial events were reported highest in the age group of 50-59 and 60-69. The distribution of events in male and female was roughly equal. The mixed or the combined arterial and venous was equally distributed in age group 30-39,40-49,50-59 and 60-69 and the distribution of cases in female and male was roughly equal. The venous events were reported highest in the age group of 40-49, 50-59 and 60 – 69 years. The occurrence in female was higher than in the male.

Overall, there were information on platelet count was available in (67.5%) of case reports, PF-4 antibodies were positive in 26% reports, negative in 21% reports, unknown or pending in 52% case reports, D-dimer levels were reported in 39% of the case reports, however, in many reports the units were not specified. The total number of confirmed cases were (14%), probable cases were (15%), possible cases were (35%), unlikely (0.03%) and criteria not met cases were (35%).

The highest number of cases were reported from EEA (34.5%) while it received 48.15 million doses of the total worldwide doses.

The most common confounding factors in descending order of frequency in all 2644 cases were autoimmune conditions, malignancy, past history of heparin therapy, obesity and concomitant use of contraceptives. The most common confounding factors in the confirmed reports were past history of heparin use and malignancy. The dates and the type of heparin administered were not reported in all cases.

MAH's conclusion

Based on currently available data, no new safety information concerning TTS was identified. The current risk minimisation measures described in the product information are considered adequate.

From the data identified during the reporting period and also taking into account the cumulative experience, no updates to the VAXZEVRIA CDS or RMP are warranted at this time.

Thrombosis in combination with thrombocytopenia/TTS is contained in Section 4.4 (Special warnings and special precautions for use) and 4.8 in the VAXZEVRIA CDS. In addition, VAXZEVRIA is contraindicated (CDS Section 4.3) for use in any persons who have experienced thrombosis in combination with thrombocytopenia with any COVID-19 vaccine. Finally, thrombosis in combination with thrombocytopenia/ TTS is listed as an Important Identified Risk in the Core and EU RMPs for VAXZEVRIA. As such, the topic will continue to be kept under close safety surveillance by AstraZeneca and further actions will be taken as deemed appropriate.

Rapporteur assessment comment:

Cumulatively, up to 28 December 2022, 2644 cases (2632 serious, 1918 medically confirmed) of thrombosis in combination with thrombocytopenia (TCP) have been reported, of which 287 cases were reported after the 2nd dose and 15 cases after a booster dose (dose 3 or 4). During the current reporting interval, 322 cases (260 initial, 62 follow-up) were received.

Cumulatively, the majority of the cases were reported in the UK (31%), Australia (17%) and Germany (13%). Median age (55 years), median time to onset (12 days) and gender distribution (52% females) were similar to the previous PBRERs. Overall, 80% of the cases occurred within 21 days after vaccination (compared to 88% of the fatal cases).

Location of thrombotic events: Most frequently reported PTs were similar to PSUR#3: Pulmonary embolism (n=747), Thrombosis with thrombocytopenia syndrome (n=531), CVST (n=462), Thrombosis (n=435), DVT (n=428), Portal vein thrombosis (n=187) and Cerebral venous thrombosis (134).

Reporting rates for TTS, in the UK and EEA (Table 138 and 139 of the PSUR#4): Overall EEA TTS reporting rate with risk window of 42 days was estimated at 14.77/million doses (7.91/million when considering confirmed, probable and possible cases). Reporting rate in EEA was highest post dose 1, in individuals <60 years (18-49y:~39 cases/million doses, 50-59y:~33/million; all cases). EEA TTS reporting rate (42d risk window) following dose 1 (26.85/million) was clearly higher than following dose 2 (1.4/million). These estimates were in line with UK reporting rates following dose 1 (22.41/million) and dose 2 (3.85/million). The TTS reporting rate (42d risk window) following a Vaxzevria booster dose was estimated at 31.3/million doses in the EEA (1 case with TTO≤42d; estimated exposure: 31,951 administered booster doses), 16.9/million doses in the UK (1 case with TTO≤42d; 59,155 administered booster doses) and 0.27/million doses in Brazil, where the majority of the TTS cases post booster dose originated from (9 cases with TTO≤42d; 32.86 million administered booster doses).

The MAH provided **observed versus expected** (O/E) analyses for TTS and for CVST with TCP, with results in line with PSUR#2 and PSUR#3.

The MAH applied the MHRA **Case Classification** for TTS to all cases: 1726 (65%) cases were categorized as confirmed/probable/possible (14% = confirmed, 15% = probable and 36% = possible), the remaining 35% of the cases did not meet the criteria and 1 case was considered unlikely.

Fatal cases: 482 of the 2644 TTS cases had a fatal outcome (case fatality rate (CFR) of 18% compared to 17% in PSUR#2 and PSUR#3). Twenty-eight (28) fatal cases were reported after Dose 2, 5 fatal cases after Dose 3 and 1 fatal case after Dose 4. The CFR was highest within individuals <40 years of age (23-26%) and higher in females (21%) than males (15%). Overall CFR for TTS has decreased since the start of the signal (14% in April 2021 compared to 22-40% in January-March 2021). There was an increased fatality rate from December 2021 (28%) to August 2022 (29%) and in November 2022 (35%) compared to April-November 2021 and September-October-December 2022, but the absolute number of TTS cases received per month has declined since November 2021 leading to more fluctuations in the monthly CFR.

Moreover, in cases where the onset date was not reported, the date the case was initially received by the MAH was used to calculate the CFR over time.

TTS after Dose 2: Up to 28 December 2022, 287 cases of TTS following the second dose were retrieved (compared to 260 cases in PSUR#3). Majority were male (55%; previous PSUR#3 59%) with median age 66 years and median TTO 13 days. Pulmonary embolism (122 cases) followed by DVT (70 cases) was most frequently reported. Twenty-eight (28) cases had a fatal outcome, corresponding to a CFR of 10%, which is lower than the CFR for dose 1 cases (19%).

TTS after booster dose: Cumulatively, 19 cases of TTS following a booster dose were retrieved, of which 15 cases occurred after a Vaxzevria booster (12 cases after Dose 3 and 3 cases after Dose 4) and 4 cases after a mRNA booster. Ten cases originated from Brazil and one case each from Ecuador, UK, Mexico, Italy and Germany. The vaccinee received primary vaccination series with Vaxzevria in 2 cases, with other COVID-19 vaccines (Comirnaty and/or CoronaVac) in 9 cases and in the remaining 4 cases the primary vaccination series were not reported. Six cases were reported in females and eight cases in males. Median age was 28 years and median TTO 12 days. Five cases had a fatal outcome (CFR=33%), of which four were reported after Dose 3 and one after Dose 4. Two cases were classified as confirmed TTS cases, 2 cases as probable TTS cases (including 1 fatal case) and 5 cases as possible TTS cases (including 3 fatal cases) according to the MHRA Case Classification for TTS. The remaining 6 cases did not meet the criteria, including one fatal case. The MAH states that no confirmed cases of TTS following a heterologous Vaxzevria booster have been identified, however the PRAC Rapporteur finds the fatal cases in young vaccinees from Brazil worrisome (Table 151; Cases [redacted] and [redacted]). **In the next PBRER, the MAH should update the cumulative review on TTS after booster dose and discuss the need to update the SmPC Section 4.4, paragraph on 'Thrombosis with thrombocytopenia syndrome' and paragraph on 'Risk of very rare events after a booster dose'. [Request for the next PBRER]**

Mechanism of TTS: The MAH reviewed new literature regarding the potential mechanism of action of TTS with Vaxzevria. The meeting report of Buoninfante et al. (2022) summarizes an EMA workshop's discussion on the epidemiology, clinical presentation and biological mechanisms of TTS after adenovirus vector COVID-19 vaccination. The recent evidence on the interaction between PF4 and the adenovector from Vaxzevria and JCovden point towards a model in which binding of the capsid protein of both adenovectors, ChAdOx1 and Ad26, to PF4 results in complex formation and subsequent downstream activation of PF4-specific B-cells (pre-existing B-cell clones encoding pathogenic anti-PF4 IgG according to the MAH's working hypothesis). The produced anti-PF4 antibodies then cause prothrombotic activation of several cells in the blood. The MAH's hypothesis is that the nature of the individual host response determines whether TTS is induced upon exposure to the ChAdOx1-PF4 complex. However, several gaps in the understanding of TTS remain to be elucidated.

Marietta et al. (2022) noted that the Ad26 and Ad5 AdV vectors used in JCovden and Sputnik V have lower negative surface charges compared to ChAdOx1, which is consistent with the lower incidence of VITT observed in recipients of these vaccines. Furthermore, a higher proportion of host-cell proteins, active proteases and unassembled hexon proteins, which elicit an inflammatory response, has been found in Vaxzevria as compared to JCovden. A different intensity of the inflammatory response elicited by different AdV vaccines can play a role in the production of the functionally active PF4 antibodies involved in the development of VITT.

Other literature: Müllerová et al (2023) estimated prepandemic background TTS event rates, including by type of thrombosis/thromboembolism and age group, using Truven MarketScan US health insurance claims database. Prepandemic background TTS incidence was estimated at 9.8–11.1 per 100 000 person-years. Event rates stratified by sex and age show that the prepandemic TTS event rates were typically higher in males than in females and increased with age. The most common prepandemic TTS subtypes

were DVT with thrombocytopaenia (6.6 (6.1 to 7.2) per 100K PY) and PE with thrombocytopaenia (3.9 (3.5 to 4.4) per 100K PY). CVST with thrombocytopaenia was very rare (0.2 (0.2 to 0.4) per 100K PY).

CVST with Thrombocytopenia: data presented were similar to the data presented in PSUR#2 and PSUR#3.

In conclusion, no new safety information concerning TTS could be identified.

2.3.2. Important Identified Risk (EU-specific) – Thrombocytopenia, including immune thrombocytopenia

Please note that Thrombocytopenia, including immune thrombocytopenia data is not reproduced here (see Appendix R3 - Section 2.2.1 of the PBRER).

MAH's Summary

AstraZeneca continued to review the safety information for Thrombocytopenia including immune thrombocytopenia from sources including clinical trials, post-marketing reports, and the published literature for the reporting period.

A review of the post-marketing data did not identify any index case or a new safety signal. There were no case reports indicating recurrence (after the first and second dose of the vaccine).

There was no significant difference noted between the cumulative and reporting period in terms of the volume and distribution of cases.

There were 91 (3.2%) reports with fatal outcome, with majority of 54 (59.3%) of 91 cases reported in females. Overall, the death rate was higher in age group over 50 years (59 out of 80 cases, where age was reported) and 43 (47.2%) cases out of 91 were in patient with thrombocytopenia associated with bleeding.

Out of the 2853 cases, 542 (19%) cases met the Brighton Collaboration Criteria (BCC) definition for Thrombocytopenia level 1 criteria, 628 (22%) cases met the BCC Level 2 and 1683 (59%) cases met the BCC Level 4.

Out of the total 2853 case reports received for Thrombocytopenia without co-reported thromboembolic events, the WHO-UMC causality was assessed as follows: 1752 (61.4%) cases were assessed as Possible and in 1358 (77.5%) out of 1752 cases, the assessment was based solely on the reasonable TTO parameter and no information was available on assessments of other etiologies, or the vaccinees' medical history, comorbidities, concomitant medications, etc. For the remaining 394 (22.5%) of 1752 cases this assessment was based on a reasonable TTO although the event could also be explained by the vaccinees' diseases. 899 (31.5%) of case reports were assessed as Unassessable/Unclassifiable, 196 (6.9%) cases were assessed as Unlikely, 6 (0.2%) cases assessed as Probable-Likely.

Overall, none of the cases met WHO-UMC criteria for Certain (including immune thrombocytopenia).

A review of the published literature did not identify any new safety information on this topic in association with VAXZEVRIA.

The results of the O/E analyses for all thrombocytopenia cases in risk windows 21 and 42 days (along with unknown TTO for both risk windows) suggest that observed cases were significantly less than expected cases.

Additionally, AstraZeneca validated a signal for Immune Thrombocytopenia as mentioned in previous PBRER (29 December 2021 to 28 June 2022) and closed during the current reporting period. See section 16.2.5 of PBRER.

MAH's Conclusion

From the data identified during the reporting period, and also taking into account the cumulative experience, no new information was identified on Thrombocytopenia, including immune thrombocytopenia.

This topic is appropriately covered in the EU SmPC (section 4.4 and 4.8) and EU RMP.

Rapporteur assessment comment:

"Thrombocytopenia, including immune thrombocytopenia" (ITP) is listed in the EU-RMP as an important identified risk. In the EU-SmPC section 4.8, "Thrombocytopenia" is listed with frequency 'common' and "Immune thrombocytopenia" is listed with frequency 'not known'. In addition, the risk of thrombocytopenia including ITP is described in section 4.4 .

While mild and transient thrombocytopenia was a common finding from clinical trial, the cases reported from post-marketing experience contain a high proportion of serious cases (92%). Less severe cases remain probably undiscovered.

Five (5) of the 91 fatal cases were reported during this PSUR period. The reported cause of death was variable and, in many cases, involved more than one event. These causes of death are similar to other causes of death reported previously.

During the reporting period, a literature search found 2 articles including **32 literature cases** in total.

Regarding event with co-reported bleeding: 142 reports (83 initial and 59 follow-up reports) without co-reported thromboembolic events were considered for analysis: Thrombocytopenia alone without any associated haemorrhage was reported in 105 case reports (73.9%), Thrombocytopenia with spontaneous bleeding in 36 reports (25.4%), and Thrombocytopenia with menstrual bleeding in 1 report (0.7%).

An international network cohort study (Xintong Li et al 2022) from five European countries (France, Germany, Netherlands, Spain, UK), and the US showed a 30% increased risk of thrombocytopenia after first dose VAXZEVRIA compared with first dose BNT162b2 vaccination. Also, a trend towards an increased risk of venous thrombosis with thrombocytopenia was observed after a first vaccine dose of Ad26.COV2.S compared with BNT162b2. The authors concluded that although rare, the observed risks after adenovirus-based vaccines should be considered when planning further immunization campaigns and future vaccine development.

Overall, information collected on thrombocytopenia including immune thrombocytopenia does not modify the conclusion of previous assessment. No change to the SmPC sections 4.4 and 4.8 is warranted.

Taking into consideration the review of the risk 'Thrombocytopenia, including immune thrombocytopenia'], no further action is considered warranted at this stage.

2.3.3. Important Identified Risk (EU-specific) – Guillain-Barré Syndrome

Please note that GBS data is not reproduced here (see Appendix R3 - Section 2.2.2 of the PBRER).

MAH's summary

During the period covered by this report (29 June 2022 to 28 December 2022), **216 cases reported** (118 initial reports and 98 follow-up reports), out of which 139 (64.4%) were reported by healthcare professionals (medically confirmed).

Out of the 216 cases, **33** of the cases fulfilled **BCC 1 level criteria**, **26** of the cases fulfilled **BCC 2 level criteria** and **3** of the cases fulfilled **BCC 3 level criteria**. When these 62 are assessed according to WHO-UMC causality criteria 2 did not have sufficient information to do a causality assessment and were assessed as "Unassessable/unclassifiable", 5 were assessed as "Unlikely", and **55 were assessed as "Possible"** causality to VAXZEVRIA.

Out of the 55 cases assessed for WHO-UMC causality deemed as "Possible", **47 had limited information** on other aetiologies, medical history, concomitant medications, etc., and **8 cases had risk factors or confounders**. Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, relevant risk factors that were present, or concomitant medications that could potentially contribute to the development of the event.

The review of GBS cases post COVID-19 booster dosing did not show any significant safety concern.

There is high variability in the data for the **observed versus expected analysis** of cumulative cases reported, making an assessment on causal association not possible. The majority of the stratifications and analysis suggest that **the observed cases are less than expected** for all three risk windows (14 days, 30 days and 42 days). However, some analysis for global reports, UK and the EU-UK-Brazil-Australia suggest observed cases are more or significantly more than expected. However, it is important to note that the mainstream of reported cases correlate with the period of peak pandemic activity, suggesting a potential role of COVID-19 infection in causing GBS (Coronavirus (COVID-19) in Australia, Coronavirus (COVID-19) in Brazil, Coronavirus (COVID-19) in Canada, Coronavirus (COVID-19) in Europe, Coronavirus (COVID-19) in the UK). Seasonal fluctuations in the incidence of GBS with a higher incidence in winter compared to summer is also a consideration.

MAH's conclusion

Based on the review of available evidence from literature and from reports in the safety database on the topic of GBS, AstraZeneca considers that there is not sufficient evidence to confirm any particular clinical features associated with vaccination or establish a causal association with VAXZEVRIA.

AstraZeneca will continue to closely monitor GBS as part of our surveillance activities (nervous system disorders, including immune mediated neurological conditions) and take further actions as deemed necessary.

From the data identified during the reporting period, and also taking into account the cumulative experience, no new information on GBS warrant any changes in the EU SmPC.

Rapporteur assessment comment:

The MAH provided a review of the 216 cases (118 initial and 98 follow-up) reported during the interval period. Among them, 62 cases fulfilled the BCC levels 1-3 criteria, with most of the cases (76%) assessed as possible with limited information.

Cumulatively, 1849 cases were reported, mainly from UK (31%), Australia (12%), Brazil (10%), Germany (10%) and India (5%). In total, 36 cases had a fatal outcome.

Pattern and variant of GBS: In the reporting period, 9 cases of GBS had facial diplegia/bifacial weakness as symptoms. However, none of those cases described the GBS variant of interest (i.e. bifacial weakness and paraesthesia [BWP]).

In the literature, Tamborska et al., 2022 observed from an open-access online system surveillance study that GBS cases reported after COVID-19 vaccination presented a different pattern compared to the IGOS[4] cohort, i.e. **facial weakness** was common (i.e. **63%** of cases vs 36% in IGOS; p<0.00001) with an unusually large number of patients having the **facial diplegia with paraesthesia** (n=10; **14%**).The authors noted that although the clinical presentations in their study differed from the IGOS cohort, the disease severity and outcome were similar. The observed age distribution of patients with GBS after Vaxzevria also differed from that of background GBS data before the pandemic (i.e. greater proportion in 50-59 age group, and lower proportion of subjects with an antecedent infection reported).

Osowicki et al. 2022[5] brought some additional insight on the impact of COVID-19 vaccine-related GBS. Their case series study (Australia), identified 38 reports of GBS with Vaxzevria, including mainly typical sensorimotor cases (n=26), but also variants such as 4 cases of acute paraparetic GBS and **2 cases of BWP**. One of the BWP cases was reclassified as chronic inflammatory demyelinating polyneuropathy after further clinical deterioration and nerve conduction studies shortly after a 2nd dose of vaccine (Comirnaty). The study with a mean follow-up of 252 days allows to monitor **self-reported quality of life scores**. The most frequently reported challenges were associated with lower limb function. Fatigue was also described as one of the most disabling symptoms, interfering with work, family or social life.

O/E analysis: Observed versus expected analysis only showed a significant increase when cases with unknown TTO were included in the analysis with a 14 day risk period. A O/E ratio >1 is also observed in the stratified analysis for women aged 50-59 years old. These findings are similar to those observed in the previous PSUR.

Of note, the O/E analysis performed by EMA (Cut-off date 07.12.2022) found a significative imbalance using both a 30 and 42 days risk period (i.e. O/E ratio [95%CI] of 1.37 [1.24-1.52] and 1.22 [1.1-1.34] respectively).

Literature: the MAH's literature review identified 2 papers of interest:

- García-Grimshaw et al.,2022 performed a **retrospective study** through **passive epidemiological surveillance** in **Mexico**, aiming to report nationwide GBS incidence as AEFI among adult vaccinees (n=81,842,426 doses of COVID-19 vaccines, period from 24 Dec 2020 to 29 Oct 2021): the overall observed GBS incidence was 1.19 (95% CI 0.97-1.45) cases per 1.000.000 administered doses, with higher incidence observed in recipients of Ad26.COV2-S (3.86 [1.50-9.93] cases per 1.000.000) and BNT162b2 recipients (1.92 [1.36–2.71]. cases per 1.000.000). The **observed incidence for Vaxzevria** recipients was **0.96 [0.70–1.32] cases per 1.000.000** administered doses.

- Tamborska et al., 2022 conducted a **UK**-wide, **open-access, online system surveillance study** (cohort of 70 patients, period from 01 Jan 2021 to 30 Jun 2021): 96% of cases received VAXZEVRIA (n=67; 65 with 1st dose), and 4% BNT162b2 (n=3; all 1st dose). The causal association with the vaccine was classified as probable for 56 (80%, all ChAdOx1), possible for 12 (17%, 10 ChAdOx1) and unlikely for two (3%, 1 ChAdOx1).

In addition, the PRAC Rapporteur identified 2 other papers of interest:

- Osowicki et al., 2022 present a case series of GBS reports submitted between Feb and Nov 2021 to the

[4] IGOS cohort : cohort of European or American patients from the International GBS Outcome Study (IGOS)
[5] Osowicki J, Morgan HJ, Harris A, Clothier HJ, Buttery JP, Kiers L, Crawford NW; SAEFVIC and VicSIS investigators. Guillain-Barré syndrome temporally associated with COVID-19 vaccines in Victoria, Australia. Vaccine. 2022 Dec 12;40(52):7579-7585. doi: 10.1016/j.vaccine.2022.10.084. Epub 2022 Nov 7. PMID: 36357291; PMCID: PMC9637534.

enhanced spontaneous surveillance system (**SAEFVIC**) in Victoria, **Australia** following vaccination with either Vaxzevria or an mRNA vaccine (BNT162b2 or mRNA-1273): there were 41 total cases of GBS reported to SAEFVIC following Vaxzevria (n = 38), Comirnaty (n = 3), or Spikevax (n = 0) vaccines. The **observed GBS incidence rate exceeded the expected background rate** for Vaxzevria only, with **1.85 reports per 100,000 doses following dose 1**, higher than the expected rate of 0.39 hospital admissions per 100,000 adults within 42 days of vaccination.

- **Walker et al., 2022**[6] present a **SSCS** in **England** using the Open SAFELY platform to estimate the incidence rate ratio for GBS, transverse myelitis and Bell's palsy (7,783,441 ChAdOx1 vaccinees: there was an increased rate of **GBS** (N = 517; **IRR 2.85; 95% CI 2.33–3.47**) and **Bell's palsy** (N = 5,350; **1.39; 1.27–1.53**) following a first dose of ChAdOx1 vaccine, corresponding to **11.0 additional cases of GBS** and **17.9 cases of Bell's palsy per 1 million vaccinees if causal**. For GBS this applied to the first, but not the second, dose. There was no clear evidence of an association of ChAdOx1 vaccination with transverse myelitis (N = 199; 1.51; 0.96–2.37). The authors notice a **higher estimates of excess cases** (compared to Patone et al. 2021[7]; i.e., 11.1/mo vs 3.8/mo) which may reflect higher ascertainment of GBS in their study using linked data and including a longer time period possibly less affected by reduced healthcare attendance during the pandemic. The **association between 1st dose of Vaxzevria vaccination and Bell's palsy** hospital admissions was observed in Patone et al., 2021 and replicated in Walker et al. 2022. It is agreed that this **could perhaps have been driven by** GBS presenting with facial diplegia and/or by the **BWP variant**. Finally, the relative increase in both **GBS** and Bell's palsy post-vaccination was **higher among individuals aged 40–64 years** compared to those over 65 years (i.e., IRR of 3.65; 2.78-4.79 vs IRR of 2.12; 1.53-2.93 for GBS). The authors concluded that age-specific estimates **should be considered for benefit-risk analyses of vaccination**, which is fully supported.

Table - Characteristics of cases in ChAdOx1 vaccine analyses and incidence rate ratios of Guillain-Barré Syndrome following ChAdOx1 vaccination (from Walker et al. 2022).

Primary analysis, stratified by age		
18–39 years	N (%)	35 (6·8)
	Baseline	1 (reference)
	Post-vaccination[2]	2·56 (1·15–5·71)
40–64 years	N (%)	255 (49·3)
	Baseline	1 (reference)
	Post-vaccination[2]	3·65 (2·78–4·79)
65–105 years	N (%)	227 (43·9)
	Baseline	1 (reference)
	Post-vaccination[2]	2·12 (1·53–2·93)

Overall conclusion: information becoming available during the period under review did not raise any new safety concern. Data from the literature confirmed the association between GBS and Vaxzevria vaccination. More particularly, the SCCS performed by Walker et al. suggests an increased risk of GBS after the administration of the first dose but not after the second dose. No information regarding booster were available in this study. Besides, the risk seems to be higher in the 40-64 years age group. According to the study of Osowicki et al., the challenges related to lower limb function and fatigue are the most

[6] Walker JL, Schultze A, Tazare J, Tamborska A, Singh B, Donegan K, Stowe J, Morton CE, Hulme WJ, Curtis HJ, Williamson EJ, Mehrkar A, Eggo RM, Rentsch CT, Mathur R, Bacon S, Walker AJ, Davy S, Evans D, Inglesby P, Hickman G, MacKenna B, Tomlinson L, Ca Green A, Fisher L, Cockburn J, Parry J, Hester F, Harper S, Bates C, Evans SJ, Solomon T, Andrews NJ, Douglas IJ, Goldacre B, Smeeth L, McDonald HI. Safety of COVID-19 vaccination and acute neurological events: A self-controlled case series in England using the OpenSAFELY platform. Vaccine. 2022 Jul 30;40(32):4479-4487. doi: 10.1016/j.vaccine.2022.06.010. Epub 2022 Jun 7. PMID: 35715350; PMCID: PMC9170533.

[7] Patone M, Handunnetthi L, Saatci D, Pan J, Katikireddi SV, Razvi S, Hunt D, Mei XW, Dixon S, Zaccardi F, Khunti K, Watkinson P, Coupland CAC, Doidge J, Harrison DA, Ravanan R, Sheikh A, Robertson C, Hippisley-Cox J. Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection. Nat Med. 2021 Dec;27(12):2144-2153. doi: 10.1038/s41591-021-01556-7. Epub 2021 Oct 25. Erratum in: Nat Med. 2021 Nov 29;: PMID: 34697502; PMCID: PMC8629105.

disabling symptoms associated with GBS post-COVID-19 vaccination. Finally, some studies suggest that COVID-19 vaccination may be associated with the BWP variant of GBS. However, this should be further confirmed by more robust studies.

As previously discussed, the PRAC Rapporteur considers that a causal association between Guillain-Barré and Vaxzevria should be considered at least a reasonable possibility (disagreement with the MAH's opinion). Currently, GBS is **appropriately described in the EU-PI** (sections 4.4 and 4.8) **and in the EU-RMP** (important identified risk). Moreover, GBS will continue to be closely monitored as part of the surveillance activities including routine PhV and PASS. No further action is considered warranted at this stage.

2.3.4. Important potential risk (EU-specific) – Thrombosis

2.3.4.1. Thrombosis

Please note that Thrombosis data is not reproduced here (see Regional Appendix R3 - Section 2.1.1, and Sections 15.2.4 and 15.2.5 [Health Authority Requests] of the PBRER).

MAH's summary

A review of the post-marketing data did not identify any index case or a new safety signal. There were no case reports indicating recurrence (after the first and second dose of the vaccine). A total of 1036 cases were received in the reporting period compared to 2567 for the previous period (29 December 2021 to 28 June 2022). Cumulatively 19486 cases have been received.

Frequently reported thrombosis events (>70 events) included Thrombosis with thrombocytopenia syndrome (244, 18.4%), Pulmonary embolism (173, 13.0%), Cerebrovascular accident (151, 11.4%), Deep vein thrombosis (112, 8.4%), and Cerebral venous sinus thrombosis (87, 6.5%).

The highest number of cases were received from UK 221 cases (21.3%) followed by Brazil 186 cases (18.0%), Germany 148 (14.3%) and Australia with 74 cases (7.1%). A total of 449 case reports were reported in females, 444 were reported in males, and in 143 cases the gender was not reported. Out of 1036, 1 case occurred in the adolescence population. The overall median age was 55 years with a range of 17 to 94 years for all cases where age was reported.

There was a higher proportion of fatal cases (182/1036, 17.6%) in the interval compared to the cumulative fatality rate (1646/19486, 8.4%). The large number (51) of follow up reports in the interval accounts for higher fatality rate for the interval. Of the initial reports, 38 (29.0%) were from Brazil.

The overall cumulative thrombosis fatality rate was highest (14.9%) in vaccinees aged 80+ years and most of these reports were in vaccinees with underlying comorbidities. In the 18-29 (38/77, 49.4%), 30-39 (42/123, 52%), and 40-49 (59/159, 37.1%) years age group, the fatal cases were due to thrombosis in combination with thrombocytopenia which may explain increased fatality rate in vaccinees aged < 50 years.

The results of the O/E analyses for all Thrombosis cases in risk windows 14, 28 and 42 days suggest that observed cases were significantly less than expected cases for all stratifications.

MAH's conclusion

From the data identified during the reporting period, and considering the cumulative experience, no new information on Thrombosis was received during the reporting period that changes the present

understanding and description of the important potential risk. No changes to the EU SmPC and EU RMP are warranted at this time.

Rapporteur assessment comment:

During the period under review, 1036 cases (786 initial and 250 follow-up) reporting 1329 AEs (1319 serious) were retrieved for the AESI of Thrombosis. About 60% of identified cases (620) were medically confirmed. Cumulatively up to 28 December 2022, 19,486 cases reporting Thrombotic events, with and without thrombocytopenia, were retrieved.

The reported cases show similar information/trends regarding gender and age distribution (median age 55 years, 50% females), TTO (median TTO 12 days), type of thromboembolic event and outcome as in the previous PSURs. The case fatality rate for the reporting interval is 17.6% compared to a cumulative case fatality rate of 8.4%. The higher fatality rate for the interval is partially due to the large number of fatal follow-up reports (51 out of 182 fatal reports (28%)) received during the interval. About one third of the initial reports originated from Brazil.

Out of the 1036 case reports, 115 occurred after dose 2 and 5 occurred after dose 3. There were no cases where thromboembolic events occurred both after dose 1 and dose 2 (potential 'rechallenge' cases).

As requested in the AR of the previous PSUR#3, the MAH provided a tabular summary of the fatal cases reporting a thrombotic event after Vaxzevria dose 3 or dose 4 (see section 15.2.5 of the PSUR#4). Cumulatively, 25 fatal cases were identified. Twelve of these cases were assessed as 'Unassessable' because the TTO was not reported, 2 cases as 'Unlikely' due to an implausible temporal relationship and 11 cases as 'Possible'. All 'Possible' cases either contained insufficient information for comprehensive assessment or reported confounders. No new safety concerns were identified from these fatal cases post dose 3 or dose 4.

The MAH performed overall O/E analyses using global data and O/E analyses by age and gender using UK data. All analyses were carried out with risk windows of 14, 28 and 42 days. None of the O/E analyses showed a disproportionality and observed cases were significantly less than expected for all stratifications.

The PRAC rapporteur agrees with the MAH's conclusion and to continue to closely monitor this issue.

2.3.4.2. Venous Thromboembolism (VTE)

(From Health Authority requests – 15.2.4 Venous Thromboembolism)

Background

In the updated assessment report received from the PRAC EMA (PRAC PAR (EMEA/H/C/PSUSA/00010912/202206) for the VAXZEVRIA PBRER (review period: 29 December 2021 to 28 June 2022), further information on the topic of Venous thromboembolism has been requested as follows:

The MAH is requested further investigate VTE by providing an updated literature review, with a focus on new relevant epidemiological studies.

AstraZeneca's responses to these requests are provided in the subsections below.

AstraZeneca performed a literature search for the period 29 June 2022 to 28 December 2022 in Embase and InsightMeme databases to identify any new articles discussing Venous Thromboembolism with COVID-19 vaccines, including VAXZEVRIA using the following search terms: venous thromboembolism,

venous thrombosis, deep vein thrombosis, embolism, embolus, blood clot, infarction, occlusion, lung infarction, pulmonary thrombosis, cerebrovascular stroke, stroke, cerebral stroke, acute stroke, transient ischemic attack, ischemic strokes, brain vascular accident, brain infarction, intracranial venous thrombosis (ICVT).

The search yielded 129 articles (comprised of case reports, meta-analyses, and epidemiological studies). After review four full-text articles were considered relevant for discussion, (Burn Roel et al 2022 Ohaeri et al 2022). Two of the new studies by Burn Li et al 2022 (already discussed in the last PBRER) had previously been included as pre-publications in medRxiv and have now been published in a peer-reviewed journals, and the articles from medRxiv were hence replaced by the published studies. As these two studies (Burn Li et al 2022, Burn Roel et al 2022) following publication in peer-reviewed journals reported a longer follow-up period the effect estimates have been updated accordingly. Adding the new studies to the ones that had been included in the last PBRER resulted in a total of 14 studies (Table 6).

Cerebrovascular venous and sinus thrombosis (CVST), pulmonary embolism (PE) and Deep vein thrombosis (DVT)

Five studies out of the 14 assessed the association between VAXZEVRIA and CVST (Table 6 and Table 7), two of which reported a statistically significant association Burn Li et al 2022 and three did not find a significant association (Laporte et al 2021, Hviid et al 2022, Ohaeri et al 2022). Six studies out of 14 assessed the association between VAXZEVRIA and PE, three of which found no association (Burn Roel et al 2022, Hviid et al 2022, Li Burn et al 2022), one reported a decreased risk in those 70 or over, (Whiteley et al 2022), one found an increased risk after VAXZEVRIA vaccination (Botton et al 2022), and one found an increased risk after dose one and a decreased risk after dose 2 (Burn Li et al 2022). Five out of 14 studies assessed the association between VAXZEVRIA and DVT, whereof one found an increased risk after VAXZEVRIA vaccination (Hviid et al 2022), one found a decreased risk in those 70+ (Whiteley et al 2022), two found no association (Burn Li et al 2022, Burn Roel et al 2022) and one found an increased risk in one database but no association in the meta-analysis of all included databases Li Burn et al 2022 (Table 7 and Table 8).

Other venous thromboembolic events

Other venous thromboembolic events included in the studies included Portal vein thrombosis (PVT) (two studies, no association found in either (Laporte et al 2021, Whiteley et al 2022), intracranial venous thrombosis (ICVT) (one study that found an association in those <70 years old (Whiteley et al 2022), cerebral venous thrombosis (CVT) (one study that found an association in those below the age of 65 years (Andrews et al 2022), splanchnic venous thrombosis (SVT) (3 studies, where neither found an association (Burn Li et al 2022, Burn Roel et al 2022, Hviid et al 2022) and Mesenteric thrombosis (MEST) (one study that found no association (Laporte et al 2021) (Table 7 and Table 8).

Overall venous thromboembolic events (VTE)

Eleven studies out of 14 assessed the association between VAXZEVRIA and VTE, two reported no statistically significant association (Burn Roel et al 2022, Li Burn et al 2022, Li et al 2022) and one reported a decreased risk in those 70 or older (Whiteley et al 2022), one reported a decreased risk for those 70-79 and an increased risk for woman younger than 50 (Corrao et al 2022) six reported an increased risk after VAXZEVRIA vaccination (Hippisley-Cox et al 2021, Laporte et al 2021, Al Bakr and Alaithan 2022, Andrews et al 2022, Chen et al 2022, Dag Berild et al 2022, Rahman and Seidler registered 02 July 2021) and one reported an increased risk after dose one and a decreased risk after dose two (Burn Li et al 2022) (Table 7 and Table 8).

The majority of the studies assessing the association between VAXZEVRIA and VTE reported an association between exposure to VAXZEVRIA and an increased risk of VTE. The associations were found in

the SCCS studies that compared post vaccination time to control time in the cases, and cohort studies using non-vaccinated or historical controls. In the studies that presented results stratified by sex and age this increased risk was only reported in younger age groups and in women (Andrews et al 2022, Corrao et al 2022). Relative risks by sex and age group (for the studies where these estimates were available). The highest relative risk was reported by Laporte et al 2021, who found those vaccinated with VAXZEVRIA were 3.68 times more likely to experience VTE compared to historical controls. However, this study only adjusted the effect estimate for sex and age and did not exclude participants with history of study outcomes, making confounding likely. Other studies reported between a 10% (corresponding to 66 excess case per 1 million vaccinations, Hippisley-Cox et al 2021, and 2.43 times the risk (corresponding to 23,207 citizens vaccinated per one harmful event among women of less than 50 years of age, (Corrao et al 2022) and a risk difference of 8.35 cases (95% CI 0.21 to 16.49) of DVT per 100,000 vaccinations in frontline health care personnel consisting mainly of younger women (Hviid et al 2022).

Table 6 - Design overview of large population-based studies and AstraZeneca's comments

Reference, Country	Data source	Time period	Design	Comparator	AstraZeneca comments
England (Whiteley et al 2022)	Primary care (GPES), covid and vaccination (NIMS, GDPPR), secondary care (HES, SUS) pharmacy (NHS BSA), and death registrations.	08 December 2020 to 18 March 2021	Cohort study	Unvaccinated or pre-vaccination person time	Adjusted for several confounding factors. End date before diagnostic effort was expected to be concentrated in people receiving AZD1222. Unmeasured confounding and misclassification of confounding factors is probable.
England (Hippisley-Cox et al 2021)	COVID and vaccination (NIMS, GDPPR), secondary care (HES, SUS), and death registrations.	01 December 2020 to 24 April 2021	Self-controlled case series (SCCS)	Exposed time periods (after vaccination or SARS-CoV-2 infection) compared with unexposed baseline periods in people with the outcome of interest (excluding the pre-risk interval)	SCCS method widely used in vaccine research. Robustness of the findings for most outcomes. Detailed data for risk periods after vaccine exposure. Less severe cases from primary care not included. Selection bias by including only those with outcome.
France (Botton et al 2022)	SNDS (France), hospital discharge diagnoses linked to vaccination files, 18 to 74 years old	06 February 2021 to 20 July 2021 for AZD1222.	Self-controlled case series (SCCS)	Three weeks following the first dose, and if applicable the second and third doses. All other observation periods were considered reference periods.	Large study population representing the population of France with high vaccine exposure. SCCS design widely used in vaccine research Crude case definitions used for thrombosis. A case-only analysis risks selection bias by including only those individuals pre-disposed to experiencing thrombotic events.

Reference, Country	Data source	Time period	Design	Comparator	AstraZeneca comments
England (Andrews et al 2022)	Vaccination (NIMS), secondary care (SUS), and death registrations.	30 November 2020 to 18 April 2021	Cohort study	Unvaccinated period with an offset for population at risk (person days).	Less severe cases not included. Vaccinated cohort was compared to an unvaccinated cohort, but only for few confounders were adjusted for, not including health relevant comorbidities. This may have led to an overestimation of RIs.
Spain (Laporte et al 2021)	CMBD register (discharge diagnoses), Catalonia, Spain	01 January 2021 to 18 April 2021.	Cohort study with historical controls	General population in Catalonia on 01 January 2019 with follow up to 31 December 2019	Differences in study periods when using historical controls can lead to confounding. Adjusted for age and sex only, thus risk of residual confounding.
Denmark, Norway and Finland (Dag Berild et al 2022)	The Norwegian Immunization Register SYSVAK, the Finnish National Vaccination Register, and the Danish Vaccination Register (exposure) and the national patient registers (outcome)	01 January 2020 to 16 May 2021.	Self-controlled case series	The risk period was 28 days postvaccination. The control period was 01 January 2020 to 14 days prior to vaccination, or COVID infection.	Nationwide registers including the whole populations used. However, less severe cases from primary care not included. Patient acted as their own control; therefore, time invariant confounding was controlled for. Selection effect by including only those with outcome Control period included 2020 to allow adjustment for seasonal variability, this may have introduced a bias, since access to health care may have been affected by the pandemic. A pre-risk period of 14-days was used to ensure events did not influence subsequent exposures.

Reference, Country	Data source	Time period	Design	Comparator	AstraZeneca comments
Malaysia.(Ab Rahman et al 2022)	Malaysia Vaccine Administration System (MyVAS) database and the Malaysian Data Warehouse (MyHDW), a national health data repository that collects data from public and private hospitals in Malaysia	01 February 2021 to 30 September 2021	Self-controlled case series	The risk period was 21 days postvaccination. The control period was between 01 February 2021 and 30 September 2021, except a 14-day pre vaccination risk window and the vaccination day (day 0).	Nationwide registers including the whole populations used. About 8% were vaccinated with AZD1222. Less severe cases from primary care not included. Patient acted as their own control; therefore, time invariant confounding was controlled for. A pre-risk period of 14-days was used to ensure events did not influence subsequent exposures. Selection effect by including only those with outcome. Due to the vaccination roll out the sample have a large proportion of frontline health workers, elderly, and risk groups. Opt-in stream for the ChAdOx1-S vaccine was introduced in May 2021-due to high demand it was reintroduced to regular roll out.
Multicountry Chen et al 2022	Pubmed, Embase, Cochrane COVID-19 Study Register, Cochrane Library, Chinese National Knowledge Infrastructure, Wanfang	Published 01 January 2020 to 20 October 2021 .	Systematic review and meta-analysis	Unvaccinated population or population that received placebo	Great heterogeneity among the studies, the I^2 of most AEs was above 90%. Grouped viral vector vaccines: Ad26.COV2.S, ChAdOx1 and Sputnik V Study population in some studies are comprised of patient groups such as transplant recipients or cancer patients, while some includes health care

Reference, Country	Data source	Time period	Design	Comparator	AstraZeneca comments
	Data Knowledge Service Platform (Wanfang) and SinoMed.				workers, health care workers with previous severe allergic diseases, and the general population. The adverse event rates of venous and arterial thrombosis would differ between these populations and to meta-analyse them makes interpretation difficult.
Lombardy, Italy (Corrao et al 2022)	The Regional Health Service (RHS) management, the registry of patients with a confirmed diagnosis of SARS-CoV-2 infection and the COVID-19 vaccination registry	27 December 2020 to 03 May 2021	Cohort study	Unvaccinated or pre-vaccination person time, matched on sex and age 1:10	The outcomes were measured in a hospital setting, so they did not include milder cases treated in primary care. A large number of health conditions were considered as confounders and adjusted for. Residual confounding still probable. Population-based but only include one region.
Denmark (Hviid et al 2022)	The Danish vaccination register and the Danish National Patient Register	27 December 2020 to 13 April 2021	Cohort study	Unvaccinated risk time from all individuals starting on 27 December 2020. Those who were still unvaccinated after 28 days then contributed with another 28-day observation period, and so forth until any vaccination, event, or	Only included frontline personnel: health care and social services workers. Adjusted for several confounding including comorbid conditions associated with risk for severe COVID-19 using inverse probability weights. Outcomes measured in a hospital setting- milder cases not included. The median age at study start was 44 years, and 82% of participants were female.

Reference, Country	Data source	Time period	Design	Comparator	AstraZeneca comments
				censoring, whichever came first	
UK 2022 (Burn Li et al 2022)	Clinical Practice Research Datalink (CPRD) AURUM (primary care medical records)	08 December 2020 and 02 May 2021. Follow up time was 28 days from their first vaccination.	Cohort study with historical controls	A general population background cohort included people in CPRD as of 1 January 2017. Follow-up for this cohort ran up to 31 December 2019.	Differences in study periods when using historical controls can lead to confounding. Primary care data, possible underestimation of outcomes diagnosed in hospital. Adjusted for age and sex only, thus risk of residual confounding.
Spain, (Burn Roel et al 2022)	SIDIAP, Catalonia, Spain	27 December 2020 to 23 June 2021	Cohort study with historical controls	Historical controls present in the database 1 January 2017 followed until 31 December 2019	Differences in study periods when using historical controls can lead to confounding. Historical general population cohort were younger and healthier, compared to vaccinated cohorts, reflecting vaccination guidelines adjusted for age and sex only, thus risk of residual confounding.
(Li Burn et al 2022)	Clinical Practice Research Datalink Aurum (UK CPRD) Information System for Research in Primary Care with minimum basic set of hospital discharge data (CMBD-HA; Spain SIDIAP)	December 2020 to the latest data release available in each of the contributing databases (ie, mid-2021).	Retrospective Cohort Study	Active comparators, vaccinated with BioNTech, Pfizer vaccine	Only data from UK CPRD, Germany DA had sufficient cases to be reported separately, Netherlands IPCI and France LPD were included in the meta-analysis. The combined VTE variable also contained arterial TE, MI and ischemic stroke. Propensity score matched on age, sex, index year, and index month, Romano's adapted

Reference, Country	Data source	Time period	Design	Comparator	AstraZeneca comments
	Integrated Primary Care Information (Netherlands IPCI) IQVIA Longitudinal Patient Data France (France LPD) IQVIA Disease Analyser Germany (Germany DA)	Follow-up was to 28 days after vaccination			Charlson Comorbidity Index, CHA2DS2-VASc, congestive heart failure, hypertension, vascular disease, and total number of medicines, procedures, and measurement records. Primary care data, possible underestimation of outcomes diagnosed in hospital.
(Ohaeri et al 2022)	Secure Anonymized Information Linkage (SAIL) GP data from Wales, linked to NHS Wales.	01 January 2020 to 28 March 2021.	Retrospective Cohort Study	The pre-exposure period (the same participant could contribute both exposed and unexposed time under observation to the study)	Low vaccination exposure in the study period (34.0%) could affect generalisability. Adjusted for the confounders: age, sex, ethnicity, deprivation, comorbidity, and exposure to both SARS-CoV-2 virus and vaccination within 28 d of each other. Correlation between study participants as a person could contribute to both exposed and unexposed time were not considered in the statistical analysis.

BSA Business Services Authority; CMBD- Minimum Basic Data Set; CoV-2- Coronavirus -2; COVID-19- Coronavirus Disease Of 2019; CPRD- Clinical Practice Research Datalink; DA- Disease Analyser; GDPPR- General Practice Extraction Service Data for Pandemic Planning and Research; GPES- General Practice Extraction Service; HES- Hospital Episode Statistics; IPCI- Integrated Primary Care Information; LPD- Longitudinal Patient Data; MI- Myocardial Infarction; MyHDW - Malaysia Data Warehouse; MyVAS- Malaysia Vaccine Administration System; NHS- National Health Service; NIMS- National Immunisation Management System; RHS- Regional Health Service; SAIL- Secure Anonymized Information Linkage; SARS- Severe Acute Respiratory Syndrome; SCCS- Self-Controlled Case Series; SIDIAP- Spanish population primary care database; SNDS- French Administrative Health Care Database; SUS- Secondary Uses Service; TE- Thromboembolism; UK- United Kingdom; VTE- Venous Thromboembolism.

Table 7 - Summary of large population-based studies on relative risk of studied events

Reference, Country	Design (time window)	Relative risk (95% Confidence interval)				
		VTE	CVST	PE	DVT	Other VTE
Whiteley et al 2022, England	Cohort study (fully adjusted rates 1-28 days)	<70 years: 0.97 (0.90–1.05), 70+years: **0.58 (0.53–0.63)**		<70 years: 0.95 (0.85–1.05), 70+years: **0.54 (0.48–0.61)**	<70 years: 0.99 (0.87–1.12), 70+years: **0.63 (0.54–0.74)**	PVT: <70 years: 1.00 (0.24–4.15), 70+years: 0.61 (0.10–3.71) ICVT: <70 years: **2.27 (1.33–3.88)**, 70+years: 0.67 (0.20–2.18)
Hippisley-Cox et al 2021 England	SCCS (8-14 days)	**1.10 (1.02 to 1.18)**	**4.01, (2.08 to 7.71)**			
Botton et al 2022, France	SCCS (8-14 days only the treatment studied)			**1.30 (1.04–1.62)**		
Andrews et al 2022 England	Cohort study (4-13 days fully adjusted rates)	15-39 years: **2.2 (1.7-3.0)**, 40-64 years: **1.3 (1.1-1.4)**, 65+ years: 0.9 (0.8-1.0)				CVT: 15-39 years: **16.3 (9.9-27)**, 40-64 years: **2.7 (1.6-4.6)**, 65+ years: 0.4 (0.1-1.7)
Laporte et al 2021 Spain	Cohort study, adjusted age/sex	**3.68 (2.27–6.01)**	0.42 (0.09 to 2.01)			MEST: 0.21 (0.04–1.74), PVT: 0.63 (0.12–2.39)
Dag Berild et al 2022 Denmark, Norway and Finland	Self-controlled case series (28-days)	**1.83 (1.56 to 2.15)**				
Ab Rahman et al 2022 Malaysia	Self-controlled case series (21-days)	**2.22 (1.17 to 4.21)**				

Reference, Country	Design (time window)	Relative risk (95% Confidence interval)				
		VTE	CVST	PE	DVT	Other VTE
Chen et al 2022, multicountry.	Systematic review and meta-analysis (Differed between studies) **NOTE: viral vector vaccines**	**1.128 (1.023 to 1.1244)**				
Corrao et al 2022, Lombardy, Italy.	Cohort study (1-28 days)	Women: **<50: 2.43 (1.05 to 5.63)** 50–59: 1.53 (0.54 to 4.38) 60–69: 0.78 (0.28 to 2.18) **70–79: 0.39 (0.21 to 0.72)** 80+(no cases) Men <50: 0.29 (0.04–2.12) 50–59: 1.12 (0.34–3.69) 60–69: 0.81 (0.39–1.68) **70–79: 0.40 (0.24–0.69)** 80+: 1.18 (0.14–9.88)				

Reference, Country	Design (time window)	Relative risk (95% Confidence interval)				
		VTE	CVST	PE	DVT	Other VTE
Hviid et al 2022, Denmark	Cohort study (0-28days) **NOTE: risk difference per 100 000 vaccinations**		1.68 (-0.64 to 4.00)	0.93 (-2.35 to 4.21)	**DVT: 8.35 (0.21 to 16.49)**	SVT: 0.84 (-0.80 to 2.48)
Burn Li et al 2022 UK 2022	Cohort study, rates age standardised	**First dose: 1.12 (1.05 to 1.20)** **Second dose: 0.84 (0.73 to 0.96)**	**First dose: 4.14 (2.54 to 6.76)**	**First dose: 1.26 (1.15 to 1.38)** **Second dose: 0.79 (0.65 to 0.97)**	First dose: 1.02 (0.93 to 1.11) Second dose: 0.86 (0.72 to 1.02)	SVT: First dose: 1.22 (0.76 to 1.97) Second dose: 1.34 (0.56 to 3.21)
Burn Roel et al 2022 Spain 2022	Cohort study, rates age standardised	0.92 (0.71–1.18)		0.78 (0.52–1.16)	0.89 (0.65–1.22)	SVT: 1.09 (0.54–2.18)
Li et al 2016 (UK CPRD)	Cohort study with active comparators	First dose: 0.91 (0.78 to 1.06) Second dose: 0.87 (0.66 to 1.16)		First dose: 0.93 (0.77 to 1.12) Second dose: 0.86 (0.58 to 1.26)	First dose: 0.89 (0.71 to 1.11) Second dose: 0.93 (0.65 to 1.34)	
Li et al 2022 (Germany DA)	Cohort study with active comparators	1.61 (0.92 to 2.83)		0.69 (0.26 to 1.83)	**2.62 (1.34 to 5.13)**	
Li et al 2022 (Meta analysis of UK CPRD, Germany DA Netherlands IPCI and France LPD)	Cohort study with active comparators	First dose:1.3 (0.75 to 2.26) Second dose (UK and Germany): 0.84 (0.65 to 1.09)		First dose: 0.96 (0.79 to 1.15) Second dose (UK and Germany): 0.83 (0.58 to 1.2)	First dose:1.58 (0.56 to 4.42) Second dose (UK and Germany): 0.93 (0.66 to 1.31)	

Reference, Country	Design (time window)	Relative risk (95% Confidence interval)				
		VTE	CVST	PE	DVT	Other VTE
Ohaeri et al 2022	Cohort study comparing to the pre-exposure period		1.40 (0.95 to 2.05)			

CPRD- Clinical Practice Research Datalink; CVST: Cerebrovascular venous and sinus thrombosis; CVT- Cerebral venous thrombosis; DA- Disease Analyse; DVT-Deep vein thrombosis; IVCT- intracranial venous thrombosis; IPCI- Integrated Primary Care Information; LPD- Longitudinal Patient Data; , MEST: Mesenteric thrombosis; PE: Pulmonary embolism; PVT: Portal vein thrombosis; SCCS- Self-Controlled Case Series ; SVT: splanchnic venous thrombosis; UK United Kingdom; VTE: venous thromboembolism.

Table 8 - Sex and age stratified results, exclusion of previous cases and definition of VTE

Study	Sex differences	Age differences	Previous cases excluded	Definition of VTE
Li et al 2022	Only in CPRD (UK) Men:0.88 (0.7 to 1.11) Women:0.92 (0.74 to 1.14)	Only in CPRD (UK) 30-39:1.38 (0.48 to 3.93) 40-49:0.75 (0.39 to 1.45) 50-59:0.68 (0.44 to 1.05) 60-69:0.81 (0.53 to 1.23) 70-79:1.01 (0.79 to 1.3) 80-89:1.11 (0.77 to 1.59)	No	SNOMED codes for: deep vein thrombosis or pulmonary embolism, cerebral venous sinus thrombosis, splanchnic and visceral vein thrombosis ischaemic stroke, myocardial infarction, arterial thromboembolism as a composite of ischaemic stroke, and other rare arterial thromboembolisms such as intestinal infarction (codes not included due to long list)
Ohaeri et al 2022	Men: 1.47 (0.95-2.28) Women:1.16 (0.66-2.06)	<50: 1.00 (1.00-1.00) 50+: 5.23 (4.43-6.17)	Yes 365 day washout period.	CVST hospitalization or GP contact identified using International Classification of Diseases-10 (ICD-10) codes in PEDW or Read codes in WLGP (codes not included due to long list)
Dag Berild et al 2022	Women, RR:2.46 (2.06-2.94) Men, RR:1. 47 (1.17-1.86) NOTE: Stratified analysis is for coagulation disorders a measure that included venous thrombosis, arterial thrombosis, disseminated intravascular coagulation, purpura and other haemorrhagic conditions,	1987 or later RR: 3.79 (2.29-6.29) Born 1972-1986 RR: 2.85 (1.96-4.13) Born 1971 or earlier: RR:1.80 (1.54-2.11)	Yes, a washout period of 3 years (2017-2019).	ICD-10 codes Pulmonary embolism I26 Phlebitis and thrombophlebitis of femoral vein I80.1 Phlebitis and thrombophlebitis of other and unspecified deep vessels of lower extremities I80.2 Phlebitis and thrombophlebitis of lower extremities, unspecified I80.3 Phlebitis and thrombophlebitis of other sites I80.8 Phlebitis and thrombophlebitis of unspecified site I80.9 Portal vein thrombosis I81

Study	Sex differences	Age differences	Previous cases excluded	Definition of VTE
	thrombocytopenia and thrombotic microangiopathy.			Other venous embolism and thrombosis I82
Ab Rahman et al 2022	Men RR: 1.62 (0.75, 3.51) Women RR: 5.34 (1.45, 19.7)	Age <60 RR: 2.92 (1.23, 6.92) Age ≥60 RR: 1.38 (0.50, 3.85)	Yes, those who had records of hospital admissions for the same diagnosis in the two years before the study period were excluded.	ICD-10 codes: Include pulmonary embolism, lower limb venous thrombosis, splanchnic thrombosis, other venous thrombosis (I80, I80.1, I80.2, I80.29, I80.3, I82.2, I82.8, I82.9, I26, I26.9, I81, I82.0, I82.1, I82.3)
Corrao et al 2022	Women: <50: 2.43 (1.05 to 5.63) 50–59: 1.53 (0.54 to 4.38) 60–69: 0.78 (0.28 to 2.18) 70–79: 0.39 (0.21 to 0.72) 80+(no cases) Men <50: 0.29 (0.04–2.12) 50–59: 1.12 (0.34–3.69) 60–69: 0.81 (0.39–1.68) 70–79: 0.40 (0.24–0.69) 80+: 1.18 (0.14–9.88)		Unclear if excluded "Hospital admissions and drug prescriptions experienced within 2 years before the index date were used to investigate a list of 62 conditions possibly affecting the risks of severe/fatal clinical manifestations of SARS-CoV-2 infection, and/or venous thromboembolism"	ICD-9 codes: 415.1 Pulmonary embolism and infarction 437.6 Nonpyogenic thrombosis of intracranial venous system 451 Deep vein thrombosis 452 Portal vein obstruction 453.0 Budd-Chiari syndrome (hepatic vein thrombosis) 453.1 Thrombophlebitis migrans 453.2 Embolism of Vena Cava 453.3 Embolism and thrombosis in renal vein 557.1 Mesenteric vein thrombosis
Hviid et al 2022	Not stratified, but sample contained 81.7% females.	Not stratified, participants median age at study start	Yes, for each study outcome, persons who had that outcome between 1 January and	ICD-10 codes: Cerebral venous sinus thrombosis I636, I676 Splanchnic vein thrombosis I81, I820, I823

Study	Sex differences	Age differences	Previous cases excluded	Definition of VTE
		was 44 years (interquartile range [IQR], 32 to 54 years)	26 December 2020 were not included in the cohort for analysis of that specific outcome.	Pulmonary embolism I26 Deep venous thrombosis I801-I809, I821, I828, I829 (analysed separately, only CVT had a significant association)
Whiteley et al 2022	Men RR: 0.81 (0.75–0.87) Women RR: 0.90 (0.84–0.97)	<70 years: 0.97 (0.90–1.05), 70+years: 0.58 (0.53–0.63)	It was adjusted for: "We defined history of deep vein thrombosis (DVT) or pulmonary embolism (PE) as any record in primary care and/or hospital admission data before 8 December 2020".	Venous thromboembolic events: PE, lower limb DVT, intracranial venous thrombosis (ICVT), portal vein thrombosis, and venous thrombosis at other sites.
Hippisley-Cox et al 2021	Women 8-14 days RR: 1.17 (1.05, 1.29) Men 8-14 days RR: 1.04 (0.93, 1.16)	Age ≤ 50 8-14 days RR: 1.19 (0.96, 1.48) Age > 50 8-14 days RR: 1.09 (1.01, 1.18)	No, previous history of the outcomes are reported in Table 1.	ICD-10 I26 - Pulmonary embolism I260 - Pulmonary embolism with mention of acute cor pulmonale I269 - Pulmonary embolism without mention of acute cor pulmonale I81 - Portal vein thrombosis I81X - Portal vein thrombosis I82 - Other venous embolism and thrombosis I820 - Budd-Chiari syndrome

Study	Sex differences	Age differences	Previous cases excluded	Definition of VTE
				I822 - Embolism and thrombosis of vena cava I823 - Embolism and thrombosis of renal vein I828 - Embolism and thrombosis of other specified veins I829 - Embolism and thrombosis of unspecified vein
Andrews et al 2022	Not stratified	15-39 years: 2.2 (1.7-3.0), 40-64 years: 1.3 (1.1-1.4), 65+ years: 0.9 (0.8-1.0)	Yes, individuals with a prior admission with a thrombotic code in any of the first five diagnosis fields between 1st December 2019 and 29th November 2020 were excluded.	non-cerebral venous thrombosis included thrombophlebitis, deep venous or splanchnic vein thrombosis or pulmonary embolism- here termed "other venous thrombosis"
Laporte et al 2021	Not available	Not available	No	VTE was a composite variable of cerebral venous sinus thrombosis (CVST), mesenteric thrombosis (MesT), portal vein thrombosis (PVT)

CPRD- Clinical Practice Research Datalink; CVST: Cerebrovascular venous and sinus thrombosis; CVT- Cerebral venous thrombosis; DVT-Deep vein thrombosis; GP-General Practitioner; ICD-International Classification of Diseases; IVCT- intracranial venous thrombosis; IQR-Interquartile Range; PE: Pulmonary embolism; PEDW- Patient Episode Dataset For Wales; PVT: Portal vein thrombosis; RR- Relative Risk; SARS-Severe Acute Respiratory Syndrome; SNOMED-Systematized Nomenclature Of Medicine Clinical Terms; UK United Kingdom; VTE: venous thromboembolism; WLGP-Welsh Longitudinal General Practice Dataset.

MAH's Conclusion

AstraZeneca performed a comprehensive literature review covering period 29 June 2022 to 28 December 2022 with focus on new relevant epidemiological studies. These new relevant studies were added to the cumulative review reported in the last PBRER. The studies included in this cumulative review showed varied results, with some finding an increased risk of VTE after VAXZEVRIA vaccination and some finding a protective effect. AstraZeneca acknowledges the authors' views and suggestions; however overall literature data did not suggest a causal relationship between VAXZEVRIA and VTE. Given the heterogeneity of the published studies, AstraZeneca is of the opinion that conducting a meta-analysis of all available data would not add valuable information over the routine ongoing literature review. CVST is sufficiently characterised in the SmPC sections 4.4 and 4.8, and adequately managed through routine clinical practice with maintenance of a favourable benefit-risk balance.

Rapporteur assessment comment:

As a follow-up of the EMA LEG procedure (Post-Authorisation Measure LEG 103) and the previous PSUSA AR, the MAH was requested to provide an updated literature review to investigate VTE.

As a reminder, in the LEG 103 procedure no clinically meaningful imbalances were noted in the clinical trial data. For all safety topics, observed cases were less or significantly less than expected; however these estimates probably reflect a large percentage of under-reporting. The updated O/E analysis in the previous PSUSA did not find evidence of a signal. Review of post-marketing case reports did not identify unusual trends or patterns. Literature data suggested a possible relationship between Vaxzevria and VTE and PE, but findings were not consistent across studies with possible residual confounding. Therefore the MAH was requested to focus on new relevant epidemiological studies related to VTE.

Two new articles discussing the association between Vaxzevria and VTE (Li et al. 2022) and CVST (Ohaeri et al. 2022) were summarised and risk estimates were added to the previous summary (Table 6 - above). The table was also updated with estimates following publication of pre-printed articles (Burn Li et al. 2022 and Burn Roel et al. 2022).

The multinational study by Li et al. used the UK CPRD data and Germany DA databases to estimate incidence rate ratios of VTE after use of Vaxzevria versus mRNA based COVID-19 vaccines. For VTE and DVT, the meta-analysis was unreliable because of heterogeneity (I^2 values of 65% and 86%, respectively). No increased risk of VTE was seen after the 1st dose of Vaxzevria versus BNT162b2 either in Germany DA or UK CPRD (Table 7 above). An increased risk of DVT was seen after the 1st dose of Vaxzevria compared with BNT162b2 in Germany DA (2.62 (95% CI 1.34 to 5.13), but not replicated in UK CPRD data (0.89 (95%CI 0.71 to 1.11). No increased risk of PE was seen in either database. An important limitation of this study is the absence of hospital treatments and incomplete information on hospital outcomes, as health records from general practices and ambulatory setting are used.

Overall, the MAH highlighted the heterogeneity of the published studies and it can be agreed that it is difficult to compare the results and combine them in a meaningful way in a meta-analysis and calculate pooled estimates. As part of the MAH's PASS study, a meta-analysis of all adverse events of special interest is planned, including for VTE. The meta-analysis will combine results from the 5 European databases included in the PASS with a total sample size of over 5 million participants. The final report is expected in April 2024. To note is that this meta-analysis may face similar challenges (discussed in procedure EMEA/H/C/005675/MEA007.7). The PASS study includes the UK CPRD and Spain SIDIAP databases included in the study discussed above by Li et al.

Therefore, the PRAC Rapporteur focused on the largest cohort and case-control studies (SCCS), with at least 1 million doses of exposure to Vaxzevria or at least 100,000 person-years follow-up. These studies are summarized in the table below.

Table. Summary of large scale post-marketing studies investigating association between Vaxzevria and VTE (built by the Assessor)

Study	Total doses analyzed	Follow-up interval	Methods
Hippisley-Cox et al 2021 England	29,121,633 dose 1	8-14 days	Self-controlled case series Hospital admissions
Ab Rahman et al 2022 Malaysia	2,744,507	21 days	Self-controlled case series Hospital admissions
Burn Li et al 2022 UK	3,768,517 dose 1 1,091,660 dose 2	28 days	Cohort study (rates age standardised) CPRD data primary care database
Li et al 2022 (UK CPRD)	140 803 person years 1 893 469 participants	28 days	Cohort study with active comparators CPRD data primary care database
Andrews et al 2022 England	person-years follow-up VTE 15-39 y 277,000 40-64 y 1,060,000 65+y 987,000	4- 13 days	Cohort study (adjusted rates for several confounders) Hospital admissions
Whiteley et al 2022, England	12,481,337 dose 1 person-years follow-up	1-28 days	Cohort study (adjusted rates for several confounders) Primary care, hospital admissions

The Forest plot of relative risks of VTE for overall results and results for younger and older age-groups are presented in the figures below. The incidence rate ratios in the studies looking at overall results or the older age groups cluster at or below 1, except for the SCCS by Ab Rahman et al. Interestingly, these authors noted that due to the opt-in policy for Vaxzevria vaccination in Malaysia, this group includes those of younger age categories, unlike other countries that limited the use of Vaxzevria to the older age groups. Therefore, the population vaccinated with Vaxzevria is considered to be "healthier" than those who received other vaccines since individuals without health concerns are more likely to sign up for this cohort.

Figure. Forest plot of relative risk of VTE after Vaxzevria administration (overall) (built by the Assessor).

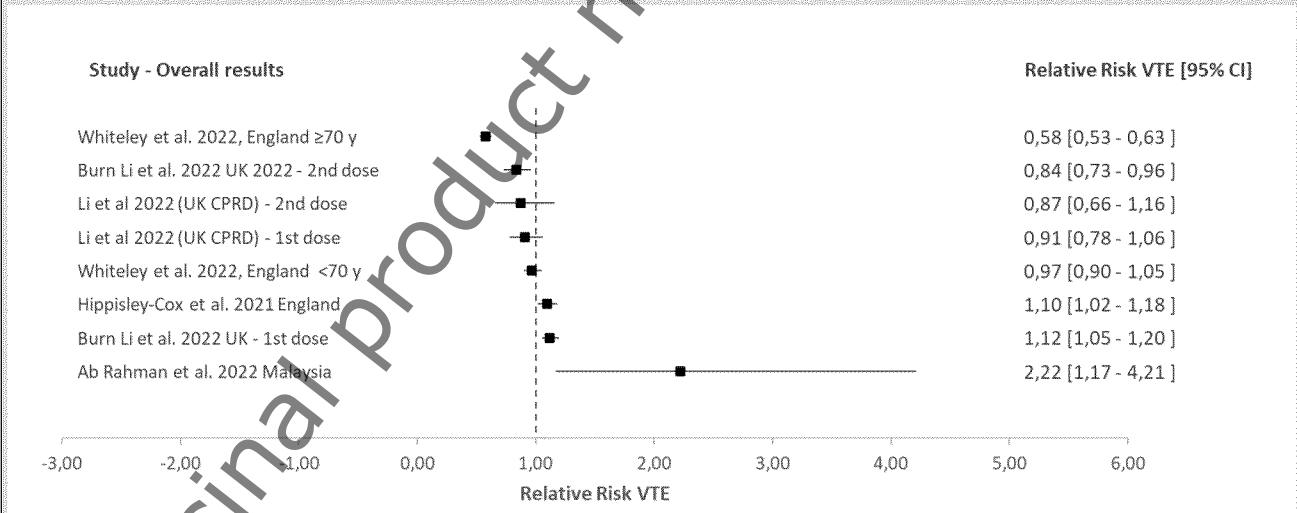
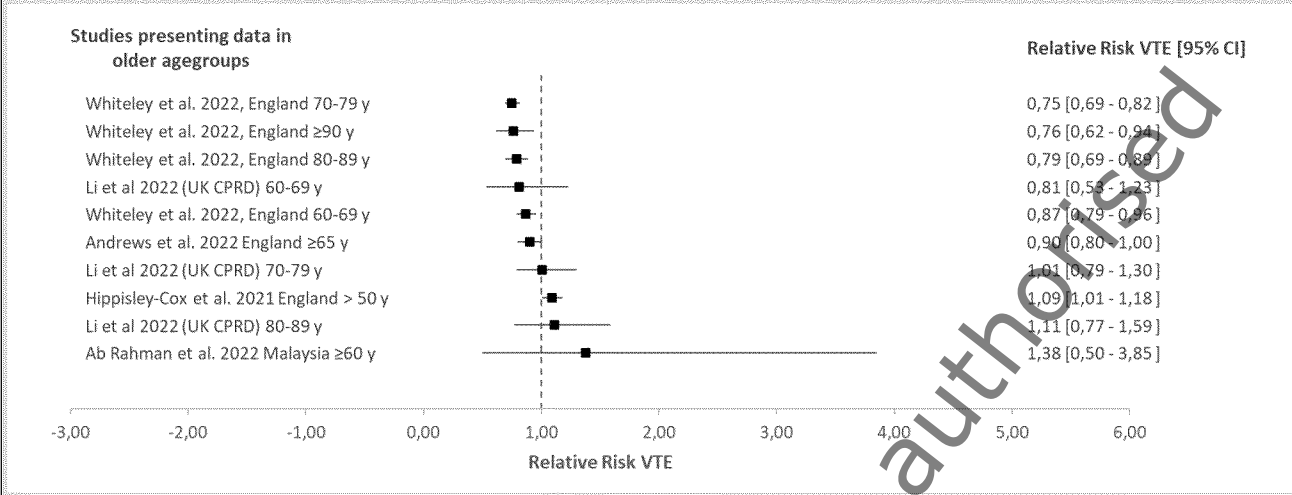


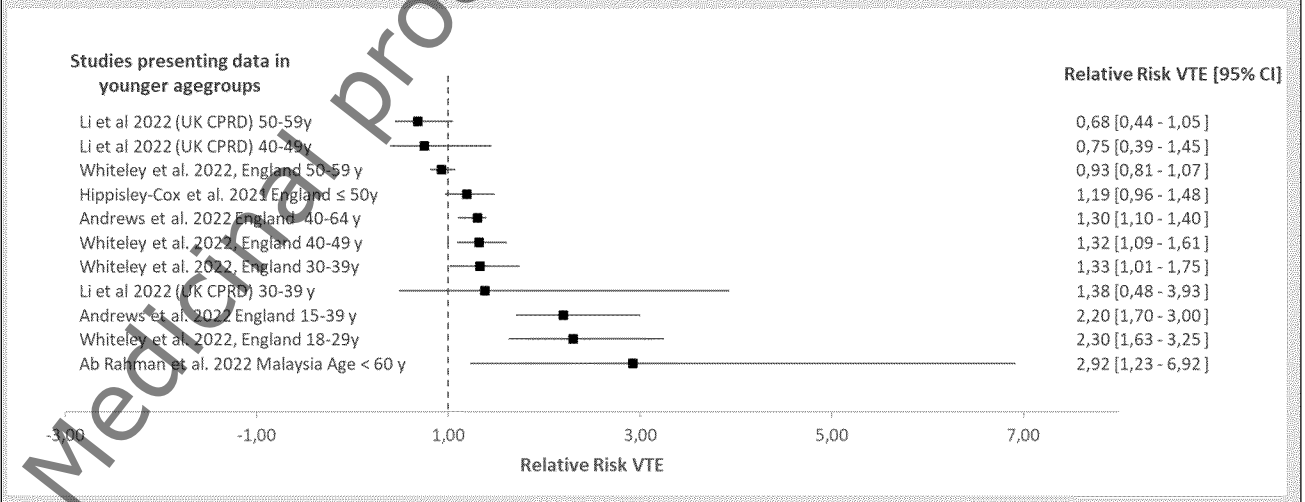
Figure. Forest plot of relative risk of VTE after Vaxzevria administration (older age groups) (built by the Assessor)



The studies presenting results for the younger age-groups consistently find incidence rate ratios for VTE clustering above 1, indicating an increased risk of VTE in this population (Figure below). Of note, the study by Li et al., where no increased risk was observed, is based on the UK CPRD databases, using primary care data without hospital linkage, while all other studies include hospital data.

Only in the study by Andrews et al, an attributable risk was calculated for VTE. Using the adjusted relative incidence for any time after a first dose of Vaxzevria in the 15-39 and 40-64 year age groups of 1.9 (95%CI 1.6-2.2) and 1.1 (95%CI 1.1-1.2) respectively, the attributable risk estimates for admissions with venous thrombosis code are respectively 36.3 (95%CI 28.8-41.8) and 16.4 (95%CI 7.5-24.9) per million doses. This corresponds to an attributable risk per 10,000 doses of 0,36 (95%CI 0.29-0.42) in the 15-39 year age group and 0,16 (95%CI 0,08-0,25) in the 40-64 year age group.

Figure. Forest plot of relative risk of VTE after Vaxzevria administration (younger age groups) (built by the Assessor)



Of note, as part of ongoing variation II/0089, final pooled analysis of COV001/2/3/5 studies are currently being assessed. Currently under discussion are a request to the MAH to consider the inclusion of deep vein thrombosis and subclavian vein thrombosis in the SmPC. These two events (for the same participant) were considered related to the study vaccine. Additionally, more information is requested on

some individual SAEs, including pulmonary embolism.

Besides, the O/E analysis performed by EMA (Cut-off date 07.12.2022) found a significative imbalance both for DVT without thrombocytopenia and for Pulmonary embolism in the younger age-groups. In the 14 day risk period, O/E for DVT without thrombocytopenia in the 30-39 years old was 1.61 [95%CI 1.28-2]. Especially in younger women observed rates were higher than expected with significant ratios between 1.66-2.19 for the women 20-49 years (20-29y: 1.72 [95%CI 1.09-2.58]/30-39 y: 2.19 [95%CI 1.69-2.8] and 40-49y: 1.66 [95%CI 1.36-2.01]. For Pulmonary embolism, O/E rates with risk period of 14 day for the 20-29 year olds was 2.58 [95%CI 1.65-3.84] and for 30-39 years this was 1.49 [95%CI 1.02-2.11]. For 20-29y olds, at 30 day risk window: 1.65 [95%CI 1.14-2.32].

In conclusion, a re-assessment of the observational studies reporting VTE, focusing on the studies including a large number of Vaxzevria vaccinees was conducted. Using a variety of study designs, this demonstrates a consistent increase in VTE among the younger age-groups. The PRAC Rapporteur considers that there is sufficient evidence to conclude there is a reasonable possibility that Vaxzevria is causally related to VTE.

A regulatory action is proposed, with updates of the SmPC section 4.4 and 4.8 to include Venous thromboembolism; the PIL should be updated accordingly. See section 3 for suggested wording [*Request for a variation*].

The RMP should be updated at the next regulatory opportunity with upgrading of 'thrombosis' from important potential risk to important identified risk. [RSI]

2.3.5. Important potential risk – CVST without thrombocytopenia

Please note that data on CVST without thrombocytopenia is not reproduced here (see Section 16.3.1.1 of the PBRER).

MAH's summary

AstraZeneca continued to review the safety information for CVST without thrombocytopenia from sources including clinical trials, post-marketing reports, and the published literature for the reporting period.

There were no case reports indicating recurrence (after the first and second dose of the vaccine). There are 597 and 37 cases for the cumulative and reporting period respectively. Out of the 597 cases, 99% of the reported cases were serious, 51 (8.5%) had a seriousness criteria of Fatal, and 131 (21.9%) Life-threatening. Median age was 51 years. There was a preponderance for female gender (60.8%) versus males (35%), and 68.5% cases were in age group 18-64 years. Cumulatively, 29 (56.8%) out of all 51 fatal cases were reported in females. There was no significant difference noted between the cumulative and reporting period in terms of the safety patterns and distribution of cases.

Of the total number of case reports cumulatively, 353 (59.1%) were medically confirmed.

Cumulatively, One (1) case met WHO-UMC causality criteria for Probable/Likely and 1 case for Conditional/Unclassified. 373 were considered as Possible, Out of 373, 145 (38.8%) were identified with relevant risk/confounding factors.

A review of the published literature did not identify any new safety information on this topic in association with VAXZEVRIA.

The results of observed versus expected analysis showed observed cases were more than expected in the general population globally. The age stratifications suggest that the O/E ratio is higher in younger age

groups than in the older age groups and that the O/E ratio is higher in females than in males. However, it is important to note that O/E analyses are complementary to routine signal detection methods, and are not designed to determine a causal relationship; confounding factors were not considered in O/E (such as possible COVID-19 infections or other possible causes for CVST without thrombocytopenia).

CVST without thrombocytopenia is an important potential risk in the VAXZEVRIA Core Risk Management Plan and the topic will continue to be kept under close surveillance by AstraZeneca.

MAH's conclusion

From the data identified during the reporting period and also taking into account the cumulative experience, AstraZeneca considers that there is currently insufficient evidence of a reasonable possibility of causal relationship between VAXZEVRIA and CVST without thrombocytopenia. CVST without thrombocytopenia is included in section 4.4 (section 4.4 Warnings and Precautions) of the CDS to inform prescribers that these events may require different treatment approaches than TTS. Healthcare professionals should consult applicable guidance. No changes to the CDS or product leaflets are warranted at this time.

AstraZeneca will continue to monitor safety information for CVST without thrombocytopenia as an important potential risk and take further actions as deemed appropriate.

Rapporteur assessment comment:

During the current **reporting period**, 37 cases (17 initial, 20 follow-up) of CVST without thrombocytopenia were retrieved. All cases were serious and 20 of them were medically confirmed. The majority of the cases were reported in females (72%). Median age was 42 years (age range: 17-63 years) and median TTO was 8 days (range 1-445 days).

Six of the 37 cases had a fatal outcome, resulting in a case fatality rate (CFR) of 16.2% compared to a cumulative CFR of 8.5%. As in PSUR#3, the higher CFR for the reporting interval is due to the large proportion of fatal follow-up reports (3 out of 6 reports (50%)) received during the interval. Confounding factors (i.e. comorbidities, risk factors, concomitant medications) were reported in 21.6% of the patients. The CVST event occurred post 2nd dose in 3 case reports and post 3rd dose in 2 cases. There were no cases with a positive rechallenge (CVST event(s) both after dose 1 and dose 2).

The MAH performed causality assessment using WHO-UMC criteria. Out of the 37 cases reported during the current interval period, 3 cases were classified as 'Unlikely', 15 cases as 'Unassessable' (including 5 of the 6 fatal cases for which the TTO was not reported), and 19 cases as 'Possible' (of which 13 with limited information and 6 with confounders).

Cumulatively, up to 28 December 2022, 597 cases of CVST without thrombocytopenia have been reported (99% serious, 59% medically confirmed), compared to 573 cases in PSUR#3. The updated cumulative review resulted in a similar age and gender distribution (median age 51 years, 61% females), and case fatality rate (8.5%) as the cumulative review provided in PSUR#3.

The results of the MAH's updated O/E analyses for CVST without thrombocytopenia were in line with PSUR#2 and PSUR#3. Observed cases were significantly higher than expected in the general population globally for all risk windows except for the risk window of 42 days when cases with unknown TTO were excluded. The age and gender stratifications suggest that the O/E ratio is higher in the younger age groups than in the older age groups and higher in females than in males.

The MAH reviewed new literature on CVST without thrombocytopenia in association with Vaxzevria and retrieved 5 relevant articles. Krzywicka et al. (2022) found an increased rate of CVST without thrombocytopenia in recipients of Vaxzevria (3.2 (95% CI 2.8–3.7) per million) compared to the other vaccines (Spikevax: 0.6 (95% CI 0.3–1.1), Comirnaty: 0.5 (95% CI 0.4–0.7), Jcovden: 0.0 (95% CI 0.0–

1.3) per million). The age-stratified risk of CVST without thrombocytopenia after Vaxzevria vaccination was the highest in the 18- to 24-year-old group and the lowest in the ⩾60-year-old groups. The multicentre cohort study of Perry et al. (2021) did a direct comparison between 70 patients with VITT-associated CVST and 25 patients who developed CVST after vaccination but without VITT and showed that patients with VITT-associated CVST were younger, had fewer risk factors and were more likely to have received Vaxzevria. Furthermore, CVST without thrombocytopenia had a milder phenotype (in terms of presentation, severity and outcome), which was comparable to the CVST cases seen prior to the COVID-19 pandemic (Sánchez van Kammen, 2021). Another study of Sánchez van Kammen et al. (2021) showed that prior to the COVID-19 pandemic, baseline thrombocytopenia was uncommon in CVST patients (8%), and platelet factor 4/heparin antibodies were rare. A disproportionality analysis performed by Kan et al. (2022) suggested a stronger CVST signal for Adenovirus (Jcovden) compared to mRNA-based (Comirnaty, Spikevax) COVID-19 vaccines. The data covered only the US, where Vaxzevria was never used.

As initially discussed in MSSR07, the PRAC Rapporteur disagrees with the MAH's conclusion on causality. A causal association between CVST without thrombocytopenia and Vaxzevria should be considered at least a reasonable possibility. Cerebrovascular venous and sinus thrombosis is listed with frequency unknown in section 4.8 of the SmPC and a warning on the risk of CVST without thrombocytopenia was included in section 4.4.

In conclusion, no new safety information concerning CVST without thrombocytopenia could be identified. The current risk minimisation measures described in the product information are considered adequate. The MAH should continue to closely monitor cases of CVST without thrombocytopenia, present updates in the next PSURs, and discuss relevant literature.

2.3.6. Important potential risk –Immune-mediated neurological conditions / Nervous system disorders, including immune-mediated neurological conditions during the reporting period

Cumulatively, a total of **38164 cases** from literature, clinical studies, non-interventional studies and spontaneous sources were reported within the concept of immune-mediated neurological disorders. This includes a total of **2609 cases** reported **during the period under review**.

The **most commonly reported PTs** (interval) were **Paraesthesia (1289)**, **Hypoaesthesia (924)**, **Guillain-Barre syndrome (GBS) (189)**, Neuralgia (176), Sensory disturbance (116), Sensory loss (59), Neuropathy peripheral (53), Multiple sclerosis (30), **Myelitis transverse (28)**, **Encephalitis (25)**, Small fibre neuropathy (23), Optic neuritis (18), Polyneuropathy (18), Chronic inflammatory demyelinating polyradiculoneuropathy (17), Demyelination (17), **Acute disseminated encephalomyelitis (15)**, Multiple sclerosis relapse (11), Neuritis (10), Noninfective encephalitis (10), **Miller Fisher syndrome (9)**, Myelitis (9), Peripheral sensory neuropathy (8), **Encephalitis autoimmune (7)**, Encephalopathy (7), Demyelinating polyneuropathy (6), Myelin oligodendrocyte glycoprotein antibody-associated disease (6), Encephalomyelitis (5).

2.3.6.1. Encephalitis, including fatal

Please note that the Encephalitis data is not reproduced here (see Section 16.3.1.2.1 of the PBRER).

MAH's Summary: Of the **70 cases** received during the **reporting period**, 53 (75.7%) of vaccinees were from the age group of 18-<65 and median age was found to be 47 years. In 42 (60.00%) cases, the events were reported to have occurred after the first dose, 5 (7.14%) case reports after the second

dose of vaccine, and dose was not reported in 23 (32.86%) case reports. There was no report of recurrence of events.

Review of all cases during the interval period revealed **no clear pattern in clinical presentation or medical history**. There is a **wide range in time to onset** (TTO) of cases from vaccination (0-405 days). The **median TTO** for all the cases was **11 days**. Thirty-four (34) (48.57%) out of 70 cases were within the risk window of 2-42 days. All the 70 cases were serious. Case fatality rate is variable and dependent on causative factor (Wang et al 2022 [A]). The review of 2 case reports with fatal outcome did not identify any substantial evidence of a causal association between encephalitis and VAXZEVRIA. No changes were identified for interval data considering both safety patterns and volumes.

Based on **Brighton Collaboration criteria** approach, out of the 70 cases, **6 fulfilled level 2 criteria, 19 fulfilled level 3 criteria**, 44 fulfilled level 4 criteria, and 1 case fulfilled level 5 criteria. 5 (7.14%) cases were evaluated with alternative causal factors noted and the remaining cases were evaluated with limited information to make any comprehensive causality assessment. The review of post authorization case reports did not find any evidence of a causal association between encephalitis and VAXZEVRIA.

The **observed versus expected analysis** of cumulative cases for encephalitis showed that observed cases occurred **significantly less frequently than expected** for all cases (385) and cases with BCC 1-3 (69), all age stratifications in EEA/UK, Brazil, and Australia, and risk windows. The contribution of under-reporting cannot be estimated, but observed cases are significantly below expected and do not indicate any disproportionality.

Overall, the clinical pattern of case presentation and numbers of reports are broadly consistent with what might be expected from the natural epidemiology of encephalitis, and there was no specific biological mechanism for development of encephalitis post vaccination with VAXZEVRIA.

MAH's conclusion: From the data identified during the reporting period and taking into account the cumulative experience, there is currently insufficient evidence of a causal association between encephalitis and VAXZEVRIA.

VAXZEVRIA CDS Section 4.4 includes warnings on Neurological events: "Very rare events of demyelinating disorders, including Guillain-Barré syndrome (GBS), have been reported following vaccination with VAXZEVRIA. A causal relationship has not been established. As with other vaccines, the benefits and potential risks of vaccinating individuals with VAXZEVRIA should be considered". In addition, encephalitis (immune mediated neurological condition/ nervous system disorders, including immune mediated neurological conditions.) is considered as an Important potential risk in the Core and EU RMPs for VAXZEVRIA. No further updates to the VAXZEVRIA CDS or RMP are warranted at this time. As such, the topic will continue to be to be closely monitored as part of AstraZeneca's ongoing surveillance for the important potential risk of immune-mediated neurological conditions.

Rapporteur assessment comment:

The MAH provided a review of the **70 interval cases** of encephalitis, including a causality assessment according to the WHO-UMC. During the reporting period, the **majority** of identified cases were **follow-up** reports (45 out of 70). The review of cases using the BCC criteria and the WHO-UMC causality assessment scale does not provided any new relevant information.

The **O/E analysis** cleared showed an O/E ratio **significantly lower than 1**.

The literature review performed by the MAH did not identify any relevant articles other than several case reports (9 papers describing 13 cases of encephalitis).

In conclusion, available data did not raise any new safety signal. Close monitoring of encephalitis as part of the ongoing surveillance for the important potential risk of Nervous system disorders, including

immune-mediated neurological conditions is appropriate. No further action is considered warranted at this stage.

2.3.6.2. Transverse Myelitis

Please note that the Encephalitis data is not reproduced here (see Section 16.3.1.2.2 of the PBRER).

MAH's Summary: The pathogenesis TM is thought to be immune-mediated from infection, para-infectious processes, autoimmune disease, or paraneoplastic processes. The exact mechanism of TM following immunization is unknown.

There were **10 cases of TM** (fulfilling at least BCC 3 criteria) received **during the reporting period**, of these, 9 were assessed to be classified as "Possible" according to WHO-UMC causality criteria (as either "Possible" with limited information/ "Possible" with confounders). Seven of the 9 cases were classified as "Possible" with Limited Information based solely on the TTO parameter (reasonable TTO considered) as there was insufficient case information (such as vaccinees' medical history, comorbidities, concomitant medications, etiological work-up etc). For the remaining four cases the event could also be explained by the vaccinees' diseases or other medications.

In addition, an observed versus expected analysis of cumulative cases meeting Brighton collaboration criteria levels 1-3 showed that the observed number of TM cases fulfilling case definition are either less than or significantly less than the number of expected cases in all risk windows.

MAH's Conclusion: The information from this updated periodic review found insufficient evidence for a new or emerging signal regarding Transverse Myelitis and VAXZEVRIA. No changes to the CDS or RMP are recommended for Transverse Myelitis. As such, the topic will continue to be to be closely monitored as part of AstraZeneca's ongoing surveillance efforts for the important potential risk of immune mediated neurological conditions.

Rapporteur assessment comment:

The MAH provided a review of the **35 interval cases** reporting 9 events of myelitis and 28 events of myelitis transverse. 24 were initial reports and 11 were follow-up reports. The median age was 48 years (range 25-76 years) and the male-to-female ratio was 1:1.

The review of cases using the BCC criteria and the WHO-UMC causality assessment scale includes 10 cases BCC L2-3 (no BCC L1 cases) and 20 cases assessed as possibly related with vaccination (all with confounders or limited information). The review does not highlight a particular CSF picture or neuronal antibodies presentation.

The updated **O/E analysis** provide similar results compared to those presented in the previous PSUR.

Of note, the O/E analysis performed by EMA (Cut-off date 07.12.2022) found a significative imbalance using both a 30 and 42 days risk period in the age group 40-49 yo (i.e. O/E ratio [95%CI] of 2.74 (1.42 - 4.79) and 2.5 (1.33 - 4.27) respectively). The imbalance is highest in women in both risk periods (i.e. 5.79 (2.32 - 11.92) and 5.56 (2.39 - 10.95) respectively)

The **literature review** performed by the MAH did not identify any relevant articles. In addition, the PRAC Rapporteur identified 1 other paper of interest which does **not show any clear evidence of an association of ChAdOx1 vaccination with transverse myelitis** (N = 199; **IRR of 1.51; 95% CI 0.96–2.37**) when assessed through a SCCS in England using the Open SAFELY platform (Walker et al.,

2022)[8].

In conclusion, available data did not raise any new safety signal. As previously discussed, the PRAC Rapporteur considers that a **causal relationship between Vaxzevria and Transverse Myelitis is at least a reasonable possibility** (disagreement with the MAH's opinion). The risk of transverse myelitis is considered to be **appropriately described in the current EU-PI** (Warning in **section 4.4**; TM listed in **section 4.8**). Close monitoring of transverse myelitis as part of the ongoing surveillance for the important potential risk of Nervous system disorders, including immune-mediated neurological conditions is appropriate. No further action is considered warranted at this stage.

2.3.6.3. Acute disseminated encephalomyelitis (ADEM)

Please note that the Encephalitis data is not reproduced here (see Section 15.2.1 [Health Authority Request] of the PBRER).

MAH's summary

On review of AstraZeneca's Global Safety Database **cumulatively to 28 December 2022**, a total of **83 cases of ADEM** with the use of VAXZEVRIA have been received (excluding 5 potential duplicates). All of the reported cases were serious, including 58 (70%) medically confirmed cases.

Dose: The majority of the cases were reported after the 1st dose (77 events occurred after 1st dose, and 8 after 2nd dose [dose unknown for 18 events]. No events were reported after booster dose or after both dose 1 and dose 2 (recurrence).

Age/Gender: The **age** range was 22 to 90 years with a **median of 52.5 years**; within the age range (19 to 61 years) mentioned by Schwarz et al 2001. 44 (**53%**) cases were reported in **female** vaccinees suggesting no gender prevalence.

Seriousness/Outcome: In 52 cases, ADEM was reported to cause hospitalization, and 14 cases were life-threatening. In 49 cases ADEM was considered a medically important event. In 27 cases the events had a favourable outcome (recovering/resolving/resolved).

Five (**5**; 6%) cases had a **fatal outcome**; **3 cases** assigned causality of **possible with limited information** and 2 cases assigned causality of unlikely as per WHO-UMC causality. One (1) case met BCC level 1, 2 cases met BCC level 2, and 1 case met BCC level 3. The **case fatality rate of 6%** is in line with previously document case fatality rates in ADEM (5% to 50%; Borlot et al 2011).

TTO: The **median TTO was 9 days** (range 0 to 186 days) [*TTO reported in 62 (75%) cases*].

BCC criteria and causality assessment[WHO-UCM criteria]: **4** cases fulfilled **BCC level 1**, **25** fulfilled **BCC level 2**, **7** fulfilled **BCC level 3** of the diagnostic criteria for certainty.

Of the 36 cases fulfilling BCC level 1,2 or 3, **none** of the cases met WHO-UMC causality criteria for **Certain or Probable/Likely**; **6 cases** were assessed as **"Possible" with confounders**, **23 as "Possible" with limited information**, and 3 as "Unlikely". The remaining 4 cases had insufficient case details for a comprehensive causal assessment.

Anti-MOG antibody: On review of the 83 cases of ADEM, 20 cases had information on anti-MOG antibody status: 8 cases were anti-MOG positive, 11 cases were anti-MOG negative and in 1 case the anti MOG

[8] Walker JL, Schultze A, Tazare J, Tamborska A, Singh B, Donegan K, Stowe J, Morton CE, Hulme WJ, Curtis HJ, Williamson EJ, Mehrkar A, Eggo RM, Rentsch CT, Mathur R, Bacon S, Walker AJ, Davy S, Evans D, Inglesby P, Hickman G, MacKenna B, Tomlinson L, Ca Green A, Fisher L, Cockburn J, Parry J, Hester F, Harper S, Bates C, Evans SJ, Solomon T, Andrews NJ, Douglas IJ, Goldacre B, Smeeth L, McDonald HI. Safety of COVID-19 vaccination and acute neurological events: A self-controlled case series in England using the OpenSAFELY platform. Vaccine. 2022 Jul 30;40(32):4479-4487. doi: 10.1016/j.vaccine.2022.06.010. Epub 2022 Jun 7. PMID: 35715350; PMCID: PMC9170533.

status was unknown. **No specific trend with respect to MOG antibody positive status** ADEM in individuals vaccinated with VAXZEVRIA was seen.

O/E analysis (Tables 30-34 of PBRER): the O/E analysis of all ADEM cases suggested that **overall**, the observed numbers were **significantly less than the expected** numbers **in the 42-day risk windows**. The observed numbers were **greater than expected** in a few **sub group stratifications** and may be explained by reporting bias for increased reporting of cases with a shorter risk window for the passive event reporting of rare diseases. Review of cases in these subgroups where observed numbers were above expected showed that most cases had insufficient information to make any causality assessment.

Literature and Mechanism of action: A review of the literature did not find any new epidemiological studies concerning ADEM and VAXZEVRIA vaccination. The review of mechanisms proposed by the authors suggests both vaccine-specific and patient susceptibility factors. However, no conclusive evidence linking proof of mechanism in either a mechanism-based study or further exploration of mechanism in the same case were identified. No new safety signals were identified from review of literature.

MAH's conclusion

The information from this updated cumulative review found insufficient evidence for a new or emerging signal regarding ADEM and VAXZEVRIA. No changes to the CDS or RMP are recommended. The topic 'acute disseminated encephalomyelitis' will continue to be closely monitored as part of AstraZeneca's ongoing surveillance activities for the important potential risk of nervous system disorders, including immune-mediated neurological conditions.

Rapporteur assessment comment:

The MAH performed an updated cumulative review as requested. The search of the safety database identified 83 cases of ADEM, excluding potential duplicates (compared to 80 cases in previous PSUR). The median age was 52.5 years (range 22-90) and the male-to-female ratio was 4.5 to 5.3.

The MAH's review of cases using the BCC criteria and the WHO-UMC causality assessment scale identified **4 cases classified as BCC L1 with a possible causal** association, and **25 cases classified as BCC L2-3 possibly related to vaccination**. No cases were assessed with a probable or certain causal association. The MAH provided clarification on BCC classification and causality assessment in the responses to RSI (see Appendix 01). Except 1 case BCC L1 for which the PRAC Rapp still considers a probable causal association, the updated review of BCC classification and causality assessment is agreed.

The updated O/E analysis provide similar results compared to those presented in the previous PSUR.

The literature review performed by the MAH identified 18 articles presenting case reports which were discussed as part of the cumulative review. No new epidemiological studies were found by the MAH. After the DLP, a systematic review of ADEM following COVID-19 vaccination was published by Nabizadeh et al., 2023[9]. The authors identified 54 ADEM cases including 35 patients vaccinated with Vaxzevria. Cases occurred more frequently after the first dose. The authors highlighted the challenging differential diagnosis spectrum of ADEM and conclude that it is not clear that ADEM could be a potential complication of COVID-19 vaccination but suggest that neurologists should be aware of serious neurological consequences that may arise after COVID-19 immunization, in particular for the ChAdOx1.

In conclusion, available data did not raise any new safety signal. More robust epidemiological data are still missing to further evaluate the association. It is agreed that ADEM should continue to be closely monitored and discussed in the next PSUR as part of the ongoing surveillance activities for the important

[9] Nabizadeh F, Noori M, Rahmani S, Hosseini H. Acute disseminated encephalomyelitis (ADEM) following COVID-19 vaccination: A systematic review. J Clin Neurosci. 2023 May;111:57-70. doi: 10.1016/j.jocn.2023.03.008. Epub 2023 Mar 22. PMID: 36963124.

potential risk of nervous system disorders, including immune-mediated neurological conditions. No further action is considered warranted at this stage.

2.3.7. Important potential risk – Vaccine-Associated Enhanced Disease (VAED) / Vaccine-Associated Enhanced Respiratory Disease (VAERD)

Please note that VAED/VAERD data is not reproduced here (see Section 16.3.1.3. of the PBRER).

Summary of interval data

On review of 304 cases of VAED/VAERD received during the reporting period, a majority (215 out of 304, 70.7%) of them were reported as serious, of which 118 cases were medically confirmed, and 35 out of 304 (11.5%) cases reported fatal outcomes. These cases had insufficient information on dose latency, medical history, concomitant medications, baseline medical condition prior to vaccination, clinical course, diagnostic and etiologic workup, and storage and transport conditions of the vaccine, which precluded a proper causal assessment. No hypothesized mechanism/pathways have been identified to date. No new safety information on this topic was identified through the review of the literature.

At the end of the reporting period, the important potential risk VAED/VAERD is reclassified and removed from the list of safety concerns and the justification for removal is presented below:

VAED including VAERD is a theoretical risk highlighted by the Regulators based on the previous preclinical models, although it has not been observed in clinical studies nor in the post-authorization experience with any COVID-19 vaccine. On the contrary, more COVID-19 related morbidity and mortality has been observed in unvaccinated populations globally. Cumulatively up to 28 June 2022, 2139 case reports (88% reported as serious) of potential VAED/VAERD were retrieved from the post-marketing setting, however there were no confirmed reports of VAED/VAERD. There is insufficient evidence of a reasonable possibility of a causal association between VAED/VAERD and VAXZEVRIA and the risk is neither considered as 'potential' nor 'important' and hence removed from the list of safety concerns. Updated data from the post-marketing experience (with > 2.2 billion doses administered globally) do not support the initial supposition and there is no reasonable expectation that additional pharmacovigilance activity could further characterize the risk. This risk will continue to be monitored through routine pharmacovigilance activities.

Conclusion

Based on the evaluation of the available data during the reporting period and considering the cumulative experience, the important potential risk of VAED/VAERD is removed from the list of safety concerns.

Rapporteur assessment comment:

During the interval period covered by this report, 320 events from 304 cases (175 initial and 129 follow-up) were retrieved. Cumulatively 2420 case reports of potential VAED/VAERD were identified (2537 events). The 5 most frequent events were Pneumonia (981), COVID-19 pneumonia (400), Coagulopathy (393), Respiratory failure (204) and Pneumonitis (109).

The MAH has removed the important potential risk of VAED/VAERD from the list of safety concerns based on the evaluation of the available data during the reporting period and considering the cumulative experience. This is not endorsed.

It is acknowledged that no signal related to VAED/VAERD has been raised up to date. However, considering that this issue will be assessed through the PASS using EU/UK databases (D8111R00006), VAED/VAERD should remain in the important potential risks until the results of the study are available. This has been discussed and agreed in the variation II/0084/G.

The MAH is requested to review the list of safety concerns and maintain Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) in the important potential risks. However, it is agreed that data from spontaneous reporting should not be discussed in next PSURs unless significant new information arises. Relevant data from the literature should be discussed if any [Issue for the next PSUR]

2.3.8. Other potential risks not categorised as important – AESI

Please note that AESI data is not reproduced here (see Section 16.3.3 and Appendix 8 of the PBRER).

The AESIs for the COVID-19 VACCINE ASTRAZENECA and associated PTs are listed in Appendix 7 of the PSUR. AESIs have been included for review in Section 16.3.3 and Appendix 8 of the PSUR (O/E Analyses).

AESI for which the O/E analysis resulted in a ratio >1 are presented in Table 9.

Table 9 Observed versus expected analyses for AESI and Safety Concerns in the COVID-19 VACCINE ASTRAZENECA RMP –cumulative to 28 December 2022 with rate ratio above one (built by the Assessor from Appendix 8)

Medical Concept	Observed cases	Expected cases	Risk Window (days)	Background rate/100,000 person-years	Rate ratio (CI 95%)
Anaphylaxis type reactions b	1478	576.83	2	22.6	2.56 (2.43 - 2.7)
Anaphylaxis type reactions b (including unknown TTO)	2280	576.83	2	22.6	3.95 (3.79 - 4.12)
Angioedema – Hypersensitivity c	10545	2552.36	2	100	4.13 (4.05 - 4.21)
Angioedema – Hypersensitivityc (including unknown TTO)	15589	2552.36	2	100	6.11 (6.01 - 6.2)
Acute disseminated encephalomyelitis	46	26.8	14	0.15	1.72 (1.26 - 2.29)
Acute disseminated encephalomyelitis (including unknown TTO)	67	26.8	14	0.15	2.5 (1.94 - 3.17)
Acute disseminated encephalomyelitis including unknown TTO)	76	57.43	30	0.15	1.32 (1.04 - 1.66)
GBS Overall (including unknown TTO)	992	807.57	14	4.52	1.23 (1.15 - 1.31)

Rapporteur assessment comment:

The following AESI had a Observed significantly > Expected : Anaphylaxis type reactions, Angioedema – Hypersensitivity, GBS and Acute disseminated encephalomyelitis. These events, with the except of ADEM, are included in Section 4.8 of the EU-SmPC. ADEM is discussed in 2.3.7.3 of this AR.

Taking into consideration the review of the AESIs, no further action is considered warranted at this stage.

2.3.9. Missing information – Use of VAXZEVRIA in pregnant and breastfeeding women / Use during pregnancy and while breastfeeding

Please note that data on Use in pregnant and breastfeeding women / Use during pregnancy and while breastfeeding is not reproduced here (see Section 16.3.5.1 of the PBRER).

MAH's conclusion on Use of AZD1222 in pregnant women

In summary, the cumulative and periodic reviews up and until 28 December 2022 of all reports of exposure to VAXZEVRIA during pregnancy did not identify any new safety concerns for the mother or baby. The reported adverse events are similar between the pregnant and non-pregnant populations. The results of the O/E analyses for spontaneous abortion (UK reports) suggest that observed cases are less than would be expected in the unvaccinated pregnant women.

Based on these interval and cumulative reviews of the currently available data, it is ASTRAZENECA's opinion that no updates to product labelling or RMP are warranted. Use of VAXZEVRIA during pregnancy remains as Missing information for the product and is closely monitored.

MAH's conclusion on Use of AZD1222 in Breastfeeding women

From the data identified during the reporting period, and also taking into account the cumulative experience, there is no new safety information or a safety concern identified with the exposure to VAXZEVRIA during pregnancy or while breast feeding. Use of VAXZEVRIA in pregnant and breastfeeding women/ Use during pregnancy and while breastfeeding will continue to be considered as Missing information for VAXZEVRIA.

Use of VAXZEVRIA in pregnant and breastfeeding women / Use during pregnancy and while breastfeeding will be primarily investigated in the ongoing non interventional pregnancy Registry Study (D8110C00003) of women exposed to VAXZEVRIA immediately before or during pregnancy as part of the C-VIPER Registry Consortium.

More detailed information is provided in Section 16.4.3.1 of the PBRER.

Rapporteur assessment comment:

During the reporting period, of the total **702 case reports**, there were 41 cases of spontaneous abortion (SAB), 4 with abnormal maternal outcome, 2 still birth, 11 elective abortion and 3 premature births/infants. Pregnancy outcome was not available for the majority of the cases.

A total of **41 pregnancy cases resulted in spontaneous abortion**, of which 39% (16 out of 41) were reports from consumers and 56% (23 out of 41) of the reports were medically confirmed, with 46.3% of the reports being from the UK and 24.4% from Brazil. O/E analysis showed that spontaneous abortions were significantly lower than expected.

Of the **702 pregnancy cases, 541 cases** had reported AEs in both mothers and infants. Most of the AEs reported in these cases were known reactogenicity events (i e, headache, pyrexia, fatigue, chills, myalgia, nausea, pain in extremity and arthralgia). There were 112 cases with 327 AEs that occurred in the paediatric population, the top 3 AEs being: foetal exposure during pregnancy (69), maternal exposure during pregnancy (30) and COVID 19 (10).

During the interval period, there were **12 reports** pertaining to infant exposure to VAXZEVRIA during **breastfeeding**. Overall, 4 cases were serious (of which 1 was medically confirmed). Within these 12 reports, there were 24 events in infants following breastfeeding. Of these 24 events, 16 were serious adverse events. Most frequent reported PTs were fatigue and Pyrexia.

From the data identified during the reporting period, and also taking into account the cumulative experience, no causal relationship could be established between adverse maternal and foetal outcomes and VAXZEVRIA. No safety concerns arise from exposure to breast feeding. This is endorsed.

Taking into consideration the review of the Missing information 'Use of VAXZEVRIA in pregnant and breastfeeding women/Use during pregnancy and while breastfeeding', no further action is considered warranted at this stage.

2.3.10. Missing information – Use of VAXZEVRIA in subjects with severe immunodeficiency / Use in immunocompromised patients

Please note that data on Use in subjects with severe immunodeficiency / immunocompromised patients is not reproduced here (see Section 16.3.5.2 of the PBRER).

Request

In the next PSUR, the MAH should verify the PTs reported in fatal cases, especially regarding TTS and Thrombocytopenia.

MAH's Summary

Of the 51475 cases cumulatively of subjects with severe immunodeficiency and in immunocompromised patient's reported globally and included in AstraZeneca's post-marketing database. Cases were assessed by age, sex, type of event, and outcome.

Cumulatively 610 cases had a fatal outcome. COVID-19 and related events were reported in (1210 cases) 2.35% of the patients.

The review of available data from spontaneous reports regarding subjects with severe immunodeficiency and in immunocompromised patient's did not identify an index case or other evidence of a new or emerging signal.

The review and analysis of the available literature did not highlight any particular safety concerns with VAXZEVRIA when used in immunocompromised patients. There were no articles identified with a specific reference to any new safety concerns associated with VAXZEVRIA. However a reduced response to the primary vaccination series in ICPs compared with non-ICPs has been reported from literature studies, based on immunogenicity and VE data for VAXZEVRIA. Overall, current data suggests that an additional dose increases the immune response rate of the primary vaccination series in ICPs. In several jurisdictions, ICPs have been prioritised for additional doses after the standard primary vaccination series.

MAH's Conclusion

The cumulative review of the Use of VAXZEVRIA in subjects with severe immunodeficiency/Use in immunocompromised patients did not indicate any new safety concerns. Overall, the review of the currently available data did not reveal any new safety information in immune-compromised individuals that has not been identified in the overall population.

Use of VAXZEVRIA in subjects with severe immunodeficiency/Use in immunocompromised patients will be monitored in the Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU]) and systematic literature review (D8111R00020). Refer to Appendix 4 for additional details.

AstraZeneca will continue to monitor safety information in vaccinees with severe immunodeficiency and in immunocompromised patients as part of the routine safety surveillance activities for VAXZEVRIA and take further actions as deemed appropriate.

Rapporteur assessment comment:

As requested the MAH has verified the PTs reported in fatal cases, especially regarding TTS and Thrombocytopenia.

The 610 deaths (1.18%) reported cumulatively. Of the 610 reports, majority (90.7%) of the vaccinee age was ⩾ 50 years (median age 70 years). Most frequently (⩾ 10) reported events (PTs) with fatal outcome were: Death: 129; Pulmonary embolism: 58; Dyspnoea: 37; COVID-19: 35; Myocardial infarction: 27; Cardiac arrest: 27; Vaccination failure: 25; Cerebral haemorrhage: 24; Sudden death: 22; COVID-19 pneumonia: 22; Cerebrovascular accident: 22; **Thrombocytopenia: 22**; Pyrexia: 20; Malaise: 20; Pneumonia: 19; Multiple organ dysfunction syndrome: 17; Headache: 16; Thrombosis: 15; Vomiting: 14; Fatigue: 13; Cerebral venous sinus thrombosis: 12; Cardio-respiratory arrest: 12; Acute myocardial infarction: 11; Nausea: 11; Deep vein thrombosis: 11; Adverse event following immunisation: 10; **Immune thrombocytopenia: 10**; and Sepsis: 10.

The review of the cases did not bring new safety information. An imbalance of cases spontaneously reported in women was previously observed and is confirmed with 74% of reports in females.

A search in the literature identified following articles: 1 article showed evidence of reduced COVID-19 vaccine (BNT162b2, ChAdOx-1S) effectiveness in immunocompromised persons, 5 articles showed evidence of reduced immunogenicity of vectored and inactivated WHO Emergency Use Listing (EUL) COVID-19 vaccines in immunocompromised persons, 2 articles showed evidence on the immunogenicity of an additional COVID-19 vaccine dose in immunocompromised persons, 1 article showed neutralizing antibody response after a third SARS-CoV-2 vaccine dose, 1 article showed risk-adjusted vaccine effectiveness (VE) in solid organ transplant (SOT) recipients following SARS-CoV-2 vaccines organ transplant (SOT)

Based on the literature review and analysis, no new safety concerns were identified, other than VAXZEVRIA's known safety profile.

In conclusion, the review of pharmacovigilance data and literature did not identify new safety concerns in subjects with severe immunodeficiency. The efficacy of the vaccine in this population is uncertain and alternate protective measures should be maintained.

Taking into consideration the review of information on the 'Use of VAXZEVRIA in subjects with severe immunodeficiency / Use in immunocompromised patients', no further action is considered warranted at this stage.

2.3.11. Missing information (EU-specific) – Use in patients with autoimmune or inflammatory disorders

Please note that data on Use in patients with autoimmune or inflammatory disorders is not reproduced here (see Appendix R3 – Section 2.3.1 of the PBRER).

Summary of data

A search in the MAH's Global Safety database identified a cumulative total of **22,310 reports** in individuals with underlying autoimmune or inflammatory disorders (649 during the reporting period). There were 76.7% of the cases reported in females. There were **210** (0.9%) cases with **fatal outcome**.

Of the 22310 case reports, 725 (3.2%) cases involved 774 events of exacerbation/flares of the underlying auto-immune or inflammatory disorder following vaccination. Adverse events which are >10 included: Condition aggravated (101), Crohn's disease (43), Multiple sclerosis (35), Psoriasis (30), Rheumatoid arthritis (23), Fatigue (18), Headache (13), Psoriatic arthropathy (12), Colitis ulcerative (12), Asthma (11), Pain (10), Arthralgia (10), Dizziness (10) and Nausea (10).

The MAH did not provide information from the literature

MAH's conclusion

From the data identified during the interval and cumulative periods, an increased risk of exacerbation/flares of the underlying disease following vaccination was not seen. A difference in the safety profile of this population from that of the overall VAXZEVRIA vaccinated population was not seen. Use of VAXZEVRIA in patients with autoimmune and/or inflammatory disorders will continue to be monitored as part of surveillance activities for VAXZEVRIA.

Rapporteur assessment comment:

A search in the MAH safety database identified 22,310 cumulative cases, including 649 cases during the reporting period. The review of these new cases did not bring new safety information.

The proportion of cases in individuals with autoimmune or inflammatory underlying condition and reporting a flare of their condition remains small (3.2%).

No new important safety information came from the review of these cases.

Taking into consideration the review of the missing information 'Use in patients with autoimmune or inflammatory disorders', no further action is considered warranted at this stage.

2.3.12. Missing information – Use of VAXZEVRIA in subjects with severe and / or uncontrolled underlying disease / Use in frail patients with co-morbidities

Please note that data on Use in frail patients with co-morbidities is not reproduced here (see Section 16.3.5.3 of the PBRER).

MAH's conclusion

This review of the cumulative and periodic data in individuals with frailty, severe and/or uncontrolled underlying disease and comorbidities did not reveal any new safety concern. There was no increase in events seriousness (for all discussed topics) or severity.

In individuals with frailty, there was an increase of 51 fatal cases (34 new, 17 follow ups) reported cumulatively from the previous PBRER (88) covering the period 29 December 2021 to 28 June 2022. Due to search strategy update 51 cases were retrieved in the current cumulative output. Of note, out of the 34 new reports received by AstraZeneca, of which 32 had the onset date at an earlier point during 2021 before the start of the reporting interval. On review, there were no significant safety concerns identified.

In individuals with dispensing of or reimbursement for durable medical equipment, there was an increase of 54 fatal cases (18 new, 36 follow ups) reported cumulatively from the previous PBRER (251) covering the period 29 December 2021 to 28 June 2022. Due to search strategy update 54 cases were retrieved in the current cumulative output. Of note, out of the 18 new reports received by AstraZeneca, of which 16 had the onset date at an earlier point during 2021 before the start of the reporting interval. On review, there were no significant safety concerns identified.

In summary, no abnormal trends or significant new safety concerns were identified in the interval period with respect to the cumulative data. Majority of the adverse events reported in patients with frailty and/or uncontrolled underlying disease were either related or heavily confounded by patients' medical history and underlying disorders or were consistent with the known safety profile of the vaccine.

This cumulative and periodic review of currently available data from the use of VAXZEVRIA in subjects with frailty, severe and/or uncontrolled underlying diseases and comorbidities did not identify any new safety concerns.

This topic will continue to be considered missing information and will be kept under close surveillance by AstraZeneca.

Use of VAXZEVRIA in subjects with severe or uncontrolled underlying disease/Use in frail patients will be investigated primarily in the ongoing non-interventional post-marketing observational study using existing secondary health data sources D8111R00006 [EU/UK]) study of subgroups exposed to VAXZEVRIA. Refer to Appendix 4 of the PSUR#4 for additional details.

Rapporteur assessment comment:

This review presented the cumulative and periodic data in individuals identified as having severe and/or uncontrolled underlying disease or were identified as frail for the following categories.

Frailty: Cumulatively, 1509 cases (768 cumulative cases previously) were identified, out of which majority (75.9%) were reported in females. Of these 1509 cases, 1069 (70.8%) were serious, reported seriousness criteria were medically important (779), disability (301), hospitalization (156), life threatening (59), and death (140).

Hip Fracture: Cumulatively, 30 cases (26 cumulative cases previously) were reported. Of the 30 cases, 70% (21 cases) were reported in females and 30% (9 cases) were in males. Age ranged from 18 years to <65 years in 33.3%, 65+years in 60.0% and gender was missing in 6.7% of the reports. Of these 30 cases, 23 (76.7%) were serious, reported seriousness criteria were medically important (17), disability (5), hospitalization (8), life threatening (2), and death (5).

Cachexia: Cumulatively, 221 cases (198 cumulative cases previously) were reported. Of the 221 cases, 161 (72.9%) were serious, reported seriousness criteria were medically important (93), hospitalization (59), disability (37), life threatening (16), and death (11).

Bladder Incontinence: Cumulatively, 5194 cases (4584 cumulative cases previously) were reported: 66.9% (3475) were reported in females. Age ranged from 0 to <18 years in 0.1% (3) of the reports; 18 to <65 years in 65.8% (3420) cases, 65+ years in 25.3% (1314) and age was not reported in the remaining 8% (414) of cases. The majority of reports (79.9%) were from consumers with the remaining 20.1% being medically confirmed. 3759 (72.4%) cases were serious, reported seriousness criteria were medically important (2910), disability (574), hospitalization (1074), life threatening (291), and death (174).

Dementia: Cumulatively, 3611 cases (2802 cumulative cases previously) were reported: 66.4% (2396) were reported in females. , 2580 (71.4%) were serious, reported seriousness criteria were medically important (1805), disability (662), hospitalization (781), life threatening (251), and death (210).

Long term Frailty: Cumulatively, 950 cases (789 cumulative cases previously) were reported: 60.8% (578) were reported in females. Age ranged from 0 to <18 years in 0.1% (1 case); 18 to <65 years in 66.2% (629) cases; 65+ years in 23.1% (219) cases and age was not reported in the remaining 9.6% (91) of cases. 831 (79.0%) were serious, reported seriousness criteria were medically important (615), disability (183), hospitalization (250), life threatening (96), and death (66).

Metastatic Cancer: Cumulatively, 446 cases (789 cumulative cases previously) were reported: Age ranged from 0 to <18 years in0.2% (1 case); 18 years to <65 years in 50% (223) of the reports and 65+ years in 43.9% (196) cases. 380 (85.2%) were serious, reported seriousness criteria were medically important (258), disability (43), hospitalization (138), life threatening (51), death (65). Cases may have met more than one criteria for seriousness.

Supplemental Oxygen Use: Cumulatively, 3910 cases (2987 cumulative cases previously) were reported: 2853 (73.0%) were serious, reported seriousness criteria were medically important (1782), hospitalization (1303), disability (347), life threatening (409), and death (325).

Palliative Care: Cumulatively, 122 cases (105 cumulative cases previously) were reported: Age ranged from 18 years to <65 years in 23.0% (28), and 72.1% (88) in 65+ years. 119 (97.5%) were serious, reported seriousness criteria were medically important (69), hospitalization (56), disability (21), life threatening (27), and death (68). Cases may have met more than one criteria for seriousness.

Pressure Ulcers: Cumulatively, 4254 cases (3966 cumulative cases previously) were reported. 3007 (70.7%) were reported in females. Age ranged from 18 years to <65 years in 73.9% (3143), 17.7% (753) in 65+ years, 0.2% (9) in 0 to <18 years, 0.5% (22) in adult, and 0.1% (6) in elderly. 2363 (55.5%) were serious, reported seriousness criteria were medically important (1924), hospitalization (395), disability (334), life threatening (99), and death (59).

No abnormal trends or significant new safety concerns were identified in the interval period with respect to the cumulative data. Majority of the adverse events reported in patients with frailty and/or uncontrolled underlying disease were either related or heavily confounded by patients' medical history and underlying disorders.

No new important safety information came from the review of these cases.

Taking into consideration the review of the missing information 'Use of VAXZEVRIA in subjects with severe and / or uncontrolled underlying disease / Use in frail patients with co-morbidities', no further action is considered warranted at this stage.

2.3.13. Missing information –Use of VAXZEVRIA with other vaccines / Interactions with other vaccines

Please note that data on co-administration is not reproduced here (see Section 16.3.5.4 of the PBRER).

A cumulative review of cases reporting AEs after vaccination with VAXZEVRIA with other vaccines, including seasonal Influenza vaccine, Herpes vaccines, Pneumococcal vaccine and Varicella vaccine was undertaken.

Co-administration with Influenza Vaccine

Reporting interval: 855 cases (71.0% spontaneous cases, 28.8% non-interventional/post-marketing cases, and 0.2% from study D8110C00001) including 3644 AEs were identified.

Cumulative search: 13679 cases (89.1% spontaneous cases, 10.7% non-interventional/post-marketing cases, 0.09% literature, and 0.03% Clinical trial) including 59047 AEs were identified.

Co-administration with Herpes vaccine

Reporting interval: There were no cases were reported involving use of VAXZEVRIA with Herpes vaccine in the reporting interval.

Cumulative search: 3 cases were identified.

Co-administration with Pneumococcal Vaccine

Reporting interval: 70 cases (all spontaneous) including 172 AEs were identified.

There was 1 case with fatal outcome reported during this period. The assessment of the fatal case is presented below:

Case ID [redacted]: This consumer report concerns a 71 years old patient of unknown gender. The medical history was not reported. On 09 February 2021, the patient received first dose of VAXZEVRIA for an unknown indication. On 26 April 2021, the patient received second dose VAXZEVRIA for an unknown

indication. On 11 June 2021, the patient started treatment with Pneumococcal Vaccine. On 20 October 2021, the patient experienced Guillain-Barre syndrome. On an unknown date, the patient experienced Hypertension and Pneumonia aspiration. The patient died from the event of Guillain-Barre syndrome. It was not known whether an autopsy was performed. The cause of death was Guillain-Barre syndrome and Pneumonia aspiration.

MAH's Comment:. This case concern a 71 year old subject with fatal outcome event caused by GBS and pneumonia aspiration following two doses of Vaxzevria and one dose of Pneumococcal Vaccine. Due to limited information on medical history and concomitant medication, the evaluation did not find evidence to suggest a causal relationship between the events and VAXZEVRIA.

Cumulative search: 445 cases (93.9% spontaneous cases, 5.8% non-interventional/post-marketing cases, and 0.2% literature cases) including 1774 AEs were identified.

Co-administration with Varicella vaccine

Reporting interval: 42 cases (all spontaneous) including 114 AEs were identified.

Cumulative search: 96 cases (94.8% spontaneous cases, 4.2% non-interventional/post-marketing cases, and 1.0% Clinical trial) including 316 AEs were identified.

MAH's discussion

The most common adverse events reported of VAXZEVRIA when co-administered with other vaccines were similar to VAXZEVRIA when given alone. In most cases, there was limited information. There were no additional reports received regarding Use of VAXZEVRIA with other vaccines.

At the end of the reporting period, this missing information is reclassified in the Core RMP and removed from the list of safety concerns and the justification for removal is presented below:

Adequate safety data are available to evaluate whether the VAXZEVRIA safety profile differs when taken concomitantly with other vaccines. The safety of VAXZEVRIA taken concomitantly with other vaccines was evaluated based on the cumulative post-marketing experience as of 28 December 2022 in individuals who concomitantly received non-covid-19 vaccines including 13679 reports with influenza vaccines, 3 reports with herpes vaccines, 445 with pneumococcal vaccines and 96 reports with varicella vaccines. There is no evidence to suggest that the use with other vaccines results in a specific safety concern, or a different outcome to previously identified risks. Furthermore, there is no reasonable expectation that ongoing pharmacovigilance activities could further characterize the safety profile with respect to interactions with other vaccines. Therefore, interactions with other vaccines is no longer considered relevant for inclusion as missing information.

MAH's conclusion

Based on the evaluation of the available data during the reporting period and considering the cumulative experience, this missing information of: Use of AZD1222 with other vaccines is removed from the list of safety concerns.

Rapporteur assessment comment:

A cumulative review of cases of concomitant administration of Vaxzevria with seasonal Influenza vaccine, Herpes vaccines, Pneumococcal vaccine and Varicella vaccine was performed.

Among the co-administration subset, majority of the reported events were mainly reactions as seen with Vaxzevria alone and are mainly consistent with the known Vaxzevria safety profile. No increase in severity/frequency has been described but this will be further assessed in the PhV plan.

The MAH has removed the missing information of: Use of AZD1222 with other vaccines from the list of

safety concerns based on the evaluation of the available data during the reporting period and considering the cumulative experience. This is not endorsed.

It is acknowledged that the review of spontaneous data on co-administration did not reveal any new significant information. However, considering that this issue will be assessed through the PASS using EU/UK databases (D8111R00006), 'Interactions with other vaccines' should remain in the missing information until the results of the study are available. This has been discussed and agreed in the variation II/0084/G.

The MAH is requested to review the list of safety concerns and maintain Interactions with other vaccines in the missing information. However, it is agreed that data from spontaneous reporting should not be discussed in next PSURs unless significant new information arises. Relevant data from the literature should be discussed if any [Issue for the next PSUR]

2.3.14. Missing information (EU-specific) – Long-term safety

Please note that data on long-term safety is not reproduced here (see Appendix R3 – Section 2.3.2 of the PBRER).

Evidence source

There are no known risks with a potentially delayed onset, with the exception of the theoretical concern of VAED/VAERD. There is currently no evidence suggesting an adverse long-term safety concern.

At 6-months follow-up from Study D8110C00001 the AEs observed were consistent with the safety findings at the primary analysis. In the VAXZEVRIA group, a small proportion of SAEs and AESIs were reported, with no clinically meaningful findings. Overall, VAXZEVRIA remains well-tolerated up to 6 months post dose.

Population in need of further characterisation

Long-term safety will be evaluated through follow-up in ongoing clinical studies (D8111R00006, COV001/002/003/004/005 and D8110C00001) in the VAXZEVRIA clinical development programme.

MAH's conclusion

Taking into account the cumulative experience globally, no new risks with a potentially delayed onset have been observed or are anticipated related to VAXZEVRIA and the long-term safety is no longer considered as missing information and removed from the list of safety concerns.

Rapporteur assessment comment:

The MAH has removed the missing information of Long-term safety from the list of safety concerns based on the cumulative experience. This is not endorsed.

It is acknowledged that the review of spontaneous data on co-administration did not reveal any new significant information. However, no signal related to long-term safety has been raised. However, it is an area of missing information which is investigated in the PASS study D8111R00006 using EU/UK databases. 'Long-term safety' should remain in the missing information until the results of the study (feasibility study report and/or final study report) are available. This has been discussed and agreed in the variation II/0084/G.

The MAH is requested to review the list of safety concerns and maintain Long-term safety in the missing information. [Issue for the next PSUR]

2.3.15. Other safety issue – Fatal events

Please note that data on fatalities is not reproduced here (see Section 6.3.2 of the PBRER).

MAH's conclusion

From the review of data available during the reporting period for all fatal case reports (including sudden death) and also taking into account the cumulative experience along with the O/E analysis of fatal cases there is no new safety information identified on this topic in association with VAXZEVRIA.

Rapporteur assessment comment:

Cumulatively through 29 December 2020 to 28 June 2022, there have been 6897 fatal cases (6399 cumulative cases previously). Out of 6897 cases, age of vaccinees was reported in 5711 cases (83%). In 2933 (51%) of the 5711 case reports, the vaccinees were aged 65 years and above. The median age of the fatal cases was 65 years. Out of 6897 cases, gender was reported in 6510 cases (94%). There were 2945 females (45%) and 3565 males (55%).

Cumulatively, of the 6897 case reports with fatal outcome, 4237 (61%) were medically confirmed and 2660 (39%) were consumer reports. **Cumulatively, 58 fatal cases were reported with booster dose (including 41 interval cases)**. Of the 6897 cases, 402 (6%) were reported as sudden Death.

Cumulative O/E analyses were conducted for fatal cases, and were stratified by age group and gender where administration data was available. **O/E was significantly below 1 for all subgroups.**

Cumulatively, **out of 402 cases reported as sudden death**, 222 (55.2%) cases contained the PT of sudden death, 179 (44.5%) cases contained the PT of sudden cardiac death and 1 (0.25%) case reported sudden unexplained death in epilepsy. 336 (84%) cases were medically confirmed and 66 (16%) were consumer reports. TTO was available in 190 (47%) cases, including 56 cases (29%) with a time to death ranging from 0 to 263 days after receiving the first dose of the vaccine and 16 cases (40%) where time to death ranged from 0 to 121 days after receiving the second dose. The causes of death were identified in 255 cases (63%) and included the mainly sudden cardiac death; dyspnoea; pulmonary embolism (PE); pyrexia; cardiac arrest; myocardial infarction; fatigue; acute myocardial infarction; cardio-respiratory arrest. In 67% of the cases, the cause of the deaths was due to pre-existing medical condition or risk factors. Upon review of the cases cumulatively, no new trend or pattern was observed in the cases reported with sudden death.

Among the cases reporting fatal outcome, no specific pattern regarding underlying conditions or cause of death could be identified. **No new safety concerns were identified.**

Taking into consideration the review of the risk 'fatal events', no further action is considered warranted at this stage.

2.3.16. Other safety issue – Lack of efficacy from post-marketing

Please note that data on lack of efficacy is not reproduced here (see Section 6.3.1 of the PBRER).

MAH Conclusion

Review of all the lack of efficacy reports did not demonstrate any specific trend or safety information associated with use of VAXZEVRIA. There was a decrease in the number of case reports for lack of efficacy during this **interval** (**2,716**) compared to the previous PBRER (16,964). Cumulatively, of the 25,335 lack of efficacy reports, there have been 160 fatal cases. [There were **8 fatal cases** in the interval reporting period]. Also noted that 82.8% of the reports (2,248/2,716) during the reporting interval and 87.2% (22,099/25,335) of the reports cumulatively were from Austria. This is due to a local

reporting system where cases from the epidemiological reporting system for COVID-19 are linked with the vaccination passport and submitted to Eudravigilance/AstraZeneca in bulk.

Rapporteur assessment comment:

No new important safety information was identified on lack of efficacy/effectiveness in post-marketing experience. No further action is considered warranted at this stage.

2.3.17. Health Authority requests – Menstrual disorders

Please note that Menstrual disorders data is not reproduced here (see Section 15.2.2 of the PBRER)

Request: The MAH is requested to provide and discuss an updated literature review of Menstrual disorders. Besides, the MAH is requested to further discuss the serious cases requiring hospitalization and the cases resulting in death.

AstraZeneca response: Please refer to Section 15.2.2 in the PBRER (reporting period 29 June 2022 to 28 December 2022).

MAH's summary

Cumulative review of case reports

Cumulatively, a total of 419 reports of Menstrual disorders serious cases requiring hospitalization with the use of VAXZEVRIA have been received, and 2 cases resulting in death. The median age was 41 years for Menstrual disorders serious cases requiring hospitalization and 44 years for cases resulting in death. A total 195 cases of Menstrual disorders serious cases requiring hospitalization occurred after first dose, 155 after second dose, and one case after booster dose. Amongst 125 events with reported outcome 'recovered' or 'recovered with sequelae,' the event duration was reported in 72 [57.6%] events. The median duration of events was 7 days (0-273 days), while 39 (54.1%) had resolved within 8 days of onset. Of the total number of case reports cumulatively of Menstrual disorders serious cases requiring hospitalization, 77 (18.4%) were medically confirmed.

The TTO median was 16 days and among the events with TTO most of them (58.7%) occurred within 28 days post vaccination. Most of events (54.6%) were reported in age groups 45-54 (26.4%), 35-44 (26%), and 25-34 (23.1%).

The most reported menstrual disorders category was 'other' followed by heavy menstrual blood loss, and amenorrhoea/oligomenorrhoea. Menstrual disorders can be very diverse and different per individual. Although the reported menstrual events were categorised in 8 categories, many of the reports contained multiple menstrual events and fell into multiple categories.

The most frequent co-reported AEs were known systemic and local reactions. These are very common reactions and were to be expected.

A total 47.7% of menstrual disorder events had not resolved at the time of reporting. It is possible that, women reported their complaints before they fully recovered which is understandable since menstrual disorders such as amenorrhoea and irregular menstrual cycle generally can take a longer time to recover.

From the review of the medically confirmed cases requiring hospitalization with complete case details, no index case was found. All cases listed confounders or had insufficient information such as treatment details, medical history and/or concomitant medications.

Literature summary

As pointed out in Von Woon et al 2022, Lagana et al 2022, Muhaidat et al 2022, Wang et al 2022 [D], Dellino et al 2022, Edelman et al 2022, Caspersen et al 2023, Trogstad et al 2022, Farland et al 2022,Qashqari et al 2022, Molina -López et al 2022, Zhang et al 2022 articles, there seems to be an association between COVID-19 vaccination (regardless of type) and menstrual disorders. Overall, the abnormalities were self-limiting. The study by Abdel -Moneim et al 2022 found that there was no association between menstrual disorders and vaccination.

Many of the literature available recommended future work to examine the potential biological mechanisms that may explain an association between COVID-19 vaccination and menstrual disorders. Some authors propose the effect of immune response activation on menstrual cycle, systemic inflammatory response, stress, impact on HPO axis, hypercoagulative state and vaccine-induced thrombocytopenia.as an explanation of menstrual changes. The design of most studies reviewed did not consider control groups, hence it is impossible to make causal inferences from them. The actual incidence rate of menstrual disorders with COVID-19 vaccination is still unclear due to problems of overestimating, underestimating and biases. However, there seem to be more calls for studies designed particularly to aid the determination of causal inference and also confirm biologic mechanisms that will adequately explain the effects of COVID vaccination on menstrual disorders.

Overall Summary

Upon further review of the serious cases requiring hospitalization and the cases resulting in death, there was insufficient information on menstrual history, investigations performed, and treatment details available in these reports. These findings do not provide more insight on the possible relationship between VAXZEVRIA and menstrual disorders.

From the review of the literature, many of the literature available recommended future work to examine the hypothesized biological mechanisms that may explain an association between COVID-19 vaccination and menstrual disorders.

In summary, the review of available data from spontaneous reports and literature did not identify an index case or other evidence of a new or emerging signal.

Conclusion

The information from this updated cumulative review found insufficient evidence for a new or emerging signal regarding Menstrual disorders and VAXZEVRIA. No changes to the CDS or RMP are recommended, and Menstrual disorders will continue to be monitored as part of AstraZeneca's ongoing surveillance activities.

Rapporteur assessment comment:

As requested the MAH provided and discussed an updated literature review of Menstrual disorders. The MAH further discussed the serious cases requiring hospitallzation and the cases resulting in death.

Cumulative review of the cases requiring hospitalization and the cases resulting in death (DLP 28 December 2022)

Cumulatively**, a total of 21651 cases** have been identified and **a total of 28063 adverse events** of interest were reported. Out of 21651 cases, **423 cases with 520 events** of Menstrual disorders were reported with the **seriousness criteria of hospitalisation and 2 further cases with 2 events resulted in death**. In 4 cases gender was reported as male (coding error).

Of the remaining 419 (516 events) serious cases requiring hospitalization:

• ***Dose***: **195 (46.6%), 155 (37.1%), 0 and 1** cases were **reported after the first dose, second dose,** first + second dose and third dose, respectively.

• ***Age***: the median age was 41 years. Age was known for 462 events: ~90% events were reported in women aged 25-54 years and ~10% events were reported in women aged from 55-65 years.

• ***Time to Onset***: TTO was known for 489 events (95%):

~62% of the events with known TTO were reported within 28 days post vaccination; **median TTO was 16 days**.

• ***Seriousness***: 516 serious events requiring hospitalization, additional reported seriousness criteria were medically important event (258 [50%]), disability (115 [22.3%]), congenital anomaly (9 [1.7%]), life threatening (40 [7.7%]).

Reported PTs (n=516) : The menstrual disorder category of **'Other'[10] (33.9%)** was the most reported menstrual disorders category followed by **Heavy menstrual blood loss (28.5%)** and **Amenorrhoea/oligomenorrhoea (10.7%).**

Among category 'other': most frequently reported PTs were **Vaginal haemorrhage (109),** Menstrual disorder (45), Uterine haemorrhage (14). Most of the events (59.4%) were resolved/resolving/resolved with sequalae. Out of 34 events with a known duration, 24 (70.6%) had resolved within 14 days of onset, presumably within one menstrual cycle.

Heavy menstrual blood loss: Most frequently reported LLTs was Heavy periods (52), followed by Heavy menstrual bleeding (22), Bleeding menstrual heavy (21), Prolonged heavy periods (15), and Menorrhagia (15). For most women the duration of the bleeding was either unknown or the woman was not recovered yet (53.1%). However, in the medically confirmed reports 50% heavy menstrual blood loss events had resolved. Out of 29 events with a known duration, 14 (48.3%) had a bleeding duration of less than 14 days.

Amenorrhoea/oligomenorrhoea: Most frequently reported LLT was Irregular periods (23), followed by Menstrual cycle shortened (7), Menstruation irregular (7), Menstrual irregularity (6), and Frequent periods (4). For most women the duration of the bleeding was either unknown or the woman was not recovered yet (74.5%).

• **Outcome**: Outcome was known for 465 (90.11%) events.

Majority of the events were not recovered at time of reporting (246 events [52.90%]). A total of 219 events (47.09%) had resolved/resolved with sequelae/resolving. When known (in 67 events), **the median duration of events was 6.5 days (0-273 days),** while 35 (52.2%) had resolved within 8 days of onset.

Of the total 28063 events of Menstrual disorders reported, 2 events (0.01%) in **2 cases were reported with fatal outcome** (DLP 28 December 2022) cumulatively through DLP 28 December 2022, and both were consumer reports. These cases were confounded by underlying diseases and lacked information for causality assessment.

Recurrence case reports: There were no serious cases requiring hospitalization indicating a recurrence.

• **Medically confirmed cases**: **77 (18.4%) cases were medically confirmed.** The median TTO in these cases was 29.5 days. **Of 52 case reports without any reported confounders the reason for hospitalization was attributed to the event vaginal haemorrhage in 32 (61.5%) reports.** The median age was 35 years. 37 (71.1%) cases had reported outcome recovered/recovering/recovered with sequelae. When known (in 7 cases), the median duration of events was 4 days (1-30 days), while 5 (71.4%) had resolved within 8 days of onset.

[10] Anovulatory cycle, Menstrual disorder, Menstrual headache, Vaginal haemorrhage, Uterine haemorrhage, Abnormal uterine bleeding

Literature

The MAH identified and discussed following publications:

A global, retrospective cohort study (Edelman et al, 2022) of prospectively collected data compared vaccinated individuals [vaccinated cohort : BNT162b2 n=9929; mRNA-1273 n=2608; **ChAdOx1 nCoV-19 n=1353**; Ad26.COV2.S n=283] with the unvaccinated group and showed an adjusted increase in menstrual cycle length of less than one day with both first and second vaccine doses. Individuals who received two doses of a covid-19 vaccine in a single cycle had an adjusted increase in cycle length of 3.70 days compared with the unvaccinated. Cycle length changes did not remain in the cycle after vaccination, except in the group that received two vaccine doses in one cycle, where cycle length changes were attenuated but still increased compared with the unvaccinated group. **Cycle length changes due to covid-19 vaccination appear similar across the different vaccine types. No differences found in menses length in any group of vaccinated individuals, compared with the unvaccinated cohort.**

A retrospective questionnaire based study (Dellino et al 2022) conducted on Italian patients (100 women aged 18–45) vaccinated for SARS-CoV-2 in the period between April 2021 and April 2022. Forty-three (43%) participants received Pfizer/ BioNTech mRNA vaccine, 32% received Moderna mRNA vaccine and **25 % received the ASTRAZENECA vaccine**. The average onset of menstrual irregularity was 13 days (1–18) from inoculation of the vaccine. Of these, 90% were after the second dose and 10% were after the third dose for an average duration of 45.5 days; 15% of the total of these women reported irregularities already after the first dose of vaccine, which reappeared after the second/third dose. Twenty-three (23%) had menstrual delay and 77% had abnormal uterine bleeding (AUB), of which 47% had metrorrhagia, 30% had menometrorrhagia and 23% had menorrhagia. For AUB the highest numbers are with ASTRAZENECA vaccine, while for delayed menstruation the numbers are less than with other vaccines. On limitation of the study is that it was not possible to consider a control c-group in Italy during the period under review. Menstrual irregularities were observed in women of childbearing age in which menstrual irregularities occur in an estimated 14% to 25% of women.

A questionnaire-based study (Abdel -Moneim et al 2022) in Saudi Arabia on 956 women, aged from 18 to 40 years old, to screen females who have been infected with SARS-CoV-2, regardless of their vaccinal status. The current study did not find any significant variation when using different vaccines with single or double doses. **Authors conclude that there is no association between COVID-19 vaccination and the development of menstrual cycle changes.** Authors propose that SARS-CoV-2 infection might be responsible for extending menstrual changes beyond six months, as detected in the current study.

Literature suggesting mechanism

The proposed mechanisms from published literature are provided below:

Roncati et al 2022 propose that after vaccination, a **hypercoagulative state** may rarely occur and involve fenestrated capillaries in the pituitary, where the blood flow is significantly decelerated. The pre-existing interconnected small branches and the trans-sellar arterial blood supply usually are sufficient collaterals, but sometimes they could be inadequate to the high blood demand from the pituitary gland, thus promoting the onset of micro ischemic events and subsequent menstrual abnormalities.

Kurdoglu 2021 proposes that **vaccine-induced thrombocytopenia**, immune system activation, stress, anxiety, and depression during the pandemic could be possible mechanisms for menstrual disorders.

Wang et al 2022 The immune response induced by both mRNA and adenovirus-vectored vaccines may **temporarily affect the hypothalamo-pituitary-ovarian (HPO) axis**, which could lead to menstrual disturbances.

Caspersen et al 2023 and Farland et al 2022 propose the effect of **immune response activation on menstrual cycle driving hormone** as an explanation of menstrual changes. The pathophysiological mechanisms are yet unknown.

Farland et al 2022 additionally propose that changes in their menstrual cycle following VAXZEVRIA vaccination, may be due to normal menstrual cycle variability observed in the general population. Authors mention several hypothesized mechanisms through which vaccinations may influence menstrual cycles, including **inflammation, endogenous hormone levels, and/or immune cells in the endometrium**.

Conclusion

Overall, the review of serious menstrual disorder cases (n=419) requiring hospitalization shows a temporal relationship where majority of the cases reported after first (46.6%) and second dose (37.1%) and majority of the events occurred within 28 days post vaccination. Most frequently reported events were 'Others (i.e. Vaginal haemorrhage, Menstrual disorder, …)' (33.9%) followed by Heavy menstrual blood loss (28.5%) and Amenorrhoea/oligomenorrhoea (10.7%). Majority (52.90%) of the events were not recovered at time of reporting. Only a limited number of cases (18.4%) were medically confirmed and had TTO of 29.5 days. In the literature, two studies suggested that COVID-19 vaccination may be associated with menstrual disorders and one study did not observed such an effect. Additionally in the literature, few observational and interventional studies suggest a range of plausible mechanisms of action. However, the exact mechanism of action of Vaxzevria to cause menstrual disorders remains to be elucidated. Here again, the studies relate to a wide range of menstrual disorders. Moreover, the studies present some limitations and biases, and mainly include mRNA vaccines.

In conclusion, the review of menstrual disorder cases requiring hospitalization/death and literature did not bring any new significant information on menstrual disorders and Vaxzevria. **Taking into consideration the review of the menstrual disorder cases requiring hospitalization/death and literature, no further action is considered warranted at this stage. More relevant information is expected to be provided from the updated review of the literature.**

2.3.18. Health Authority requests – Hearing loss (HL)

Please note that Hearing loss data is not reproduced here (see Section 15.2.8 of the PBRER)

Request: The MAH is requested to provide and discuss an updated review of hearing loss cases with a recovered with sequelae or not recovered outcome.

AstraZeneca response: Please refer to Section 15.2.8 in the PBRER (reporting period 29 June 2022 to 28 December 2022).

MAH's Summary

Cumulatively till 28 December 2022, a total of 1034 reports of HL with a outcome of 'Recovered with sequelae' or 'Not recovered' with the use of VAXZEVRIA have been received, of which 1021 (98.7%) of the 1034 cases were reported from spontaneous sources.

486 (69.5%) of the reported events occurred after first dose, 208 (29.8%) after second dose and 5 (0.7%) after booster. The review of HL cases post COVID-19 booster dosing did not show any significant safety concern.

Of the 1034 cases reports, 39 cases were initial ICSRs whereas 995 cases received follow-up information. 127 (12.3%) of the 1034 cases were medically confirmed, and 79.1% of the reported events were serious. In 85 (7.9%) events, HL was reported to cause hospitalization and in 655 (61%) events HL was considered a medically important event. The majority of these cases are from the regulatory authority

source with limited scope of follow up. In addition, the cases have insufficient information about the sequalae that was reported as outcome.

Cumulatively through DLP, distribution of most frequently co-reported events in case reports for HL with outcome of 'Not recovered' or 'Recovered with sequelae' and distribution of most frequently co-reported events in case reports for HL concludes that the most frequently co-reported PTs for HL are Tinnitus, Headache, Dizziness and Fatigue. This is as expected as these PTs often are symptoms related to HL.

Out of 1073 events, 178 events were pertaining to unilateral hearing loss while 25 events were pertaining to bilateral hearing loss. This distribution precludes any trend of a singular etiopathogenesis of a systemic insult (such as parenteral vaccination) which is expected to show either a unilateral or bilateral presentation. This is also supported by the case onset window – majority of the events had onset within 0 to 28 days, however, the TTO ranged widely from 0-455 days, with the median of 5 days.

Five (8.8%) events were identified to have reoccurrence or worsened after the 2nd dose. In the recurrence case, the latency of recurrence was not reported. However, for the worsened event scenario, the latency varied widely (5 days after dose 2 and 1 month after dose 2), which do not suggest any particular trend. Diagnosis details such as audiometry or Tuning fork examination was not available in any of the cases. None of the cases reported any etiological workup. Hence reoccurrence cannot be comprehensively confirmed.

Median age was 55 years (range: 18 to 93 years). Gender was reported in 1006 cases, of which there is a female preponderance (eg, female = 61.4% and male = 38.6%).

Out of the 1034 cases, 5 (0.5%) fulfilled BCC level 1, 1 (0.1%) fulfilled BCC level 2 and 6 (0.6%) fulfilled BCC level 3. Of the 5 cases fulfilling BCC level 1: 4 cases were assessed as possible with limited information and 1 case were assessed as unassessable/unclassifiable with limited information. The one case fulfilling BCC level 2 were assessed as possible with limited information. Of the 6 cases fulfilling BCC level 3: 1 case were assessed as possible with risk factors/confounders and 4 cases were assessed as possible with limited information. Treatment was reported in 6 cases report out of 12 cases with BCC 1-3, treatment included steroids (intratympanic, oral and IV), antibiotics (not specified), ear drops (not specified), oral antivirals, and vitamins. Remaining 6 other case reports did not provide any detail for treatment in their narratives.

On review remaining 1022 cases fulfilling BCC Level 4 and 5, 98 cases were medically confirmed serious, of which 43 cases had additional confounding factors and unlikely related to VAXZEVRIA. In the remaining 55 of the 98 cases, just 4 of them reported HL treatment, such as steroids (3) and corticoids (1), no trend cannot be concluded due to insufficient information. On review of 127 (12.3%) medically confirmed cases, 4 (3.1%) cases met BCC level 1, 1 (0.8%) case met BCC level 2 and 3 (2.4%) of the cases met BCC level 3. The WHO-UMC causality was assessed as follows: Possible with risk factors/confounders in 33 (26%) cases; Possible with Limited information in 62 (48.8%) cases; Unlikely in 13 (10.2%) cases; Unassessable/Unclassifiable with risk factors/confounders in 9 (7.1%) cases; Unassessable/Unclassifiable with limited information in 10 (7.9%) cases.

In summary, on review of available data from AZ safety database of HL did not identify an index case or other evidence of a new or emerging signal.

The annual reporting rate of all cases of HLT 'Hearing loss' (1793 cumulatively) is 0.2/100 000 which is lower than the reported annual incidence of SNHL from an observational study (OBS) done by Nieminen et al 2022, although this is not a direct comparison. The exposure for VAXZEVRIA is 466115644 doses administered (cumulatively through DLP 28 December 2022). In the same study the authors also compared the incidence rate of SNHL following COVID-19 vaccination to the background rates and concluded that there is no evidence of an increased risk of SNHL following COVID-19 vaccination. Other

large observational studies also reported similar findings (Yanir et al 2022 article and Formeister et al 2022).

MAH's Conclusion

This updated cumulative review found insufficient evidence for a new or emerging signal regarding HL and VAXZEVRIA. No changes to the CDS or RMP are recommended for HL, and the Company therefore proposes discontinuation of presentation of this topic in future PBRERs, and monitoring through routine pharmacovigilance and ongoing surveillance activities.

Rapporteur assessment comment:

As requested the MAH provided an updated review and discussion on hearing loss cases with a recovered with sequelae or not recovered outcome.

Cumulative review of hearing loss cases with a recovered with sequelae or not recovered outcome (DLP 22 December 2022)

The MAH's databases search identified **1034 reports of hearing loss with the outcome of recovered with sequelae (75 events) or not recovered (998 events)**. No information on sequalae is available.

Of the 1034 cases (1073 events), 127 (12.3%) were medically confirmed and 849 (79.1%) cases were reported serious. Of these 1034 cases/1073 events:

• **Dose**: **486 (69.5%) cases** were reported **after the first dose**; 208 (29.8%), 5 (0.7%), 0 (0%) and 5 (8.8%) after second, third, fourth and multiple doses [unknown dose in 335 cases].

• **Age/Gender**: The age ranged from 18 to 93 years (**median: 55 years**). 618 (61.4%) cases were reported in females.

• **TTO: median TTO was 5 days**. Most of the cases with known TTO (690; xx%) reported events within 0-28 days after vaccination.

• **Reported PTs**: **hypoacusis** (n=387, 36.05%), **deafness neurosensory** (n=332, 30.94%), **deafness unilateral** (n=178, 16.58%), **sudden hearing loss** (n=89, 8.29%) and deafness (n=48, 4.47%) were the most reported events. Tinnitus (n=620, 34.6%) and headache (n=450, 25.1%) were the most commonly co-reported events.

• **Brighton Collaboration Classification Assessment**: Out of 1034 total cases, **5** (0.58%) cases fulfilled **BCC Level 1** criteria, **1** (0.09%) fulfilled **BCC Level 2** criteria, **6** (0.48%) fulfilled **BCC Level 3** criteria. Majority (98.83%) of the cases fulfilled BCC level 4 criteria. In the remaining 8 cases the occurrence of SNHL was excluded (Level 5).

The MAH's BCC assessment criteria is comparable to updated BCC assessment criteria recently published (March 12, 2023)[11] . A follow-up period of 6 weeks is recommended after each dose of vaccine.

• **WHO-UMC causality assessment** (for cases with BCC level 1-3 = n=12): causality was considered as Possible with risk factors/confounders for 1 case, Possible with Limited information for 9 cases.

• **Recurrence and worsening case reports**: Cumulatively, in 5 (8.8%) out of 1034 case reports, the event of HL occurred after 1st and 2nd dose. Of the 5 case reports, 1 (20%) case report was medically confirmed.

Annual reporting rate

The annual reporting rate of all cases of HLT 'Hearing loss' (1793 cumulatively) is 0.2/100 000 which is

[11] AESI Case Definition in a Companion Guide for Sensorineural Hearing Loss (SPEAC project). https://brightoncollaboration.us/sensorineural-hearing-loss-aesi-case-definition-companion-guide/

lower than the reported annual incidence of SNHL from an observational study (OBS) done by Nieminen et al 2022, although this is not a direct comparison. In the same study the authors also compared the incidence rate of SNHL following COVID-19 vaccination to the background rates and concluded that there is no evidence of an increased risk of SNHL following COVID-19 vaccination. In particular, adjusted incidence rate ratios estimated after 1st and 2nd dose of Vaxzevria were aIRR (95%CI) of 0.4 (0.2-0.8) and 0.6 (0.3-1.4) respectively.

Conclusion

Overall, the review of cases (cumulative, interval and medically confirmed) shows a temporal relationship where majority (69.5%) of the cases reported after first dose and majority of the events occurred within 14 days post vaccination. Median TTO was 5 days. However, out of the 1034 case reports, only **12** (1.16%) cases fulfilled **BCC Level 1-3** criteria and **1014** (98.06%) fulfilled **BCC Level 4** criteria. All of these cases either had confounder or limited information. The annual reporting rate of all cases of HLT 'Hearing loss' (1793 cumulatively) is 0.2/100 000 which is lower than the reported annual incidence of SNHL from an observational study (OBS) done by Nieminen et al 2022, although this is not a direct comparison.

Available data does not raised any new safety signal.

Taking into consideration the review of the previous request for monitoring Hearing loss, no further action is considered warranted at this stage. It is agreed to continue the monitoring as of ongoing surveillance activities and to discuss the topic only in case that new safety information arises.

2.3.19. Health Authority requests – Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy)

Request from the previous PSUR:

The MAH is requested to further search for literature on GN/SN following COVID-19 vaccination, with a special focus to Adeno-vectored vaccines, relapse and flare up, and measured kidney alterations after vaccination.

MAH response (summary)

Please note that Glomerulonephritis and Nephrotic syndrome (GN/NS) data is not reproduced here (see Section 15.2.3 of the PBRER)

Literature review

A total of 29 literature case reports in 16 articles were received for adenovector vaccines (27 for VAXZEVRIA and 2 for Janssen vaccine) and included:

- Minimal Change Disease: 8 cases
- Antineutrophil Cytoplasmic Antibodies (ANCA) associated glomerulonephritis: 6 cases
- IgA nephropathy: 5 cases
- Collapsing glomerulopathy: 2 cases
- FSGS, Worsening of C3 glomerulonephritis, membranous nephropathy, membranoproliferative glomerulonephritis: 1 case

Relevant articles

Bronz et al 2022 performed a systematic review of the literature aiming to determine whether COVID-19 or vaccination against SARS-CoV-2 may be temporally related to a new onset, or a flare, of an

immunoglobulin A-mediated disorder; 87 cases report were identified, 47 related to Berger glomerulonephritis and 40 to Henoch-Schönlein vasculitis. Among them, 28 cases had medical history of an immunoglobulin A-mediated disease. No cases of Berger glomerulonephritis were reported for Adeno-vectored vaccines (94% of cases occurred after mRNA vaccination)

Ma et al 2022 collected 37 cases related to COVID-19 vaccination and membranous nephropathy (MN). In total, 20 articles were highlighted, which included a total of 37 cases reports, of which 20 of them (54.1 %) were a new diagnosis and 17 (45.9 %) were reported as relapse or worsening syndrome.

Canney et al 2022 provided a retrospective population-level cohort study in British Columbia, Canada: exposure to any SARS-CoV-2 vaccine was not associated with an increased risk of disease relapse (hazard ratio [HR]=1.08; 95% confidence interval [CI], 0.65 to 1.8). An interaction analysis suggested that the relative risk of disease flare associated with any vaccine exposure was not significantly different on the basis of the type of glomerular disease (P value for interaction= 0.45).

The absolute risk of disease relapse after COVID-19 vaccination, after 210 days of follow-up with the 1st dose of COVID-19 vaccine was near zero for all types of glomerular disease. The absolute increase in risk associated with a 2nd or a 3rd dose of COVID-19 vaccine varied from 1%-2% in those with ANCA-GN, minimal change disease, membranous nephropathy or FSGS to as high as 3%-5% in those with IgA nephropathy or lupus nephritis, compared with the cumulative risk of a disease flare after 210 days of follow up in the absence of a COVID-19 vaccine and ranged from 6% (95% CI, 2% to 9%) in patient with membranous nephropathy to 19% (95% CI, 12% to 25%) in those with lupus nephritis.

There was no clear association between the type of COVID-19 vaccine and the risk of disease relapse (COMIRNATY: HR=0.99 [95% CI, 0.55 to 1.78]; SPIKEVAX: HR=1.3 [95% CI, 0.58 to 2.99]; VAXEVRIA: HR=1.64 [95% CI, 0.22 to 12.12]).

MAH comment: An analysis of three relevant literature articles did not find any evidence of increased observed frequency of glomerulopathies in particular for adeno-vectored vaccines, compared to expected rates in general population. A further focus on literature cases for glomerulopathies and adeno-vectored vaccines did not find any significant safety concerns. There was insufficient evidence for a conclusive mechanism for glomerulopathies following VAXZEVRIA vaccination or adeno-vectored vaccines and that evidence from mRNA vaccine types cannot be comprehensively extrapolated to all other vaccines.

Potential Mechanism of action

In the updated review none of the articles provided relevant new hypothesised mechanism of action for Glomerulonephritis and Nephrotic Syndrome (Including IgAN) in association with mRNA or VAXZEVRIA.

MAH's Conclusion

Based on the review of the currently available data, AstraZeneca considers that there is insufficient evidence to conclude a causal association between VAXZEVRIA and Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy). It is AstraZeneca's opinion that no updates to CDS or RMP are warranted at this time.

Rapporteur assessment comment:

Following a PRAC request, the MAH performed a literature search and retrieved 29 cases. Some cases were classified as possible according to UMC causality assessment. However cases were confounded by underlying pathology. Three systematic reviews, including a Self-controlled Case series study did not reveal evidence for an increased risk of glomerulonephritis.

The MAH concluded that there is insufficient evidence to conclude a causal association between VAXZEVRIA and Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy and that no updates to CDS or RMP are warranted at this time**. The MAH conclusion is endorsed.**

Taking into consideration the review of the risks or the previous request for monitoring no further action is considered warranted at this stage. This topic should no longer be discussed in future PBRERs, unless significant new safety information arises.

2.3.20. Health Authority requests – Severe cutaneous adverse reactions (SCAR)

Please note that SCAR data is not reproduced here (see Section 15.2.7 of the PBRER)

Request: In the assessment report received from the PRAC (PRAC PAR (EMEA/H/C/PSUSA/00010912/202112) for the VAXZEVRIA PBRER (review period: 29 December 2021 to 28 June 2022), the PRAC requested AstraZeneca to provide a cumulative review of cases of SCARs reported with VAXZEVRIA, as well as a review of the literature, and to discuss on the need to update the PI on this topic.

Pre-Clinical Data:

There is no pre-clinical data on SCARs with VAXZEVRIA.

MAH's Summary of clinical data:

On review of the clinical study data, no safety concerns were identified for SCARs with VAXZEVRIA. No AEs of SCARs were identified from the United States (US) study (DCO4). Two AEs of mild Exfoliative rash were "reported as non-serious" from the Oxford studies (one each from COV002 and COV003 respectively). As per the Investigator, one case was possible related whilst the other was not related to VAXZEVRIA. In both cases, there was limited information on medical history, concomitant medications, etiological and diagnostic work-up.

MAH's Summary of Review of Cases

In the assessment report received from the PRAC (PRAC PAR (EMEA/H/C/PSUSA/00010912/202112) for the VAXZEVRIA PBRER (review period: 29 June 2022 to 28 December 2022), the PRAC requested a review of SCARs in this PBRER. Cumulatively, a total of 415 SCARs cases concerning 423 events were reported in AstraZeneca's global Safety database. Cases were assessed by age, sex, type of event and outcome. A female (65.1%) prevalence versus male (34.9%) was expressed. The median age was 56 years. The majority (88.4%) of events were reported after Dose 1. In 1 case, the event (PT: Erythema Multiforme) occurred after Dose 1 and subsequently reappeared after Dose 2 of the vaccination. The recurrence case was assessed against the WHO-UMC causality criteria as 'Probable', due to temporal relationship, and considering recurrence, and the fact that it is not likely that any other confounder was present during both occurrences and absent in between. Amongst 423 SCARs events, 391 (94.2%) were serious of which 3 (0.8%) resulted in death, 94 (22.2%) events had favourable outcome (either 'recovered' or 'recovered with sequelae). Event duration was reported for 52 (55.3%) cases of which majority 29 (55.8%) were resolved after 7 days. The risk window for the SCARs topic was considered as 0-42 days except for DRESS and AGEP. The risk window for DRESS was considered as 0-28 days whereas for AGEP this was taken as 0-21 days. The time to onset (TTO) was available in 330 (78.0%) case reports and ranged from 0 days to 269 days (median: 4 days) of which 271 (82.1%) case reports were within TTO range of 0-21 days, and 281 (85.2%) case reports were within range of 0-28 days. Amongst 415 cases, 2 (0.5%) cases met WHO-UMC causality criteria for 'Probable/Likely' (PT: Erythema Multiforme) and 293 (70.6%) were considered as 'Possible', of which 78 (26.6%) were identified with relevant

risk/confounding factors. Of 415 cases, 2 fatal cases were assessed against the WHO-UMC causality criteria as 'Possible and limited information' respectively. None of the fatal cases reported detailed autopsy results. The O/E analysis results for SCARs showed observed cases to be significantly less than expected for all age, global and EU/UK reports.

A review of the literature suggests various hypothesized mechanisms for development of SCARs in association with COVID-19 vaccines.

Fatal cases

Case ID [redacted]: This medically confirmed case concerns a 78-year-old elderly male patient who experienced dermatitis exfoliative generalized, Stevens-Johnson Syndrome (SJS), Disseminated Intravascular Coagulation (DIC), multiple organ dysfunction syndrome, Acute kidney injury, cholestasis, subdural haematoma and dehydration on day 7 after Dose 1 of VAXZEVRIA. On an unknown date after vaccination, the patient died, all events mentioned above were considered as fatal. It was not known whether an autopsy was performed. Concomitant medications included doxazosin, bisoprolol fumarate, hydrochlorothiazide/olmesartan medoxomil and acetylsalicylic acid. Chest X-ray and brain computerized tomography was done but results were unknown.

AstraZeneca Comment: Patient's elderly age, concomitant use of acetylsalicylic acid could be confounders for the event SJS. Event multiple organ dysfunction syndrome and disseminated intravascular coagulation could also have resulted in the fatal outcome. There is insufficient information on medical history, start date of concomitant medication, clinical course of the events, etiological and diagnostic workup, treatment details, and autopsy details. Hence this case is causally assessed as "Possible with limited information".

Case ID [redacted] This consumer report concerns a 23-year-old male patient who experienced dermatitis bullous, pruritus, pyrexia and lip discolouration on day 1 after Dose 2 of VAXZEVRIA and died on the same day. The patient received Dose 1 of unspecified COVID-19 vaccine. As reported by patient's mother, next day after Dose 2, the patient was not hungry and around noon patient looked normal. However, at around 3.45 pm, his mother was shocked to see him with his lips turning green. An hour later dark spots appeared on his chest. Patient died about 24 hours after receiving his Dose 2 dose of vaccine. An autopsy was performed, cause of death was reported as dermatitis bullous, pruritus, pyrexia and lip discolouration.

AstraZeneca Comment: This is a consumer report, and there is no information reported for medical history (ultraviolet light therapy, psoriasis, lichen planus, diabetes, rheumatoid arthritis), concurrent conditions (infections, skin injury, iron deficiency anaemia, cyanosis), risk factors, clinical course, detailed diagnostic and etiologic workup (complete physical exam with dermatological assessment, skin biopsy, indirect immunofluorescence, complete blood profile and blood chemistry panel, blood culture, relevant imaging studies and complete autopsy report) and treatment details. Hence this case is causally assessed as "Possible with limited information'.

Literature overview

On review of cumulative literature search through 28 December 2022, 234 articles were further assessed. 211 articles did not have adequate relevant information to require further review. No epidemiological articles with relevant new safety information were identified. 19 articles describing VAXZEVRIA in association with SCARs were discussed in the previous review of ICSRs retrieved from the AstraZeneca Global Patient Safety Database. No new safety concerns regarding SCARs and association with VAXZEVRIA was identified. Upon review of relevant articles related to SCARs subsequent to COVID-19 vaccination, mechanism of actions postulated are: May be due to the inactivated vaccine component or the adjuvant (1); Triggering a Th2-polarized inflammatory reaction (1); A T-cell-driven, Type IV

hypersensitivity reaction (1); Activation of cytotoxic T lymphocytes and the death of epidermal cell (2); and Hypersensitivity reactions, molecular mimicry, immune cross-reactivity and autoimmunity, allergy to vaccine excipients, and reactivation of latent viral infections (1).

MAH's Conclusion

Based on the review of cumulative information from clinical, post-marketing and literature articles, AstraZeneca considers that there is insufficient evidence to suggest a causal association between SCARs and VAXZEVRIA. No changes to the CDS or RMP are recommended for SCARs. SCARs will continue to be monitored as part of AstraZeneca's routine safety surveillance activities for VAXZEVRIA. AstraZeneca will no longer discuss this topic in future PBRERs, unless significant new safety information arises.

The event of cutaneous vasculitis is included as an ADR in section 4.8 of the VAXZEVRIA CDS.

Rapporteur assessment comment:

As requested the MAH provided a cumulative review of cases of severe cutaneous adverse reactions (SCARs) reported with VAXZEVRIA, as well as a review of the literature, and discussed the need to update the PI on this topic. This was requested following a signal report of WHO-UMC of SCAR following COVID-19 vaccination (WHO-UMC, August 2022). The search strategy considered SCARs SMQ narrow excluding PT Cutaneous vasculitis. The MAH excluded Preferred Term 'Cutaneous vasculitis' from the SCARs search strategy as this event is a listed ADR in section 4.8 of the SmPC.

Clinical data

The MAH's clinical database search retrieved no cases of SCARs and two non-serious cases of AE 'Exfoliative rash'. Of these two cases, one case was possible related while the other was not related to VAXZEVRIA. Both cases had limited information on medical history, concomitant medications, etiological and diagnostic work-up.

Cumulative review of cases

The MAH's safety database retrieved a total of 415 case reports with 423 events. Of which 391 (92.43%) events were serious and 241 (58.1%) cases being medically confirmed. Of these 415 cases/423 events:

• **Dose:** 359 (88.4%) cases were reported after first dose: 40 (9.9%), 5 (1.2%), 1 (0.2%), 1 (0.2%) and 9 cases after 2nd, 3rd, 4th, multiple dose (dose 1 and 2) and unknown dose.

• **Age/Gender**: The age ranged from 18 to 94 years (median: 56 years). 259 (65.1%) cases were reported in females.

• **TTO: median TTO was 4 days**. Among the known 79.51% (330) TTO cases; 251(76.06%), 20(6.06%), 10(3.03%), 15 (4.54%), and 34 (10.30%) cases were reported in 0-14 day, 15-21 days, 22-28, 29-42 days and 43 and above, respectively.

• **Outcome:** Among the known 73.75% (312) outcome events: the outcome was reported in 26.92% (84) events as recovered, 31.08% (97) recovering, 3.20% (10) recovered with sequelae, 37.08% (118) not recovered, and 3 AEs (0.96%) had a fatal outcome [unknown outcome in 26.24% (111) events].

• **Seriousness criteria:** 288 (73.7%) events were medically important while 17 (4.3%), 59 (15.1%), 24 (6.1%), and 3 (0.8%) events assigned to Disability, Hospitalization, Life-threatening and Death. **There were 2 case reports with fatal outcome:** one medically confirmed fatal case was reported in 78 year old male patients with PTs; dermatitis exfoliative generalized, Stevens-Johnson Syndrome (SJS), Disseminated Intravascular Coagulation (DIC), multiple organ dysfunction syndrome, Acute kidney injury, cholestasis, subdural haematoma and dehydration on day 7 after Dose 1 of VAXZEVRIA. This case was confounded by concomitant medication and medical history. 1 consumer report was reported in a 23-

year-old male patient with PTs; dermatitis bullous, pruritus, pyrexia and lip discolouration on day 1 after Dose 2 of VAXZEVRIA and died on the same day. The patient received Dose 1 of unspecified COVID-19 vaccine. This case had limited information (medical history, concomitant medication etc.) for further causality assessment.

• **AE duration**: AE duration was known for 52 (55.3%) events,; 23 (44.2%) resolved within 7 days and 29 (55.8%)resolved after days. AEs duration ranged from 0 to 122 days with a **mean duration of 24 days.**

• **Reported PTs**: Among 423 events, **Erythema multiforme** (n=123, 29.07%), **Dermatitis bullous** (n=120, 28.36%), **Stevens-Johnson syndrome** (n=35, 8.27%), **Dermatitis exfoliative generalised** (n=29, 6.85%), **Drug reaction with eosinophilia and systemic symptoms** (n=29, 6.85%) and **Exfoliative rash** (n=15, 3.54%) were the most reported events.

The MAH presented a cumulative review of following PTs: Erythema multiform, Stevens-Johnson Syndrome (SJS)/Toxic, Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Acute Generalised Exanthematous Pustulosis (AGEP), Bullous Lesions (Dermatitis Bullous, Bullous Haemorrhagic Dermatosis, Generalised Bullous Fixed Drug Eruption), Other SCARs PTs.

• **WHO-UMC causality assessment:** The risk window for the SCARs topic was considered 0-42 while 0-28 days for Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and 0-21 days for Acute Generalised Exanthematous Pustulosis (AGEP) bases on published literature.

Causality was considered as Probable-Likely for 2 (0.5%) cases and as Possible for 70.8% (294) cases: Possible with risk factors/confounders. Among Possible cases, 19% (79) cases had risk factors/confounders and remaining 51.8% (215) cases had limited information. WHO-UMC causality was considered as unassessable/unclassifiable, unlikely and Conditional/Unclassified for 83 (20%), 34 (8.2%) and 2 (0.5%) cases respectively. The MAH has also presented causality assessment for individual PTs as discussed below.

The cumulative review results of these PTs resembles to overall cumulative review data (TTO, outcome etc.). The causality was assessed as possible with risk factors/confounders for the majority of the cases, followed by Unassessable/Unclassifiable with limited information as presented in a table below.

Table. Overview of SCAR case report Causality assessment (built by the Assessor)

Overview of WHO-UMC Causality Assessments for Case Reports with VAXZEVRIA reported Cumulatively through 28 December 2022							
WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	Number of Cases (Percentage)					
		Erythema Multiforme	SJS/ TEN	DRESS	AGEP	Bullous Lesions	Other SCARs
Certain	Certain	0	0	0	0	0	0
Probable/ Likely	Probable-Likely	2 (1.6%)	0	0	0	0	0
Possible	Possible with risk factors/confounders	29 (23.6%)	13 (31.7%)	1 (3.4%)	2 (20.0%)	19 (15.1%)	17 (18.3%)
	Possible with limited information	56 (45.5%)	11 (26.8%)	10 (34.5%)	7 (70.0%)	84 (66.7%)	49 (52.7%)
Unassessable/ Unclassifiable	Unassessable/Unclassifiable with risk factors/confounders	3 (2.4%)	5 (12.2%)	2 (6.9%)	0	2 (1.6%)	4 (4.3%)
	Unassessable/Unclassifiable with limited information	22 (17.9%)	9 (22.0%)	10 (34.5%)	0	12 (9.5%)	15 (16.1%)
Unlikely	Unlikely	9 (7.3%)	3 (7.3%)	6 (20.7%)	1 (10.0%)	9 (7.1%)	8 (8.6%)
Conditional/Unclassified	Conditional/Unclassified	2 (1.6%)	0	0	0	0	0
Total		123	123	29	10	126	93

Two cases of PT erythema multiforme (EM) were assessed as probable; one case was reported in 47 year old female after 1 day and after 1st and 2nd dose (recurrence) without any confounder. This case had no information on medical history/concomitant medication and relevant aetiological investigation. Second case was reported in 25 year old female on the 3rd day after 1st dose. In this case, hematological and biochemical investigations including serology (for HSV (Herpes Simplex Virus)) were normal. Histopathology revealed the presence of subepithelial bullae along with a predominantly perivascular lymphohistiocytic infiltrate in the upper dermis. The epidermis showed variable spongiosis as well as basal cell vacuolar damage. No medical history or concomitant medication were reported by subject and no confounder were present.

• **Recurrence Case Reports:** In 1 (0.2%) case out of 415 case reports of SCARs, event (PT: Erythema Multiforme) occurred with Dose 1 and a subsequently reappeared with Dose 2 of the vaccination. This cases is discussed above.

O/E analysis

Observed cases were significantly less than expected for all PTs and for all cases globally and by age and gender stratifications.

Literature

Upon search, the MAH identified 234 articles; 211 articles lacked relevant information for further review and 19 articles contains case reports discussed in the previous review of ICSRs retrieved from the AstraZeneca Global Patient Safety Database as stated by MAH.

Postulated mechanism of action related to SCAR and COVID-19 vaccination according to the literature are: : May be due to the inactivated vaccine component or the adjuvant (1); Triggering a Th2 - polarized inflammatory reaction (1); A T - cell - driven, Type IV hypersensitivity reaction (1); Activation of cytotoxic

T lymphocytes and the death of epidermal cell (2); and Hypersensitivity reactions, molecular mimicry, immune cross - reactivity and autoimmunity, allergy to vaccine excipients, and reactivation of latent viral infections (1).

Conclusion:

Overall, the review of SCAR cases (n=415 cases, 423 events) shows that the majority (88.4%) of the cases were reported after first dose and majority of the events occurred within 14 days post vaccination. Median TTO was 4 days and half of the cases resolved within 7 days. Erythema multiforme (29.07%), Dermatitis bullous (28.36%) and Stevens-Johnson syndrome (8.27%), were among the most reported events. The cumulative review of individual PTs resembles to overall cumulative review of SCAR cases. The WHO-UMC case causality analysis assessed the majority of the cases as possibly related, however, either were confounded or had limited information. In the O/E analysis, observed cases were significantly less than expected for all PTs and for all cases globally and by age and gender stratifications. Few literature suggest a range of plausible mechanisms of action. The MAH stated that 19 literature case reports were discussed in the previous review of ICSRs retrieved from the AstraZeneca Global Patient Safety Database. However the PRAC rapporteur was unable to find a discussion on these cases from previous PSUR. Therefore these cases and any new literature reports on SCARs should be reviewed and presented in next PSUR. **[Request for the next PBRER].**

Moreover, as **Erythema multiforme** was the most frequently reported PT, with 2 cases assessed as probable, the PRAC rapporteur considers this topic requires further attention. The MAH should present:

- a cumulative review of erythema multiforme (at PT level) based on data from all available sources;

- a causality assessment of the cases (using the WHO-UMC causality assessment) and discuss the cases assessed as WHO Possible, Probable or Certain;

- relevant literature data;

-a discussion on the need for updating product information and/or risk management plan, and submit proposal as required. **[Request for the next PBRER].**

2.3.21. Health Authority requests – New daily persistent headache

Please note that New daily persistent headache data is not reproduced here (see Section 15.2.9 and Appendix 13 of the PBRER)

In the updated assessment report received from the PRAC EMA (PRAC PAR (EMEA/H/C/PSUSA/00010912/202206) for the VAXZEVRIA PBRER (review period: 29 December 2021 to 28 June 2022):

> *"The MAH is requested to provide a cumulative review of cases of new daily persistent headache (NDPH) in association with VAXZEVRIA, including spontaneous reports and data from the literature and clinical trials. The analysis should include an overall discussion of the cases, as well as an individual causality assessment of each cases."*

MAH's Summary

Cumulatively, a total of fifty-three (53) reports of New daily persistent headache with the use of VAXZEVRIA have been received, of which twenty-six (26) (49.1%) of the reported events were serious. Twenty-two (22) (41.5%) had a seriousness criteria of Medically Important, three (3) (5.7%) of Disability and four (4) (7.5%) of Hospitalisation. Median age was 49 years. 37 (74%) were females and 13 (26%) were males.

10 events (83.3%) events occurred after first dose, 2 (16.7%) after 2nd dose, and for 41 events the dose was unknown. There were no recurrence cases reported.

Of the total number of case reports cumulatively, twelve (12) (22.6%) were medically confirmed.

Forty-four (44) cases were assessed as probable as per the ICHD-3 diagnostic certainty criteria and nine (9) cases were unassessable. There were no cases assessed as certain according to the ICHD-3 diagnostic certainty criteria. Of these forty-four (44) cases, twenty-nine (29) were assessed as "Possible with limited information", and fifteen (15) were assessed as "Possible with confounders" based on WHO-UMC causality.

There were no fatal cases reported.

MAH's Conclusion

This cumulative review of available information on this topic found insufficient evidence for a new or emerging signal regarding NDPH and VAXZEVRIA. No changes to the CDS or RMP are recommended for this topic. The topic will not be discussed in the next future PBRERs, unless significant new safety information arises.

Rapporteur assessment comment:

As requested, the MAH provided a cumulative review of cases of **new daily persistent headache (NDPH)** in association with Vaxzevria, including an overall discussion of cases with causality assessment and data from literature.

The diagnostic criteria of New daily persistent headache according to the International Classification of Headache Disorders, 3rd edition (ICHD-3) are presented below:

Type of Headache	Certain new daily persistent headache	Probable new daily persistent headache
Diagnostic criteria	A. Persistent headache fulfilling criteria B and C B. Distinct and clearly remembered onset, with pain becoming continuous and unremitting within 24 hours C. Present for >3 months D. Not better accounted for by another ICHD-3 diagnosis.	A. Persistent headache fulfilling criteria B and C B. Distinct and clearly remembered onset, with pain becoming continuous and unremitting within 24 hours C. Present for ≤ 3 months D. Not fulfilling ICHD-3 criteria for any other headache disorder E. Not better accounted for by another ICHD-3 diagnosis.

ICHD: International Classification of Headache Disorders

A systematic review and meta-analysis of NDPH including 2155 patients (Cheema et al.[12]) noted that in an estimated proportion of 40% of patients the onset of NDPH is linked to a precipitating illness or event, most commonly a systemic infection (usually a flu-like illness), stressful life event, or extracranial surgery.

Clinical Study Data: there were no AEs of NDPH in the clinical database

[12] Cheema S, Mehta D, Ray JC, Hutton EJ, Matharu MS. New daily persistent headache: A systematic review and meta-analysis. Cephalalgia. 2023;43(5). doi:10.1177/03331024231168089

Post marketing safety database:

The cumulative search till 28 Dec 2022 using the PT New daily persistent headache retrieved following cases:

- Overall, there were 53 case reports, mainly from the UK (49%), Ireland (20.8%) and Norway (9.4%). 12 cases were medically confirmed – there were no literature cases. Median age was 49 years. 37 (74%) were females and 13 (26%) were males.

- 44 cases were assessed as probable as per the ICHD-3 diagnostic certainty criteria, 9 were unassessable due to insufficient information. TTO for the probable cases was between 0-30 days (median 2 days).

- Of the probable NDPH cases, 29 cases were assessed as "Possible with limited information", and 15 were assessed as "Possible with confounders" using WHO-UMC causality assessment criteria (NDPH cases are detailed in Appendix 13 of the PBRER).

Literature: no relevant articles were retrieved.

Vigiliyze: a search by the assessor in Vigilyze (search date 28 April 2023) with PT New daily persistent headache noted more observed than expected cases for all COVID-19 vaccines. The lowest IC_{025} was for Vaxzevria (1.8 with 55 observed versus 11 expected).

Overall, MAH's conclusion is endorsed that there is insufficient evidence for a new or emerging signal regarding NDPH and Vaxzevria.

Taking into consideration the cumulative review of new daily persistent headache (NDPH) cases with Vaxzevria, no further action is considered warranted at this stage. This topic should no longer be discussed in future PBRERs, unless significant new safety information arises.

2.3.22. Health Authority requests – Myositis

Please note that Myositis data is not reproduced here (see Section 15.2.10 and Appendix 14 of the PBRER)

Rapporteur assessment comment:

On 08 Dec 2022, EMA validated a signal of myositis with Vaxzevria (EPITT 19882) after performing signal detection in EudraVigilance (EV) and reviewing the scientific literature. The signal was sent in parallel for Comirnaty and Spikevax.

At that time, 21 literature cases from 11 articles and 209 cases in EV (including 12 of the 21 literature cases) were identified. Idiopathic inflammatory myopathies (IIM) carry a significant morbidity; 75% of cases in EV are reported as serious, including 5 fatal cases. No signal of disproportionate reporting in EV for PT 'myositis' [ROR(-) 0.44, 152 cases] nor any other related term. A significant imbalance was observed in O/E analyses.

In January 2023, the PRAC confirmed the signal and requested the MAH to provide a cumulative review of all available evidence of IIM/Myositis with Vaxzevria in this PSUR.

The MAH's responses are summarised and discussed here-after.

Background information

Autoimmune myositis is characterized by inflammatory and degenerative changes in the muscles (Polymyositis, necrotizing immune-mediated myopathy) or in the skin and muscles (Dermatomyositis).

Autoimmune myositis is more common in females than males by a 2:1 ratio. The incidence is 3 to 4 times higher in African American population than in Caucasians. These disorders may appear at any age but occur most commonly from age 40 to 60 or, in children, from age 5 to 15 (Nevares 2022).

Etiology: The cause of autoimmune myositis seems to be an autoimmune reaction to muscle tissue in genetically susceptible individuals. Possible inciting events include viruses and underlying cancer (Nevares 2022). Some of suspected myotoxic drugs are statins, fibrates, immunosuppressants (glucocorticoids, leflunomide, TNF inhibitors), antimalarials (Chloroquine, hydroxychloroquine, etc.), colchicine, etc.

COVID-19 infection has been reported to be associated with various skeletal muscle complications, including myositis (Paliwal et al 2020). Hypothesised mechanisms include direct viral invasion of the myocytes or hyperinflammation syndrome (Tan et al 2022 and Galluzzo et al 2022). It is suggested that SARS-CoV-2 may be the first virus capable of infecting muscle fibres directly (Saud et al 2021).

Classification: Autoimmune myositis can be classified into 4 groups, based on histopathology and clinical presentation: Polymyositis, Dermatomyositis, necrotizing immune-mediated myopathies and inclusion body myositis (Nevares 2022).

Diagnosis: Requires as many as possible of the following 5 criteria: proximal muscle weakness, characteristic rash, elevated serum muscle enzymes (if creatine kinase is not elevated, aminotransferases or aldolase, which are far less specific than CK), characteristic electromyographic or MRI muscle abnormalities, muscle biopsy changes (the definitive test) (Nevares 2022)

Treatment: The first line treatment is with high doses of glucocorticoids (prednisolone and methylprednisolone) and in addition immunosuppressants (eg., methotrexate, azathioprine, mycophenolate mofetil, rituximab, tacrolimus) and IVIG. The 'second-line' treatments, such as CYC, rituximab, IVIG and abatacept, for patients with persistent active disease despite glucocorticoid and conventional synthetic disease modifying antirheumatic drugs (csDMARD) therapy. (Oldroyd et al 2022).

Prognosis: Long remissions occur in up to 50% of treated patients within 5 years. Relapse may still occur at any time. Overall, 5-year survival rate is 75%++. Death in adults is preceded by severe and progressive muscle weakness, dysphagia, undernutrition, aspiration pneumonia, or respiratory failure with superimposed pulmonary infection. The mortality rate in a retrospective IIM cohort (Norvegian registry; 1997-2011) was 27% (Dobloug et al 2015). Dermatomyositis and polymyositis have been linked to an increased cancer risk. Cancer, if present, generally determines the overall prognosis.

Clinical Study Data

2 AEs: 1 event of Dermatomyositis reported for a participant in the Control arm of COV003; 1 event of Psoas abscess reported for a participant in the AZD1222 arm of D8110C00001.

Review of the cases

Cumulatively, a total of **265 Myositis cases** concerning 272 events were reported globally in the Global Patient Safety Database, including 108 medically confirmed cases and 157 consumer reports.

Age/Sex: female (66.4%) prevalence vs male (33.6%); median age of 53 years.

Type of event and outcome: The most frequently reported PT were Myositis (192), **Dermatomyositis (30)**, Polymyositis (24), Autoimmune myositis (6), Muscle abscess (6), **Anti-synthetase syndrome (4)**, Immune-mediated myositis (4).

The majority (78.5%) of events were reported after Dose 1. There were no case reports of recurrence/worsening of Myositis after a subsequent dose of vaccination.

Amongst 272 Myositis events, 173 (65.3%) were serious, 5 (1.8%) resulted in death and 45 (15.5%) events had a favourable outcome (i.e., 'recovered' or 'recovered with sequelae). Majority of events (14 ; 70.0%) were resolved after 7 days (event duration reported for 20 cases).

Amongst 272 Myositis events, 253 (95.5%) cases had a new onset of Myositis as compared to 12 (4.5%) cases which had Myositis flare-up.

TTO: The TTO was available in 208 (78.5%) case reports and ranged from 0 days to 335 days (median: 6 days) of which 170 (81.7%) case reports were within TTO range of 0-28 days (risk window).

Causality assessment: According to WHO-UMC causality criteria, amongst 265 cases:

- **no cases** were assessed as **'Certain' or 'Probable (Likely)'**
- **170 (64.2%) cases** were assessed as **'Possible'**: 32 (18.8%) cases were identified with relevant risk/confounding factors; and 138 (81.2%) cases had limited information on medical history, concomitant medications, etiological and diagnostic work-up
- **57 (22%) cases** were classified as **'Unassessable'**
- **38 (14%) cases** were assessed as **'Unlikely'**

Amongst 5 fatal cases, 2 cases were within the risk window (0-28 days) and were assessed as 'Possible with confounders'; and 3 cases were outside the risk window (range: 42 days to 63 days) and were assessed as 'Unlikely'. None of the fatal cases reported autopsy results.

Relevant risk factors and confounders include chronic conditions (such as acute ulcerative colitis; post viral fatigue syndrome; pericarditis, interstitial lung disease; several pIMD; etc.), concomitant medications such as statins and fenofibrate, previous history of myositis events ; neoplasms, concurrent COVID-19 infection.

O/E analysis

Parameters:

- DLP: 28 June 2022
- Risk window: 0-7 days, 0-14 days, 0-28 days, 0-42 days
- Cases with unknown TTOs were included
- Background rate incidences: based on Svensson et al 2017
- Region: Global, EU/UK/BR/AU, and UK

Results:

The observed numbers of cases for myositis were significantly lower than the expected numbers for all age, globally and in EU/UK reports.

In the sub-group analysis stratified by country of UK, a numerical increase was observed in the age group 18-29 (7 days including unknown TTO), 30-39 (7 days including unknown TTO) and 18-29 (14 days + Unknown TTO) for UK region. Six cases were reported with the Myositis onset within 0 to 2 days of VAXZEVRIA vaccination which is considered too short (Liozon et al 2021). Cases less than 2 days from vaccination would be questionable in any causative association and may be possibly indicative of pre-existing conditions.

Quantitative data review

No signal of disproportionate reporting in EV was observed for PT of 'Myositis' [ROR (-) All 0.43, 159 Cases] or any other related term.

Mechanism

A review of the literature suggests **various hypothesized mechanisms** for development of Myositis in association with COVID-19 vaccines:

- Molecular mimicry (Gonzalez et al 2022, Chaima et al 2022, Jack et al 2022, Ding and Ge 2022 and Chen Y et al 2022)
- Bystander activation with epitope spreading (Chan et al 2022, Barisic et al 2021, Punzi et al 2022)
- Cross reactivity between antigens or to the effect of adjuvant (Bose et al 2022 and Wang et al 2022 [B])
- Genetic susceptibility (Wang et al 2022 [B], Gonzalez et al 2022 and Barisic et al 2021)
- Direct viral invasion of the myocytes or hyperinflammation syndrome (Saud et al 2021 and Jacobs et al 2022)
- Deposition of virus-antibody complexes on myocytes (Tan et al 2022 and Bose et al 2022)
- Direct myocyte injury following internalisation using ACE-2 receptor (Saud et al 2021, Chan et al 2022 and Gonzalez et al 2022)
- Damage by cytokine storm (Saud et al 2021, Tan et al 2022)
- Statin-induced Necrotizing Autoimmune Myopathy (SNAM) (Verma et al 2022)

MAH's Conclusion

Based on the review of the cumulative data, AstraZeneca considers that there is insufficient evidence to suggest a causal association between myositis and VAXZEVRIA. No changes to the CDS or RMP are recommended for Myositis and the topic will continue to be monitored as part of ASTRAZENECA's ongoing safety surveillance activities for VAXZEVRIA.

Rapporteur assessment comment:

Cumulative review of the cases

The MAH reviewed **265 case reports** of various types of **myositis**. Some characteristics of the events may be highlighted:

- The majority of cases (78%) occurred after the 1st dose. There were no case of rechallenge.
- The majority of cases occurred in subjects younger than 70 yo: 40% if 18-49 yo; 22% in 50-59 yo; 25% in 60-69yo.
- About 4.5% of cases were possible cases of flare/relapse.

The MAH did not identify any certain or probable cases. The majority of cases (64%) were assessed as 'Possible', including cases with risk factors/confounders (12%) or with limited information (52%).

A rheumatologist expert reviewed cases of interest expected to be sufficiently documented, i.e. (i) cases from the literature, (ii) fatal cases, and (iii) cases with a TTO between ~1 week and 4-6 months (or a shorter onset if reported after dose 2) and describing symptoms and/or additional exams and/or laboratory tests. Based on these criteria, **42 cases have been reviewed by the expert**.

The BE external expert noted the following:

Myositis subtypes:

- Dermatomyositis is over-represented in the reported cases (in 12 cases), as well as anti-synthetase syndrome (in 2 of cases), which is extremely rare.
- Amyopathic disease is often described which is rarely seen in the clinical setting.

Characteristics of the disease:

- Disease presenting with acute new onset, sometimes fulminant, with multisystemic involvement is not the typical presentation of autoimmune myositis. One hypothesis could be that this presentation might reflect high inflammation induced by the vaccine.
- Cases with normal CRP are also unusual in the classic presentation of the disease.
- Autoimmune myositis is a chronic disease for which resolution is not expected. Resolutive disease might suggest a reaction to the vaccine.

Causality assessment of the cases of interest (n=42)

Based on BE expert review, and according to WHO-UMC causality criteria:

- **7** cases **were assessed 'Probable'**, including **4 cases of Dermatomyositis (DM)**, 2 cases of Myositis, and **1 case of anti-synthetase syndrome (ASS)**
- **17 cases** were assessed as **'Possible'** (Myositis [8], Immune-mediated myositis [4], **DM [3]**, **ASS [1]**, and polymyositis [1])
- The remaining cases were classified as 'Unlikely' [14] or 'Unassessable' [4].

The detailed assessment of cases of interest (i.e., 23 literature cases including 3 fatal; 3 fatal cases from spontaneous reporting; 16 cases with relevant TTO and information) is provided in Appendix 02 of this report.

O/E analysis

The number of observed cases is lower than expected : O/E (significantly) <1 in the different risk windows, globally and for the region EU/UK/Brazil/Australia.

The O/E analysis shows a O/E >1 (not significant) for age groups 18-29 and 30-39 years old (in the UK, with a 7 days risk period). A O/E ratio >1 is also observed with a 14 day risk period for the age group 18-29 years old and when cases with unknown TTO were included in the analysis.

The analysis does not raise a strong signal. However. several medical conditions may be mixed. Myositis usually covers a very large panel of diseases from very mild to severe, whereas myositis reported after vaccination may target a more specific sub-type (e.g. dermatomyositis). The sub-stratification by age, gender and risk periods leads to too small numbers of cases in each group, to perform relevant statistical tests.

The MAH should provide a refined O/E analysis as discussed below.

Disproportionality analysis in EV

ROR(-) was >1 for all PTs related to myositis.

Mechanism (*BE Expert's comment*)

Several mechanism of action have been proposed for a role of the vaccine in the development of myositis but none could be firmly confirmed.

All the hypotheses are possible except the reaction to adjuvant as Vaxzevria is not adjuvanted.

Of note, myositis has been described after infection with SARS-CoV2, in particular dermatomyositis (Qian et al., 2022)[13]. Most of the articles highlighted mechanisms similar to COVID-19 infection. This suggests

[13] Qian J, Xu H. COVID-19 Disease and Dermatomyositis: A Mini-Review. Front Immunol. 2022 Jan 13;12:747116. doi: 10.3389/fimmu.2021.747116. PMID: 35095837; PMCID: PMC8792859.

that cross reactivity with S protein plays an important role in the occurrence of myositis post vaccination.

Genetic background and HLA might play a role. HLA-B*35 and DRB1*15 is linked to high-affinity interactions to S-protein T-cell epitope that triggers immunogenic responses to the S protein of SARS-CoV-2. Genetic predisposition might certainly play an important role, like for all autoimmune diseases.

Vaxzevria is known to induce an important inflammatory reaction. This could be an explanation for muscle damage and liberation of antigen.

Low grade myositis happens very often in viral infection. Viral infection induced an important release of Th1 cytokines, in particular IFN-g. The response to Vaxzevria is characterised by an important Th1 immune response which could be involved in myositis observed after vaccination with Vaxzevria. Also, autoimmune myositis is dominated by a Th1 immune response.

Autoimmune myositis after vaccination with Vaxzevria could result of the combination of release of muscles antigens in a Th1 cytokine "storm" (induced by vaccine) in a predisposed individual.

However, no definite mechanism of action has been identified to date.

Need for updating product information and/or risk management plan

The MAH concludes that there is no need to update product information or the Risk Management Plan.

The PRAC Rapporteur agrees that there is no sufficient evidence to confirm a causal association between Vaxzevria and myositis. However, myositis refers to a group of autoimmune disorders with a heterogenous and specific spectrum of muscular and extra-muscular involvement. This renders the evaluation of a causal association more difficult. Focusing on the more specific and rare event of dermatomyositis, the signal appears stronger with 4 well documented cases considered as probable and 3 cases assessed as possible (out of 30 cases).

Moreover, the systematic review performed by Ding et al, 2022 suggest that COVID-19 vaccine may induce various clinical myositis subtypes and related antibodies. In particular, among the specific clinical subtypes of myositis, reported in 27 patients, 81.5% of cases relate to dermatomyositis.

Conclusion

Taking all this information into account, the MAH is requested to provide a O/E analysis specific for dermatomyositis. Optimal background incidence rates for dermatomyositis should be used. Whenever possible, it should take into account a possible change in the occurrence of dermatomyositis during SARS-CoV-2 circulation.

Based on evidence for dermatomyositis, the MAH should discuss the need to update the product information and/or the risk management plan .

Finally, the MAH is requested to consider the monitoring of this event within the ongoing PASS "Post-marketing observational study using existing secondary health data sources".

[Request for Supplementary Information]

2.3.23. Health Authority requests – Corneal graft rejection (CGR)

Please note that CGR data is not reproduced here (see Section 15.2.11 of the PBRER)

***Background*:** Signal of corneal graft rejection (CGR) for COVID-19 Vaccine (VAXZEVRIA – EPITT 19791) was identified by PRAC in March 2022. AstraZeneca submitted the cumulative assessment of CGR in

association with VAXZEVRIA on 27 June 2022, and concluded that based on the available data there is insufficient evidence to suggest a causal association of corneal graft rejection with the use of VAXZEVRIA. Therefore, no changes to the EU-PI or RMP are warranted. On 02 September 2022, PRAC agreed with AstraZeneca's conclusion and requested to discuss any new data, including data from the literature on CGR in the next PBRER.

Global Patient Safety Database: An interval search (01 June 2022 – 28 December 2022) of the AstraZeneca Global Safety Database retrieved **no new cases** of corneal graft rejection reported to the AstraZeneca Global Patient Safety Database during the reporting period. There were 5 cases with follow up information (i.e., updates to demographic details and reporter identification information).

Literature: A literature search of the databases in Embase, InsightMeme and PubMed was conducted for relevant articles on CGR in association with VAXZEVRIA from 01 June 2022 (DLP for the last analysis) to 28 December 2022 and **no new relevant literature articles** were retrieved.

MAH's Conclusion: Based on the review of the updated cumulative data, AstraZeneca remains in its position that there is insufficient evidence to suggest a causal association between corneal graft rejection and VAXZEVRIA. It is AstraZeneca's opinion that no changes to the CDS or RMP are warranted at this time. The topic will continue to be monitored as part of AstraZeneca's ongoing surveillance activities. **AZ will not discuss the topic in future PBRERs, unless significant new safety information arises**.

Rapporteur assessment comment:

The MAH performed a literature review and a search of its safety database for interval data. No new cases nor relevant article were identified during the period under review.

In addition, the PRAC rapporteur identified papers of interest from the literature. These include several reviews of the literature (e.g. Kuziez et al., 2023; Kumari et al., 2023; Fujio et al., 2023) and two observational studies:

- Roberts et al., 2022 performed a retrospective review of cases presenting at two sites in UK and Italy, between Jan 2018 and Mar 2022 (n=566 episodes of rejection). The authors observed that from the start of vaccination programme in the UK in late Jan 2021, the median number of graft rejections per month was not significantly different to post-lockdown, pre-vaccination programme (Mar 2020-Jan 2021), p = 0.36. Similarly, at the Italian site, the median rates of rejection before and after initiation of the vaccination programme were not significantly different (p = 0.124). **No significant increase in incidence rate of rejection** in the risk period following COVID-19 vaccination was found (IRR = 0.53, p = 0.71).

- Busin et al., 2022 (Italy) used the **conditional Poisson regression model of the SCCS method** to estimate the incidence risk ratio of graft rejection after COVID-19 vaccination risk period compared with the control period. Based on outcomes of eyes that underwent keratoplasty from Jan 2018 to Dec 2020, **Cox proportional hazard models** were fitted with previous COVID-19 vaccination as a time-varying covariate: since 2018, the annual tally of diagnosed cases of graft rejection has remained relatively stable (i.e. 19 cases in 2018, 19 cases in 2019, 21 cases in 2020, and 18 cases in 2021). No significant increase in the incidence rate of rejection in the risk period after COVID-19 vaccination was found (**IRR = 0.56, 95% CI =0.13-2.28**, P = 0.70). Fitted as a time-varying covariate, previous COVID-19 vaccination was not associated with graft rejection in both unadjusted (**hazard ratio =0.77, 95% CI = 0.29-5.46**, P = 0.77) and adjusted Cox models (hazard ratio = 0.75, 95% CI = 0.10-5.52, P = 0.78).

These 2 studies do not suggest an association between COVID-19 vaccination and CGR. However, it is noted that the database used in both papers for the SCCS are the same (i.e. the institutional database of the tertiary corneal referral center Ospedali Privati Forlì "Villa Igea," Forlì, Italy). The observation periods slightly differs (i.e. Jan 2018-Mar 2022 in Roberts 2022 vs Jan 2018-Dec 2021 in Busin 2022). These data

should be confirmed by more epidemiological data.

In conclusion, data available during the period under review did not raise any new safety signal. **It is agreed to continue the monitoring as of ongoing surveillance activities and to discuss the topic only in case that new safety information arises.**

2.3.24. Health Authority requests – Histiocytic necrotizing lymphadenitis (HNL)

Please note that HNL is not reproduced here (see Section 15.2.12 of the PBRER)

Request:

On 01 September 2022, AstraZeneca received a request from PRAC to submit cumulative review of histiocytic necrotizing lymphadenitis associated with VAXZEVRIA in the next PSUR (DLP 28 December 2022). This signal was initially identified for Tozinameran (COVID-19 mRNA vaccine) – Comirnaty. As it is believed that the signal may also be relevant for VAXZEVRIA, PRAC has agreed that AstraZeneca should submit within the next PSUR (DLP 28 December 2022) **a cumulative review of all cases concerning VAXZEVRIA associated with histiocytic necrotizing lymphadenitis from all sources, including any relevant articles from literature and to discuss probable mechanism(s) of action for the occurrence of vaccine-associated histiocytic necrotizing lymphadenitis following administration of VAXZEVRIA.** The PRAC also requested that the MAH to discuss the need for any potential amendment to the product information and/or the risk management plan and make accordingly a proposal for changes to the relevant sections within this discussion.

MAH's Summary

Cumulatively, a total of 10 reports of HNL with the use of VAXZEVRIA have been received. Only 3 reports with PT of HNL were considered relevant for discussion, the other had AEs that are not consistent with HNL. 2 of the 3 cases were reported as serious and none had a seriousness criterion of Fatal or Life-threatening. Reported age was 30, 41 and 44 respectively.

2 of the events occurred after first dose and in 1 cases dose was unknown.

1 event reported outcome recovered and the event duration was reported as 54 days.

1 of the 3 cases was medically confirmed.

None of the cases met WHO-UMC causality criteria for Certain or Probable/Likely. Four were (40%) considered as Possible, 4 (40%) were identified with relevant risk/confounding factors and 2 (20%) were un-assessable due to limited information. Conclusion

This updated cumulative review found insufficient evidence for a new or emerging signal regarding Histiocytic Necrotizing lymphadenitis and VAXZEVRIA. No changes to the CDS or RMP are recommended, and the topic will not be discussed in future PBRERs, unless significant new safety information arises.

Rapporteur assessment comment:

As requested the MAH presented a cumulative review of all cases concerning VAXZEVRIA associated with histiocytic necrotizing lymphadenitis from all sources, including any relevant articles from literature and discussed probable mechanism(s) of action for the occurrence of vaccine-associated histiocytic necrotizing lymphadenitis following administration of VAXZEVRIA.

The MAH's databases search retrieved a total of 10 case reports (10 events). The MAH considered only 3 reports with PT of HNL for discussion. All 3 cases had limited information for causality assessment. The

MAH retrieved two articles hypothesized the same mechanism of action (patients with genetic components such as HLA-DPA1 and HLA-DPB1 are usually predisposed to develop mainly T cells, especially cytotoxic T cells as immune responses) with regards to Covid-19 vaccines to cause HNL. However, the exact mechanism still remains to be elucidated.

Available data did not raise any new relevant safety in formation.

Taking into consideration the review of the histiocytic necrotizing lymphadenitis, no further action is considered warranted at this stage. This topic should no longer be discussed in future PBRERs, unless significant new safety information arises.

2.4. Characterisation of risks

At the end of the reporting period, the VAXZEVRIA safety specification presented in the global core-RMP (Version 8.0, dated 10 Nov 2022) and in the EU-RMP (Version 6, dated 10 February 2023) included the following important identified and important potential risks, and missing information (see Table 10).

Table 10 - Characterisations of the safety concerns (core-RMP v8.0 [10 Nov 2022]; EU-RMP v6 [10 Feb 2023])

Safety concerns	Characterisation (DLP 28 June 2022)
Important Identified Risks	
Thrombosis in combination with thrombocytopenia[core] / Thrombosis with thrombocytopenia syndrome[EU]	*Frequency* • Post-market: **2644 cumulative cases** • Clinical-trials: **no cases** *Potential mechanism*: The exact mechanism of thrombosis concurrent with thrombocytopenia following immunisation with VAXZEVRIA is unknown. Several hypothetical biologic mechanisms have been proposed to explain the pathophysiology of thromboembolic events with thrombocytopenia following vaccination (Greinacher et al 2021 (NEJM)). Among them a study by Baker et al 2021, proposes an interaction between the ChAdOx1 vaccine vector used in VAXZEVRIA and PF4; however, it is unknown if the adenoviral ChAdOx1 interaction with PF4 is actually platelet activating or thrombogenic (causal of blood clots). Greinacher et al 2021 (NEJM) suggested that ChAdOx1 itself or proteins contained within the vaccine can bind to PF4 to form immune complexes which may drive a B-cell response causing high-titer anti-PF4 antibodies resulting in TTS. However, none of these hypotheses have been confirmed. *Risk factors*: There are no known risk factors.
Thrombocytopenia, including immune thrombocytopenia[EU]	*Frequency* • Post-market: **4975 cumulative cases**[1] • Clinical-trials: in study D8110C00001, thrombocytopenia was reported in **2 participants (<0.1%) in the VAXZEVRIA group**, and immune thrombocytopenia was reported in **1 participant (<0.1%) in the placebo group**. In the long-term safety analysis at 6-months, **1 additional event** of thrombocytopenia was reported in a participant in the VAXZEVRIA group. None of these events were serious.

Safety concerns	Characterisation (DLP 28 June 2022)
	Potential mechanism: The exact mechanism of thrombocytopenia, including immune thrombocytopenia following immunisation with VAXZEVRIA is unknown. *Risk factors*: There are no known risk factors for the development of thrombocytopenia following vaccination. In general, individuals with a history of thrombocytopenic disorder, such as immune thrombocytopenia, the risk of developing low platelet levels should be considered before administering the vaccine and platelet monitoring is recommended after vaccination as described in Section 4.4 of the SmPC.
Guillain-Barré Syndrome[EU]	*Frequency* • Post-market: **1849 cumulative cases** • Clinical-trials: **1 case of a demyelinating event** (SAE initially reported as GBS, subsequently diagnosed as Chronic inflammatory demyelinating polyradiculoneuropathy) *Potential mechanism*: Exact mechanism of GBS following immunization with VAXZEVRIA is unknown. Although the underlying aetiology and pathophysiology of GBS are not completely understood, it is believed that immune stimulation plays a central role in its pathogenesis (Sejvar et al 2011). *Risk factors*: There are no known risk factors for the development of GBS following vaccination. In general, infection with the bacteria Campylobacter jejuni is one of the most common risk factors for GBS. People also can develop GBS after having the flu or other infections such as cytomegalovirus and Epstein-Barr virus. On very rare occasions, people develop GBS in the days or weeks after getting a vaccination (CDC 2019).
Important Potential Risks	
Thrombosis[EU]	*Frequency* • Post-market: **19486 cases** • Clinical-trials: in the US study, thromboembolic events were reported in **0.1%** (23/21587 participants) in the vaccine group and <0.1% (9/10792 participants) in the placebo group. In the **long-term safety** analysis at 6-months, thromboembolic events were reported in **0.3%** in the vaccine group (n=68) vs 0.1% in the placebo group (n=14). In the pooled Oxford studies, thromboembolic events were reported in **0.1%** (7/12282 participants) in the vaccine group and 0.2% (18/11962 participants) in the control group. There were no reports of cerebral venous sinus/cerebral venous thrombosis or splanchnic vein thrombosis. One event of mesenteric vein thrombosis was reported in the control group in the Oxford studies. No concurrent AEs of thrombocytopenia or platelet count decrease were reported in participants with a thromboembolic event. *Potential mechanism*: The mechanism is unknown. *Risk factors*: There are no known risk factors identified.

Safety concerns	Characterisation (DLP 28 June 2022)
CVST without thrombocytopenia[core]	*Frequency* • Post-market: **573 cumulative cases[1]** • Clinical-trials: **no cases** *Potential mechanism*: The exact mechanism of CVST without thrombocytopenia following administration with VAXZEVRIA is unknown. *Risk factors*: There are no known risk factors for the development of CVST without thrombocytopenia following vaccination
Immune-mediated neurological conditions[core]/Nervous system disorders, including immune-mediated neurological conditions[EU]	*Frequency* • Post-market: **38164 cumulative cases**, including 2609 interval cases. During the reporting period, the most commonly reported PTs were: Paraesthesia (1289), Hypoaesthesia (924), Guillain-Barre syndrome (GBS) (189), Neuralgia (176), Sensory disturbance (116), Sensory loss (59), Neuropathy peripheral (53), Multiple sclerosis (30), Myelitis transverse (28), Encephalitis (25), Small fibre neuropathy (23), Optic neuritis (18), Polyneuropathy (18), Chronic inflammatory demyelinating polyradiculoneuropathy (17), Demyelination (17), Acute disseminated encephalomyelitis (15), Multiple sclerosis relapse (11), Neuritis (10), Noninfective encephalitis (10), Miller Fisher syndrome (9), Myelitis (9), Peripheral sensory neuropathy (8), Encephalitis autoimmune (7), Encephalopathy (7), Demyelinating polyneuropathy (6), Myelin oligodendrocyte glycoprotein antibody-associated disease (6), Encephalomyelitis (5) • Clinical-trials: In the US study, neurologic or neuroinflammatory AESIs were reported **in 0.6%** (121/21,587 participants) in the VAXZEVRIA group and 0.4% (48/10,792 participants) in the placebo group. There were 5 non-serious AEs of facial paralysis, 1 SAE of a demyelinating event in the VAXZEVRIA group (event initially reported as GBS, which was subsequently diagnosed as an SAE of Chronic inflammatory demyelinating polyradiculoneuropathy). In the pooled Oxford studies, neurologic or neuroinflammatory AESIs were reported **in 0.7%** (81/12,282 participants) in the VAXZEVRIA group and 0.8% (90/11,963 participants) in the control group. The most frequently reported events were non-serious AEs of facial paralysis (4 vs 3). There were 3 SAEs of demyelinating events (2 cases in the VAXZEVRIA group [1 case of transverse myelitis, and 1 case of multiple sclerosis in a participant with pre-existing, but previously unrecognised, multiple sclerosis], and 1 case of myelitis in the control group.) *Potential mechanism*: Several hypothetical biological mechanisms have been proposed to explain the pathophysiology of neurologic adverse reactions following immunisation; most involve the concept of immunity and the possibility that the vaccine's immunostimulatory effect results in an aberrant immunologic response (Stratton KR et al 1994).

Safety concerns	Characterisation (DLP 28 June 2022)
	Risk factors: There are no known risk factors for the development of nervous system disorders, including immune-mediated neurological conditions, following vaccination.
Missing information	
Use of COVID-19 VACCINE ASTRAZENECA in pregnant and breastfeeding women[core]/Use during pregnancy and while breastfeeding[EU]	Data from more than **400 case reports of pregnant women** or women who became pregnant after receiving VAXZEVRIA do not suggest unusual patterns of pregnancy complications or foetal/neonatal outcomes. No increased risk of maternal thrombosis in combination with thrombocytopenia has been observed. Preliminary non-clinical safety studies have not indicated any concern to date, and available non-clinical, clinical and post-marketing data do not suggest a risk to breastfed newborns/infants. As VAXZEVRIA is intended for use in mass vaccination campaigns in a large proportion of the global population, the collection of pregnancy and infant outcomes data with the aim of further characterising the safety profile in this population, is still considered necessary
Use of COVID-19 VACCINE ASTRAZENECA in subjects with severe immunodeficiency[core]/Use in immunocompromised patients[EU]	Vaccines may be less effective in severely immunocompromised subjects. Although there is no evidence that the safety profile of this population receiving VAXZEVRIA will be different to that of the general population, given the paucity of data, the possibility cannot be excluded. Use of VAXZEVRIA in subjects with severe immunodeficiency will continue to be investigated in the ongoing PASS and additional Pharmacovigilance activity (a post-marketing observational study using existing secondary health data sources and systematic literature review).
Use in patients with autoimmune or inflammatory disorders[EU]	There is no evidence from COVID-19 VACCINE ASTRAZENECA clinical studies to date that the safety profile of this population differs from that of the general population. However, given the paucity of data, the possibility cannot be excluded. Use in patients with autoimmune or inflammatory disorders will be investigated in the ongoing PASS studies.
Use of COVID-19 VACCINE ASTRAZENECA in subjects with severe and/or uncontrolled underlying disease[core]/Use in frail patients with co-morbidities (eg, COPD, diabetes, chronic neurological disease, cardiovascular disorders)[EU]	There is no evidence that the safety profile of this population receiving COVID-19 VACCINE ASTRAZENECA will be different to that of the general population, given the paucity of data, the possibility cannot be excluded. Use of VAXZEVRIA in patients with severe and/or uncontrolled disease will continue to be investigated in the ongoing PASS program (post-marketing observational study using existing secondary health data sources).
Long-term safety[EU]	There are no known risks with a potentially delayed onset, with the exception of the theoretical concern of VAED/VAERD. There is currently no evidence suggesting an adverse long-term safety concern. At 6-months follow-up from Study D8110C00001 the AEs observed were consistent with the safety findings at the primary analysis. In the AZD1222 group, a small proportion of SAEs and AESIs were reported, with no clinically meaningful findings. Overall, VAXZEVRIA remains well-tolerated up to 6 months post dose. Long-term safety will be evaluated through follow-up in ongoing clinical studies in the VAXZEVRIA clinical development programme.

[CORE] : core-RMP specific safety concern; [EU] : EU-RMP specific safety concern
1 : Cumulative data are only available at the DLP of 28.06.2022. However, no new safety issues were raised during the period under review

Rapporteur assessment comment:

During the period under review, the **safety concerns have changed**:

- VTE is now considered as an important identified risk (see Section 2.3.4.2) [RSI]
- The MAH proposed to remove the important potential risk VAED/VAERD and the missing information 'Interaction with other vaccines' and 'Long-term safety' from the safety concerns. This is not supported as these topics will be assessed through the PASS using EU/UK databases (see variation II/0084/G). [Request for the next PBRER]

3. Benefit evaluation

3.1. New information on the benefit of Vaxzevria

3.1.1. Immunogenicity against Omicron

- The MAH conducted analyses to estimate the efficacy of Vaxzevria against **Omicron** variant of concern (see 1.3.6.). The results demonstrated that an homologous booster dose of Vaxzevria increases immunogenicity to both the ancestral strain and contemporary variants, including Omicron BA.5

  In order to further characterise the neutralising antibody response induced by a **primary series vaccination** of AZD1222 and as part of an ongoing commitment to evaluate immunogenicity of AZD1222 against emerging variants, 21 pools of serum from 210 AZD1222 vaccinees have been assessed in validated pseudovirus neutralisation assays for the **Alpha, Beta, Gamma, Delta, Lambda, Mu and Omicron variants of concern** (including subvariants BA.2, and BA.4/5). Additionally, given the importance of **booster vaccines** on the effectiveness of COVID-19 vaccines against SARS-CoV-2 Omicron variants, 10 pools of 10 vaccinees receiving 3 doses of AZD1222 were also evaluated against **Alpha, Beta, Gamma, Delta, and Omicron variants**.

  Collectively, these data show that 2-dose primary series immunisation with AZD1222 have limited but statistically significant reductions in neutralising antibody potency against the Alpha, Gamma, Delta, and Mu variants of concern. More substantial reductions in geometric mean titre ratio (GMTR) were observed against the Beta, Mu, and Omicron variants, with most primary series vaccination pools having no detectable neutralising antibodies to any sublineage of Omicron. A **homologous booster** dose of AZD1222 afforded **higher levels of neutralizing antibodies** (nAbs) **to all SARS-CoV-2 strains**. Notably, GMTs to all Omicron sublineages were similar or numerically higher after a 3rd-dose booster than GMTs to the ancestral strain after a 2-dose primary series.

3.1.2. Vaccine effectiveness

- Real world studies have demonstrated high vaccine effectiveness (VE) of a 2-dose **primary series** vaccination with AZD1222 against the **Omicron** variant in a variety of settings and populations, particularly with regard to prevention of severe disease. (see Table 11)

Table 11 - Real-World Vaccine Effectiveness (VE) of a 2-dose Primary Series Vaccination with AZD1222

Study	Days Post Dose 2	Outcome	Country	Population	VE	95% Lower CI	95% Upper CI	Vaccine Sequence
Kirsebom et al 2022	175+	Hospitalization	UK	65+ years	61	49.8	69.7	AZ+AZ
Stowe et al 2022	14-174	Hospitalization with ARI	UK	18-64 years	59	31.9	75.3	AZ+AZ
Stowe et al 2022	175+	Hospitalization with ARI	UK	18-64 years	53	41.7	62	AZ+AZ
Stowe et al 2022	14-174	Hospitalization with ARI	UK	≥ 65 years	71.2	50	83.4	AZ+AZ
Stowe et al 2022	175+	Hospitalization with ARI	UK	≥ 65 years	53.1	43.4	61.2	AZ+AZ
Cerqueira-Silva et al 2022	14-69	Hospitalization or death	Brazil	≥ 18 years	41	-8.1	67.8	AZ+AZ (previously infected)
Cerqueira-Silva et al 2023	140+	Hospitalization or death	Brazil	≥ 18 years	55.4	44.6	64.1	AZ+AZ (previously infected)
Cerqueira-Silva et al 2023	14-69	Hospitalization or death	Brazil	≥ 18 years	67.5	-7.9	90.2	AZ+AZ (previously infected)
Cerqueira-Silva et al 2023	140+	Hospitalization or death	Brazil	≥ 18 years	63.2	39	77.8	AZ+AZ (previously infected)
Cerqueira-Silva et al 2023	14-59	Severe disease	Brazil	≥ 18 years	77.1	72.9	80.6	AZ+AZ
Cerqueira-Silva et al 2023	150+	Severe disease	Brazil	≥ 18 years	67.8	66.7	69	AZ+AZ
Cerqueira-Silva et al 2023	60-149	Severe disease	Scotland	≥ 18 years	78.8	31.8	93.4	AZ+AZ
Cerqueira-Silva et al 2022	150+	Severe disease	Scotland	≥ 18 years	52.8	33.3	66.7	AZ+AZ

AZ AstraZeneca; ARI Acute Respiratory Infection; CI Confidence interval; VE Vaccine effectiveness.

- In addition, a small study in a prison population in Zambia (including over 10.5% of individuals who were living with HIV) assessed **effectiveness against Omicron** (any infection or symptomatic infection). Effectiveness of an AZD1222 primary series against infection with Omicron was 89.4% (95% CI: 59.5-97.8%), whilst effectiveness against symptomatic infection with Omicron was 85.1% (95% CI: 19.5-98.0%; Simwanza et al 2022).
- More recently, a public-private partnership, **COVIDRIVE**, reported data on the **effectiveness** of VAXZEVRIA against an early SARS-COV-2 **ancestral variant** (DELTA) and the currently predominant **omicron** variant of concern. COVIDRIVE's first study is a multicountry (Belgium, Italy, Spain, and Austria) hospital-based case-control study with a test-negative case-control design (TNCC), investigating brand-specific VE against hospitalisation. A total of **561 test-positive** cases and **200 test-negative** controls are included in the primary analysis for the 'fully vaccinated with two doses' exposure definition. Data collection is a combination of data collected prospectively (ie. from Site Initiation Visit onwards) and data collected retrospectively (ie, prior to the Site initiation Visit). The overall data collection period is from 01 June 2021 to 05 September 2022.

Disease-onset occurred between November 2021 and end of January 2022. **Delta** was the dominant SARS-CoV-2 variant during the initial months of the study for 44% of patients and it was also the most sequenced variant among the cases. **Omicron** predominated during the last eight months of the study period.

For **Delta**, the adjusted VE against COVID-19 hospitalisation for those 'fully vaccinated with two doses' is estimated at 92.9% (95% CI: -15.8; 99.6), 85.0%(95% CI: 41.3; 96.2), 71.0% (95% CI: 30.7; 87.9), and 71.8% (95% CI: 34.0; 87.9) for ≤8 weeks, ≤16weeks, ≤24 weeks and ≤32 weeks since the last dose, respectively.

For **Omicron**, adjusted VE against COVID-19 hospitalization for those 'fully vaccinated with two doses' is estimated at 74.8% (95% CI: -548.9; 99.1) and -9.5% (95% CI: -462.6; 78.7) for ≤24 weeks and ≤32 weeks since the last dose, respectively. The VE estimates for Omicron are to be interpreted with caution due to an insufficient sample size.

Rapporteur assessment comment:

Immunogenicity against Omicron

The MAH submitted in November 2022 immunogenicity data against SARS-CoV-2 variants through the REC 48.3 procedure and for which the CHMP completed the assessment in February 2023.

The CHMP concluded that "*the MAH has provided updated information regarding the analysis of neutralizing activity of sera from AZD1222 vaccinees against different SARS-CoV-2 variants. The results obtained demonstrate that an homologous booster dose of Vaxzevria increases immunogenicity to both the ancestral strain and contemporary SARS-CoV-2 variants, including Omicron BA.5.*"

Vaccine effectiveness

New information on effectiveness support positive vaccine effectiveness of a primary 2-dose scheme against Omicron (literature, Zambia study).

COVIDRIVE did not provide sufficient evidence on vaccine effectiveness of Vaxzevria against Omicron (insufficient sample size, no statistical significance of results)

These data support the fat the a primary vaccination with Vaxzevria as well as homologous boos give some protection in Omicron times. Sim. Heterologous boosts are not discussed.

4. Benefit-risk balance

4.1. New information on the benefits of Vaxzevria

New immunogenicity and effectiveness data support a positive effect of prime vaccination and homologous boost vaccination with Vaxzevria against variants, including Omicron B4.5.

4.2. New information on the risks of Vaxzevria

Safety items for which a **causal relationship** is considered as **a reasonable possibility** and which are proposed for addition in section 4.8 of the SmPC:

- Venous thromboembolism

Safety items for which new safety information **does not support a causal association** with Vaxzevria:

- Glomerulonephritis and nephrotic syndrome, including IgA nephropathy
- New daily persistent headache
- Histiocytic necrotizing lymphadenitis
- Hearing loss
- Corneal graft rejection

Safety items for which a **causal relationship** with Vaxzevria is **uncertain** and further discussion is required:

- Myositis, in particular dermatomyositis
- ADEM
- Menstrual disorders
- Severe cutaneous adverse reactions (SCARs), in particular erythema multiforme

Regulatory actions were taken regarding risks already identified in the previous PSUR:

- SmPC has been updated for cutaneous vasculitis (see section 1.3.2)

Signals and safety topics identified after the data lock point:

- Pemphigus and pemphigoid, closed by EMA in April 2023: the causal relationship with Vaxzevria is uncertain and further discussion is required in next PSURs.
- Myocarditis and pericarditis, identified by EMA in April 2023: request to submit in depth analyses through a LEG (to be submitted by the end of May 2023)

Finally, it should be noted that no new risk or new level of risk was identified after a booster dose with Vaxzevria or after an heterologous boost following a primary vaccination with Vaxzevria. Uncertainties regarding the risk of TTS after an homologous vs an heterologous boost with Vaxzevria remain.

Moreover, some serious ADRs might present with a higher risk or a more severe clinical presentation in the population of younger adults. This is the case of TTS (more severe outcome), GBS (higher IRR observed in 40-64 years age group) and VTE (higher IRR observed in 15-39 and 40-64 years age group).

The PRAC Rapporteur concludes that **the safety profile of Vaxzevria changed during the reporting period**, with VTE recognised as a new important identified risk, which remains very rare.

4.3. Conclusion on the benefit/risk balance

New information on the benefit of Vaxzevria does not modify the conclusions of previous assessments.

The PRAC Rapporteur considers that based on safety information collected during the period under review [from 29.06.2022 to 28.12.2022] the B/R balance of the vaccine does not markedly change.

However, the **risks of SARS-CoV-2 infection** and the **context of treatment and prevention of the disease** have evolved. There is a body of evidence suggesting that omicron variant was less severe than the previous Delta variant[14]. New circulating sub-variants have not been shown to demonstrate a higher impact on disease severity[15]. The reduced risk for severe disease may reflect partial protection conferred by prior infection or vaccination. However, animal studies that show lower viral levels in lung tissue and

[14] DynaMed. https://www.dynamed.com/condition/covid-19-novel-coronavirus#GUID-96506C86-74CD-4B5F-B9CE-9A5BA80EAE3D
[15] WHO - XBB.1.5 Updated Risk Assessment, 24 February 2023. https://www.who.int/docs/default-source/coronaviruse/22022024xbb.1.5ra.pdf

milder clinical features (eg, less weight loss) with Omicron compared with other variants provide further support that Omicron infection may be intrinsically less severe[16].

The last Weekly COVID-19 country overview from the ECDC[17] confirmed that at the pooled EU/EEA level: "The epidemiological picture over the past 12 months since the initial large Omicron peak has been characterised by periodic waves of infection approximately every 2–3 months. There has been a general downward trend in the height of the associated peaks in reported cases, hospitalisations, ICU admissions, and deaths in this period".

Moreover, TTS, GBS, and VTE, the key risks identified for Vaxzevria, are **greater risks in young adults who benefit less from vaccination**.

The **well-established safety profile** of the vaccine, which includes serious ADRs, **has been accepted at a certain point of the pandemic**. It is becoming now challenging to balance these very severe risks with the benefits of the vaccine, in particular in the younger population, and especially after more alternative vaccines were made available.

Overall, form a regulatory perspective and without taking into account the changes in the epidemiological context, the B/R remains unchanged.

5. Rapporteur Request for supplementary information

1. **Exposure data**

   The MAH is requested to provide clarification regarding any remaining batches in the EU/EEA market (how many, in which countries) and their expiry dates. The MAH should also clarify his plans regarding the marketing of Vaxzevria in EU/EEA.

2. **VTE**

   The MAH is requested to update the RMP at the next regulatory opportunity with upgrading of 'thrombosis' from important potential risk to important identified risk.

3. **Dermatomyositis**

   - The MAH is requested to provide a O/E analysis specific for dermatomyositis. Optimal background incidence rates for dermatomyositis should be used. Whenever possible, it should take into account a possible change in the occurrence of dermatomyositis during SARS-CoV-2 circulation.
   - Based on all evidence available for dermatomyositis, the MAH should discuss the need to update the product information and/or the risk management plan .
   - Finally, the MAH is requested to consider the monitoring of this event within the ongoing PASS "Post-marketing observational study using existing secondary health data sources".

[16] UpToDate. https://www.uptodate.com/contents/covid-19-epidemiology-virology-and-prevention/print
[17] ECDC Country overview report : week 17 2023. https://covid19-country-overviews.ecdc.europa.eu/

6. MAH responses to Request for supplementary information

Question 01 - Exposure data

The MAH is requested to provide clarification regarding any remaining batches in the EU/EEA market (how many, in which countries) and their expiry dates. The MAH should also clarify his plans regarding the marketing of Vaxzevria in EU/EEA.

MAH's response

There are no remaining batches in the European Union/European Economic Area (EU/EEA) markets, and AstraZeneca has no current plans for placing VAXZEVRIA in EU/EEA markets. Considering the evolving COVID-19 environment, the changing variants of concern and the dynamic global landscape, AstraZeneca continues to review VAXZEVRIA from a global perspective and will update the Agency as soon as there are new plans for VAXZEVRIA supply in the EU/EEA.

Rapporteur assessment comment:

The MAH clarified that there are no remaining batches in the EU/EEA and no plans for placing Vaxzevria in EU/EEA markets.

Issue resolved

Question 02 - VTE

Recommendations: In view of available data on Venous Thromboembolism from the literature, the Rapporteur considers a causal relationship between COVID-19 Vaccine (ChAdOx1-S [recombinant]) and Venous Thromboembolism is at least a reasonable possibility. The PRAC Rapporteur concluded that the product information of products containing COVID-19 Vaccine (ChAdOx1-S [recombinant]) (VAXZEVRIA) should be amended accordingly.

Update of sections 4.4 and 4.8 of the SmPC to add the adverse reaction Venous Thromboembolism with a frequency very rare and a warning/precaution as stated below. The Package leaflet is to be updated accordingly.

Request: The MAH is requested to update the RMP at the next regulatory opportunity with upgrading of 'thrombosis' from important potential risk to important identified risk.

MAH's response

Venous Thromboembolism

Venous thromboembolism is a broad topic which includes common sites such as deep vein thrombosis (DVT) and pulmonary embolism (PE), and uncommon sites such as cerebral venous sinus thrombosis (CVST) (with and without thrombocytopenia), and thrombosis in other venous sites that occur in the setting of thrombosis with thrombocytopenia syndrome (TTS); the later are listed adverse drug reactions in the current EU SmPC.

Venous thromboembolism has been closely monitored under the Adverse event of special interest (AESI)/Important potential risk 'Thrombosis' for VAXZEVRIA. This topic was evaluated and discussed in the Periodic Benefit Risk Evaluation Reports (PBRERs) (with data lock points [DLPs] of 28 June 2022 and 28 December 2022), where AstraZeneca concluded that there was insufficient evidence of a causal relationship between VAXZEVRIA and VTE.

Upon carefully studying the analysis of the observational studies described in the assessment report, AstraZeneca finds that the significant heterogeneity and limitations of these studies prohibit a meaningful inference of a consistent association between VAXZEVRIA and VTE (see Appendix A for further details on observational studies, the observed-to-expected (O/E) analysis for VTE without thrombocytopenia, and VTE events from COV pooled analysis). Therefore, with consideration of the available evidence from various sources and AstraZeneca's analysis of the observational studies presented, AstraZeneca does not consider an update to SmPC Section 4.8 for inclusion of VTE as an Adverse Drug Reaction (ADR) to be warranted at this time.

The current EU SmPC has specific warnings and precaution text covering TTS and CVST in place. Taking into consideration the presence of these warning text and lack of sufficient evidence supporting a causal association for VTE, AstraZeneca opines that an update to Section 4.4 to include a warning/precaution for VTE is not warranted at this time.

RMP (RSI)

As noted above, AstraZeneca does not agree to include VTE/Thrombosis as an ADR in Section 4.8 of the SmPC. Hence, AstraZeneca remains of the opinion that "Thrombosis" should be retained as an important potential risk in the EU RMP.

Rapporteur assessment comment:

The MAH does not agree that a causal relationship between Vaxzevria and Venous Thromboembolism is at least a reasonable possibility. The MAH provided a detailed argumentation in Appendix A of the response document.

Overall MAH's comments regarding the Rapporteurs' epidemiological assessment:

- *No pooled meta-analysis or heterogeneity assessments were presented. The forest plots were presented without details of the methods or analyses used.*
- *The results, CIs, populations, follow-up times, dose regimes, age groupings, comparator groups, and settings all varied, making it statistically inappropriate to combine such studies in a forest plot and to infer a causal relationship between VAXZEVRIA and VTE in "younger age groups".*
- *All included studies were observational and hence confounding must be taken into consideration. To infer a causal relationship based on a selection of the available observational studies is not appropriate. Other type of studies, biological plausibility, and case level evidence must also be considered.*

As discussed in the previous and current AR, the assessor agrees that the heterogeneity in study design and methods make it difficult to perform meta-analysis with pooled estimates. To clarify, the figures presented in section 2.3.4.2 of the AR merely reflect the estimates from the different publications, without additional analysis. By presenting the individual study results in a visual manner, valuable insights can still be gained. It allows for exploration of potential associations and identification of trends across different study settings and populations.

The selection of the largest cohort and case-control studies with at least 1 million doses of exposure to Vaxzevria or at least 100,000 person-years follow-up is considered appropriate in this context, and these are all well-conducted pharmacoepidemiological studies.

The variation in study characteristics, such as populations, follow-up times, dose regimes, etc., is a common challenge in observational studies. While this heterogeneity may limit the ability to directly compare the studies, it does not necessarily invalidate the findings. The consideration of confounding factors is crucial in observational studies, and the assessor acknowledges their potential influence on the

observed associations. However, it is important to note that while confounding can introduce bias, it does not negate the relevance of the findings altogether.

The biological mechanism is generally difficult to prove, even for identified risks. Hypotheses are often put forward but rarely proven. To note is that during the EMA hosted workshops on TTS and myocarditis, the actual mechanism for the pathogenesis of these adverse events is not fully established and several areas require additional investigation[18,19] . This does not preclude that a causal relationship between vaccination and adverse event is at least a reasonable possibility.

While case-level evidence can also contribute to the understanding of causal relationships, they are not the sole determinants. As part of LEG 103, post-marketing data of VTE without thrombocytopenia has been reviewed by the MAH with the majority of cases considered as possible with risk factors/confounders or with limited information (7394 cases). As VTE is a multifactorial condition and various underlying risk factors may contribute to its occurrence, the case-level evidence has limitations. For this type of events, observational studies with larger samples sizes offer a more robust approach to assess the risk of VTE at a population level.

Additional Observed-to-Expected analysis of VTE provided by the MAH

- Cases: VTE without thrombocytopenia.

- Background incidence: meta-analysis of IRs from ACCESS protocol (VTENoTP; 2013, 2018 & 2019) (Willame et al 2021). VTENoTP includes DVT and PE.

- Risk windows: 7, 14, 21, and 28 day risk windows

- Stratification: age (EEA, UK, Australia, Brazil), age & sex (UK). Additional analyses also including cases with an unknown TTO, as a conservative approach.

- Results: observed cases were significantly less than expected for all stratifications.

The results should be interpreted cautiously because they may be highly dependent on the assumptions, in particular the background incidence and the level of under-reporting. It should be noted that there are huge differences between observed and expected values, sometimes less than an order of magnitude and about 4- to 6-fold times lower in young females or in Brazil. These estimates probably reflect a large percentage of under-reporting and/or other sources of bias or methodological flaws. It would be useful to explore what would be a reasonable estimation of under-reporting for each type of outcome.

As discussed in section 2.3.4.2 of the AR, analysis performed by EMA (Cut-off date 07.12.2022) found a significative imbalance both for DVT without thrombocytopenia and for Pulmonary embolism in the younger age-groups. The background rates used in the analysis are based on SIDIAP linked to hospital discharge data (Spain).

[18] Buoninfante, A., Andeweg, A., Baker, A.T. *et al.* Understanding thrombosis with thrombocytopenia syndrome after COVID-19 vaccination. *npj Vaccines* **7**, 141 (2022). https://doi.org/10.1038/s41541-022-00569-8

[19] https://www.ema.europa.eu/en/events/ema-virtual-workshop-myocarditis-post-covid-19-vaccination

DVT without Thrombocytopenia (Risk period 14 days):

Age group	Doses (Total)	N exp cases (T	N obs cases (T	O/E ratio (95% CI) (Total)	O/E ratio (95% CI) (Male)	O/E ratio (95% CI) (Female)
20-29	2758847	18.94	28	1.48 (0.98 - 2.14)	0.72 (0.19 - 1.85)	1.72 (1.09 - 2.58)
30-39	4390272	50.88	82	1.61 (1.28 - 2)	0.83 (0.49 - 1.31)	2.19 (1.69 - 2.8)
40-49	6508887	133.05	142	1.07 (0.9 - 1.26)	0.47 (0.32 - 0.66)	1.66 (1.36 - 2.01)
50-59	7592100	267.52	222	0.83 (0.72 - 0.95)	0.64 (0.53 - 0.78)	1.06 (0.87 - 1.28)
60-69	23763607	1448.06	460	0.32 (0.29 - 0.35)	0.27 (0.23 - 0.3)	0.37 (0.32 - 0.42)
70-79	9578416	991.56	246	0.25 (0.22 - 0.28)	0.23 (0.19 - 0.28)	0.26 (0.21 - 0.3)
80+	1409736	209.62	49	0.23 (0.17 - 0.31)	0.11 (0.05 - 0.22)	0.31 (0.22 - 0.42)
Total	56005826	3119.62	1297	0.42 (0.39 - 0.44)	0.32 (0.29 - 0.35)	0.51 (0.47 - 0.55)

Pulmonary embolism (Risk period 14 days):

Age group	Doses (Total)	N exp cases (T	N obs cases (T	O/E ratio (95% CI) (Total)	O/E ratio (95% CI) (Male)	O/E ratio (95% CI) (Female)
20-29	2758847	9.31	24	2.58 (1.65 - 3.84)	2.23 (0.72 - 5.19)	2.55 (1.51 - 4.03)
30-39	4390272	21.46	32	1.49 (1.02 - 2.11)	1.5 (0.84 - 2.48)	1.48 (0.86 - 2.37)
40-49	6508887	64.34	73	1.13 (0.89 - 1.43)	0.85 (0.57 - 1.21)	1.44 (1.04 - 1.95)
50-59	7592100	161.54	124	0.77 (0.64 - 0.92)	0.61 (0.47 - 0.78)	1.02 (0.78 - 1.31)
60-69	23763607	1047.69	332	0.32 (0.28 - 0.35)	0.28 (0.24 - 0.33)	0.36 (0.31 - 0.43)
70-79	9578416	759.14	217	0.29 (0.25 - 0.33)	0.29 (0.24 - 0.34)	0.28 (0.23 - 0.34)
80+	1409736	150.13	56	0.37 (0.28 - 0.48)	0.25 (0.13 - 0.41)	0.45 (0.32 - 0.61)
Total	56005826	2213.6	912	0.41 (0.39 - 0.44)	0.36 (0.32 - 0.39)	0.48 (0.43 - 0.52)

VTE events from final pooled analysis of COV001/2/3/5 studies (ongoing variation EMEA/H/C/005675/II/0089)

The MAH provided additional details on the events of DVT and subclavian vein thrombosis (1 participants): time to onset was over 100 days and 4 events of PE post unblinding wit median time to onset of 305 days (range: 216 to 400 days) after Dose 1 and 332 days (range: 181 to 336) after Dose 2. This variation is ongoing.

In conclusion, MAH's comments regarding the Rapporteurs' epidemiological assessment are noted but the opinion of the MAH is not endorsed. The additional O/E analyses provided by the MAH do not change the previous conclusions of the PRAC Rapporteur. A causal association between Vaxzevria and VTE is considered to be at least possible and updates of the SmPC and the PIL are considered warranted.

Issue not resolved

Question 03 - Dermatomyositis

- **The MAH is requested to provide a O/E analysis specific for dermatomyositis. Optimal background incidence rates for dermatomyositis should be used. Whenever possible, it should take into account a possible change in the occurrence of dermatomyositis during SARS-CoV-2 circulation.**
- **Based on all evidence available for dermatomyositis, the MAH should discuss the need to update the product information and/or the risk management plan .**
- **Finally, the MAH is requested to consider the monitoring of this event within the ongoing PASS "Post-marketing observational study using existing secondary health data sources".**

Summary of the MAH's response

The MAH provided a review of case reports of Dermatomyositis (DM) and an updated Observed-to-Expected (O/E) analysis

Review of case reports

Search criteria: Cumulative search through 14 April 2023; MedDRA PT: Dermatomyositis".

Results: The search retrieved **28 case reports of DM** (excluding 5 potential duplicates); 6 case reports were from the literature, 2 from non-interventional/post-market studies, 16 from regulatory authorities and 4 from spontaneous sources.

Most of the cases were reported from the UK (n = 6), followed by Italy (n = 4), Brazil (n = 3); Canada and Germany (n = 2 each) and from Austria, Denmark, France, India, Morocco, Philippines, Spain, Sweden, Taiwan, and the United States (n = 1 each).

Gender/Age: No gender imbalance (female [48%] and male [52%]); median age of 60 years (range from 27 to 78 years).

Seriousness and outcome: 25 (89.3%) were serious and 15 (53.6%) were medically confirmed. There were 3 fatal reports, 4 reported as life-threatening, 10 required hospitalizations, 1 reported disability, and in the remaining 7 cases, the event was considered as medically important. The outcome of the adverse event DM was reported as resolved/resolving/resolved with sequalae in 46% (n = 11), fatal in 8% (n = 2), not resolved in 46% (n = 11), and unknown for 4 events.

The 3 cases with a fatal outcome were described in the PSUR (see Section 2.3.22).

TTO/Dose: The TTO was available in 25 cases and ranged from 1 to 146 days; median TTO was 17 days; 15 (53.6%) reported DM after the first dose and 11 (39.3%) after the second dose (dose unknown in 2 cases).

Case classifications based on EULAR/ACR and WHO-UMC Causality Assessment

All 28 cases were assessed and classified according to European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) Idiopathic Inflammatory Myopathies (IIM) classification criteria (Lundberg et al 2017). In most cases, clinical details of the event, relevant laboratory values, muscle biopsy findings, electromyographic study results, and autoantibodies profiles were not provided but a conservative approach was used for classification criteria for both possibility of IIM and subgroup Dermatomyositis.

For the WHO-UMC Causality Assessment, a risk window of 0 to 28 days was considered (Stübgen 2014, Shinjo et al 2012).

The Table 12Table 12 presents the results of the EULAR/ACR classification and WHO-UMC causality assessment.

Table 12 - Overview of WHO-UMC Causality Assessments and EULAR/ACR Classifications for Dermatomyositis Case Reports with VAXZEVRIA Cumulatively through 14 April 2023

WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	EULAR/ACR Definite IIM	EULAR/ACR Probable IIM	Not Evaluable	Total Number of Cases
Certain	Certain	0	0	0	0
Probable/Likely	Probable-Likely	0	0	0	0
Possible	Possible with risk factors/confounders	0	0	5	5
	Possible with limited information	2	2	9	13
Unassessable/ Unclassifiable	Unassessable/ Unclassifiable with risk factors/confounders	0	0	2	2
	Unassessable/ Unclassifiable with limited information	0	1	2	3
Unlikely	Unlikely	1	2	2	5
Conditional/ Unclassified	Conditional/Unclassified	0	0	0	0
Total		**2**	**6**	**20**	**28**

AZ = AstraZeneca; EULAR/ACR = European Alliance of Associations for Rheumatology/American College of Rheumatology; IIM = idiopathic inflammatory myopathies; WHO-UMC = World Health Organization – Uppsala Monitoring Centre.

In the PRAC preliminary AR (see Section 2.3.22 and Appendix 02 of this report), the Assessor considered 4 cases as 'Probable'. The MAH reassess these cases and still retains the earlier position and considers these cases as "Possible' as per WHO-UMC causality assessment criteria. Details are not reproduced here and are available in the Responses of the MAH.

Risk factors/Confounders: In most (19, 82.1%) case reports, there was insufficient information with respect to either TTO, medical history/comorbidities (e.g., cardiovascular disease, respiratory disease, chronic renal disease, obesity, etc.), concomitant medication details , or clinical course for a comprehensive causal assessment. The median age for this case series is 60 years, a risk factor for cancer (~30% of DM cases are associated with an underlying malignancy, in which it is considered a paraneoplastic syndrome (Maoz et al 1998)); however, detailed cancer screening was not performed in any case. Similarly, common risk factors for cancer were not reported for most patients in this series.

Only one patient was reported to have concomitant use of atorvastatin (which may predispose to development of DM), this seems less than the use of statins in overall population of median age 60 years.

In summary, the overall limited information on risk factors for DM precluded appropriate medical assessment of causal association of VAXZEVRIA with DM in most cases.

O/E analysis

An O/E analysis was performed for all DM cases cumulative through 14 April 2023, with a 0 to 28 days risk window. The background rates were sourced from Kronzer et al 2021. A subgroup analysis based on stratifications of age group, gender for UK, and age stratified for region (UK/EU/AU and Brazil and worldwide) and risk window was also performed. As a conservative approach, all cases with TTO within 0 and 28 days and all cases with unknown TTO were included in the O/E analysis. The vaccine exposure by doses administered for the O/E analysis within the above-mentioned risk window were considered from EU, Australia, UK, and Brazil where the relevant exposure data were available. As the vaccine administration data from EU and Australia were not available for the below specified age-groups, using the recent population data from EU and Australia, the estimates of vaccine exposure for the age groups were calculated (Australian Bureau of Statistics 2021 and Statistisches Bundesamt (Destatis) 2021).

Results of the O/E analysis showed observed cases post vaccination to be less than expected with all stratifications (age group, gender and region) (see Table 13 Appendix B of the MAH's Responses for further details).

Table 13 - Observed-to-Expected Analysis of Dermatomyositis

Age group	Incidence rate /100,000 PY	Exposure	Cases with Known TTO		Cases including UNK TTO	
			Observed/ Expected cases	O/E ratio	Observed/ Expected cases	O/E ratio
Global - Overall	1.1	470230639	18/ 396.5	0.05 (0.03 - 0.07)	21/ 396.5	0.05 (0.03 - 0.08)
UK/EU/AU/BZ - Global	1.1	284863084	13/ 240.2	0.05 (0.03 - 0.09)	15/ 240.2	0.06 (0.03 - 0.1)
18-39	0.5	62038520	2/ 23.8	0.08 (0.01 - 0.3)	2/ 23.8	0.08 (0.01 - 0.3)
40-59	1.2	107808094	3/ 99.2	0.03 (0.01 - 0.09)	3/ 99.2	0.03 (0.01 - 0.09)
60-79	1.7	80371925	8/ 104.7	0.08 (0.03 - 0.15)	8/ 104.7	0.08 (0.03 - 0.15)
>80	3.2	10198020	0/ 25	0 (0 - 0.15)	0/ 25	0 (0 - 0.15)

Limitations/ uncertainties:

- Background incidence rate for DM: The incidence rate is based on the pre-pandemic/unvaccinated population (period 1995-2019; US). The data included is based on 29 confirmed DM cases by Kronzer et al 2021. The majority of observed cases were from the UK followed by EEA and Brazil. The geographic and environmental factors (viral infections in particular) can be a risk factors for DM in general. The geographic distribution of myositis specific antibodies for Mi-2 and its association with UV radiation and proximity to the equator area was observed (Aguilar-Vazquez et al 2021).
- The incidence rate considered for O/E analysis was based on the confirmed cases (29 cases) included in the analysis by Kronzer et al 2021. The O/E analysis was performed by combining the diagnostically confirmed and unconfirmed cases and the observed cases were significantly lower than expected.
- Time to onset: Given the limitations of spontaneous reports and including cases with unknown TTO with short risk window stratifications would lead to over-estimation of observed events resulting in a high O/E ratio.
- The O/E analyses does not account for confounding/risk factors which might be present in the cases. Also, when stratified by age/gender, there are small numbers of cases in each stratification, which should be considered when interpreting the significance of the results.

Update of PI/RMP

Cumulative review of dermatomyositis (clinical trial and post-marketing data) is presented in Appendix B of the MAH's Responses. Based on the review of available cumulative data, the MAH considers that there is insufficient evidence to suggest a causal association between dermatomyositis and VAXZEVRIA. No changes to the Company Core Data Sheet (CDS)/product information or RMP are recommended for dermatomyositis and the topic will continue to be monitored as part of AstraZeneca's ongoing safety surveillance activities for VAXZEVRIA.

PASS study

The request to include the event of dermatomyositis within study D8111R0006 (MEA007) is currently under consideration and discussions with the post-authorisation safety study (PASS) coordinating centre, Research Triangle Institute – Health Solutions (RTI-HS), is ongoing. The outcome of these discussions will be communicated with the Feasibility Assessment Report for comparative analysis planned for submission in August 2023.

Rapporteur assessment comment:

Review of case reports

As requested, the MAH performed a cumulative review of Dermatomyositis (DM) cases.

There was no information from pre-clinical data nor clinical study data.

The cumulative review of the cases (DLP 14 April 2023) identified **28 case reports of DM**:

- The majority of cases (n=17; 61%) were from EU/UK
- No imbalance between male (52%) and female (58%) is observed
- The majority of cases occurred in subjects younger than 70 yo: 28% in 18-49 yo; 16% in 50-59 yo; 36% in 60-69yo
- 15 cases occurred after the 1st dose and 11 after the 2nd dose (unknown dose in 2 cases)

- 15 (54%) cases were medically confirmed
- 25 (89%) were serious and 3 had a fatal outcome. Two of these fatal cases (i.e., [redacted] and [redacted]) were considered as unlikely related to the vaccination; 1 case of atypical presentation of DM (i.e., [redacted]) was assessed as probably related to the vaccination (according to the BE Rheumatologist expert; assessed as possible with limited information by the MAH)

The MAH did not identify any certain or probable cases using the WHO-UMC causality scale. The majority of cases (18) were assessed as 'Possible', including cases with risk factors/confounders (5) or cases with limited information (13). The MAH also categorised DM according to EULAR/ACR[20] classification criteria. It identified 8 definite/probable cases of myositis, of which 4 were assessed as possible with limited information, 3 as unlikely and 1 as unassessable regarding causality.

The MAH re-assessed the 4 cases which were classified as probable by the BE Rheumatologist expert but retained the earlier position and considers these cases as possible with limited information.

Overall, the lack of in-depth information precludes a thorough analysis in most of the cases, in terms of diagnosis ascertainment and causality assessment. Most of DM events (20/28) were not evaluable according to the EULAR/ACR criteria. This may be due to the poor documentation of the cases and/or atypic presentation of myositis. Similarly, none of the case reports were assessed as certain for the causal relationship. Four cases were assessed as probable (by the BE expert; considered as possible with limited information by the MAH). The cumulative review does not provide sufficient evidence to confirm or rule out a causal association between dermatomyositis and Vaxzevria.

O/E analysis

An updated O/E analysis was performed for dermatomyositis and shows that the number of observed cases is much lower than expected : O/E (significantly) <1 in the risk window 0-28 days, globally and for the region EU/UK/ Australia/Brazil, and in the different age groups.

The background incidence rate used was based on Kronzer et al. 2021. The incidence was estimated from a longitudinal cohort of >500,000 individuals in the US (Olmsted County; Minnesota) from 1995 to 2019. The overall adjusted incidence of DM was 1.1 (95% CI 0.7–1.5) per 100,000 person-years which is higher than previously reported. A higher incidence in female and in older subjects is observed (see Table 3 below).

Table 3. Age- and sex-specific dermatomyositis incidence rates in Olmsted County, 1995–2019*

	Female		Male		Total	
Age, years	No.	Rate (per 100,000)	No.	Rate (per 100,000)	No.	Rate (per 100,000)
18–39	5	0.8	1	0.2	6	0.5
40–59	10	2.1	1	0.2	11	1.2
60–79	7	2.7	1	0.5	8	1.7
80+	4	5.1	0	0.0	4	3.2
Total, median (95% CI)	26	1.9 (1.1–2.6)†	3	0.2 (0.0–0.5)†	29	1.1 (0.7–1.5)‡

* 95% CI = 95% confidence interval.
† Age-adjusted to the US White 2000 population.
‡ Age- and sex-adjusted to the US White 2000 population.

In the previous O/E analysis for myositis overall (see section 2.3.22), the background IR was based on Svensson et al 2017. In this paper, IR for DM was also estimated and varied between 0.24 and 0.39 per 100,000 py (period 2007-2011; Sweden). Overall, annual myositis incidence estimates are 0.5-1 case per 100,000 adults; of which 35%-50% have DM, with peak onset between ages of 30 and 50 years[21].

Overall, the O/E analysis does not raise any signal. However, the results should be interpreted in view of the limitations and uncertainties on background IR, case ascertainment, TTO, etc. With very rare events,

[20] EULAR/ACR = European Alliance of Associations for Rheumatology/American College of Rheumatology
[21] DynaMed. Dermatomyositis. EBSCO Information Services. Accessed June 12, 2023. https://www-dynamed-com.gateway2.cdlh.be/condition/dermatomyositis

O/E analysis may be of limited value, especially when stratification results in the analysis of very small number of cases.

Disproportionality analysis in EV

The assessor ran a disproportionality analysis in EV which did not raise any signal: ROR(-) =0.25 (n=29).

Conclusion

Available evidence from the cumulative review of cases, O/E analysis and disproportionality analysis is not sufficient to confirm or rule out a causal association between dermatomyositis and Vaxzevria. It is thus agreed that no update of the PI or the RMP is needed at this stage.

However, considering the severity of the disorder and temporal association in the majority of the cases, DM should continue to be monitored. More particularly, all efforts should be made to assess DM in the PASS D8111R0006. It is noted that this is currently under consideration and will be further reviewed in the Feasibility Assessment Report for comparative analysis planned for submission in August 2023 (MEA007). **New cases of DM should also continue to be presented in the PSUR as well as the literature. [Request for the next PSUR]**

Issue not fully resolved

7. Comments from Member States

MS1 comment

We appreciate the thorough assessment of data for this PSUR. We endorse the PRAC Rapp assessment report, especially the benefit-risk assessment report performed by our colleagues.

Regarding the inclusion of venous thromboembolism, we agree that a causal relationship between the vaccine and venous thromboembolism cannot be ruled out. However, it is not clear why the frequency "very rare" is proposed. According to the footnote at the end of the table, the frequency is based on post-marketing cases. We propose to change the frequency to frequency "unknown".

Rapporteur assessment comment:

The endorsement comments are appreciated.

Regarding the inclusion of venous thromboembolism, the proposal for a frequency of 'very rare' was based on the Andrews et al, 2022. As this was the only study calculating an attributable risk for VTE, the proposal to change the frequency to 'unknown' is agreed upon.

The recommendations have been updated accordingly.

MS2 comment

Generally, the PRAC Rapporteur assessment is endorsed, that the occurrence of venous thromboembolism after Vaxzevria exposure is a reasonable possibility. But we have some editorial comments regarding the proposed variation concerning venous thromboembolism (new text **underlined and in bold**, deleted text ~~strike through~~):

SmPC section 4.4

Venous thromboembolism: Venous thromboembolism (VTE) has been observed very rarely following vaccination with Vaxzevria~~. This~~ **and** should be considered for individuals at increased risk for VTE.

Package leaflet section 2

- If you have risk factors for blood clots in your veins (venous thromboembolism (VTE)**).**

Blood disorders

~~Venous thromboembolism:~~ Blood clots in veins (venous thromboembolism (VTE)) have been observed very rarely following vaccination with Vaxzevria.

Package leaflet section 4

- blood clots in veins (venous thromboembolism (VTE)**)**

Rapporteur assessment comment:

The endorsement comments regarding venous thromboembolism are appreciated. The editorial comments are taken into account and the recommendations have been updated accordingly.

MS3 comment

We endorse the PRAC Rapporteur's conclusions and have some further suggestions for consideration with regard to the text proposed for section 4.4 on VTE.

We note that the studies presenting results for the younger age-groups consistently found incidence rate ratios for VTE clustering above 1, that in the studies (Andrews et al 2022, Corrao et al 2022) which presented results stratified by sex and age this increased risk was only reported in younger age groups and in women and that the O/E analyses results found a significant imbalance both for DVT without thrombocytopenia and for pulmonary embolism in the younger age-groups and especially in younger women. Taking this evidence into account we would suggest consideration be given to whether or not there is sufficient evidence to reflect younger age and female sex as risk factors to VTE associated with Vaxzevria.

Rapporteur assessment comment:

The endorsement comment is appreciated.

The assessor carefully evaluated whether there is sufficient evidence to establish younger age or female sex as risk factors for venous thromboembolism (VTE). According to the study conducted by Andrews et al. in 2022, a significant increase in the risk of VTE was observed among individuals aged 15-39 and 40-64 years. However, the authors did not find evidence indicating a gender effect for any outcome following the administration of a first dose of Vaxzevria. Similarly, Whiteley et al. in 2022 noted an elevated risk of venous events in individuals <50 years of age, but no gender imbalance was observed. On the other hand, Corraro et al. in 2022 and the observed-to-expected ratio suggest an increased risk in women below 50 years of age but not in men. Therefore, further confirmation is needed to establish a significant imbalance of VTE based on gender. While a clear trend indicating a higher risk of VTE with decreasing age categories is evident, it is challenging to define a specific cut-off to categorize 'younger age groups' (such as <50 years or <65 years). Consequently, the evidence is found not sufficient at this stage and it is proposed to refrain from including specific risk factors like gender or younger age in SmPC.

Appendix 01: Assessment of the responses to the questions

Responses to Issues to be addressed in the next PSUR

Request 1. Acute disseminated encephalomyelitis (ADEM)

The MAH is requested to provide a discussion of ADEM, including but not be limited to:

(i) an updated cumulative review of cases of ADEM,
(ii) an updated literature review, with a focus on new relevant epidemiological studies,
(iii) a discussion on the need to further update the PI and/or RMP.

Moreover, the MAH is requested to carefully review the evaluation of cases of ADEM as discrepancies regarding the BCC evaluation (e.g. case [redacted] classified as BCC Level 2 whereas a 4-month FU suggests a monophasic disease course) and WHO-UMC causality assessment (e.g. case [redacted] assessed as unlikely due to incorrect TTO) have been noticed.

AstraZeneca response: Please refer to the below mentioned AstraZeneca clarification response for the two cases and refer to Appendix 11 for the comprehensive evaluation of cases [redacted] and [redacted]. Please refer to Section 15.2.1 for an updated cumulative review of cases of acute disseminated encephalomyelitis (ADEM), an updated literature review, with a focus on new relevant epidemiological studies and a discussion on the need to further update the PI and/or RMP.

Rapporteur assessment comment of specific cases:

- Regarding the causality assessment, the 2 other cases ([redacted] and [redacted]) suggest a probable causal association (i.e. plausible TTO, extensive work-up to exclude other possible causes, patients without any familiar and personal history of neurological diseases or previously asymptomatic).
- Escola et al (2022) [redacted] described one case report of MOG Ab-associated encephalomyelitis 9 days after the 1st dose of VAXZEVRIA in a 43/F subject with unremarkable medical history, except for migraine. This case reported an atypical presentation of MOG Ab-associated encephalomyelitis that was consistent with bacterial infection. An autoimmune disorder was suspected and bacterial meningomyelitis was considered in the main differential diagnosis. However, an extensive infectious evaluation panel was performed for over 1500 pathogens and was not able to identify the infectious cause. Of note, the subject exhibited a low anti-Sars-CoV-2 serum titre. The 2nd dose for vaccination was an mRNA vaccine and no relapse of symptoms was observed. The PRAC rapporteur considered this case of ADEM as probably causally related with VAXZEVRIA vaccination.
- Rinaldi et al (2022) [redacted] presented a case of ADEM in a 45/M without any previous neurological history ([redacted]). The TTO was 12 days after vaccination. Serology panel was negative for recent infection but positive IgG were detected for multiple viruses known to produce latent infection (i.e. adenovirus, herpes simplex 1, HHV6, cytomegalovirus, EBV VCA, EBNA, parvovirus B19, toxoplasma, and VZV). Of note, AQP-4 antibodies were negative, but a positivity to anti-MOG was confirmed. Finally, the authors described that a 4-month follow-up showed complete recovery and no relapses, suggesting a monophasic disease course. It is therefore unclear to the PRAC Rapporteur why this case has not been considered as BCC Level 1. Moreover, as recent infections have been excluded, the case may be considered with a probable causality assessment.

Response to RSI. AstraZeneca clarification response for case [redacted] (Mumoli et al 2021): The company notes the PRAC observation that World Health Organization-Uppsala monitoring centre (WHO-UMC) causality which was originally assessed as unlikely due to an incorrect time to onset (TTO) of 12 hours which was outside the risk window (2 to 42 days). It was reported that twelve hours after vaccination, the patient developed fever associated with diffuse myalgia up to 36 hours. Seven days after vaccination, the patient experienced feeling of burning on the back followed in a couple of hours by back pain.

There is a possibility that the fever and myalgia could be prodromal symptoms of ADEM as the SARS-CoV-2 Ab levels were negative. Additionally, neutralizing antibodies and antigen-specific T-cell against SARS-CoV2 spike protein were negative.

The company is of the opinion that WHO-UMC causality would be **'possible with confounders'** as positivity of immunoglobulin-G (IgG) was found for adenovirus, herpes simplex1, Human Herpes Virus-6, and cytomegalovirus, Epstein-Barr Virus Viral Capsid Antigen, Epstein Barr Nuclear Antigen, parvovirus B19, toxoplasma, and Varicella-Zoster Virus. A positivity to anti-myelin oligodendrocyte (anti-MOG) was confirmed. These serological findings could indicate confounders. Also about one year prior, there was a single episode of vertigo lasting several hours. This could be a neuroinflammatory event of unknown etiology (relapsing remitting course).

The case was assessed as Brighton Collaboration Classification (BCC) level 1 based on neurological symptoms, brain magnetic resonance imaging (MRI) findings, improvement with steroids, resolution of brain MRI lesions at 3 months.

Rapporteur assessment comment of specific cases*:*

The reviewed causality assessment of the case is acknowledged. It is noted that despite positivity of IgG an extensive serological panel was negative for recent infections (e.g., Borrelia, syphilis, HIV, listeriosis, herpes virus, VZV, EBV, HBV, HCV, brucella, toxoplasma, CMV, and adenovirus). Moreover, the paper describes that the empirical antibiotic treatment was stopped on the basis of negativity both of PCR and cultural CSF microbiological panel (including E. coli, Listeria monocytogenes, Haemophilus influenzae, Streptococcus pneumoniae and S. agalactiae, Cytomegalovirus, Enterovirus, herpes simplex1,2,6, parvovirus, echovirus, varicella zoster virus and Cryptococcus, and JCV quantitative). Only information regarding recent herpes simplex 1 and parvovirus B19 are missing. The PRAC Rapp kindly disagrees that these factors should be considered as confounders and remains of the opinion that case [redacted] suggests a probable causal association (i.e. plausible TTO, extensive work-up to exclude other possible causes, patients without any familiar and personal history of neurological diseases or previously asymptomatic). **The overall conclusion on ADEM remains unchanged.**

Response to RSI. AstraZeneca clarification response for case [redacted] (Simone et al 2021): Based on the information available to the Company in the source document of the case [redacted] (based on a conference abstract publication), **the information on 4-months follow up could not be identified** and hence a monophasic disease course cannot be confirmed. Based on neurological symptoms, MRI findings, Anti-MOG IgG antibody positive, Borrelia IgM antibodies (suggesting possible post-infectious ADEM), improvement with methyl prednisolone, the case fulfils BCC level 2 diagnostic certainty.

Rapporteur assessment comment:

The MAH's clarification is noted. **The overall conclusion on ADEM remains unchanged.**

Response to RSI. AstraZeneca clarification response for case [redacted] (Sivji et al 2022): The company is of the opinion that WHO-UMC causality is **'possible with limited information'** as cerebrospinal fluid (CSF) glucose perturbation without pleocytosis suggested a possible metabolic etiology and clinical course post dose 2 showed fluctuations (which is inconsistent with ADEM and more consistent with chronic demyelinating disorders e.g. multiple sclerosis (MS)). Also, Follow up for ≥ 3 months showed some fluctuation during the 3 months (unusual for ADEM), but resolution after 3 months. However, there was limited information on past medical history, family history and clinical course post dose 1 for a comprehensive causal assessment. General work up for the present illness was negative without specific negatives for past infectious exposures being noted.

Rapporteur assessment comment:

The MAH's clarification is noted. **The overall conclusion on ADEM remains unchanged.**

Response to RSI. AstraZeneca clarification response for case [redacted] (Escola et al 2022): The case narrative provides some evidence of autoimmune connective tissue disorder, MOG antibodies, CSF consistent with infection, early fluctuating or variable clinical course, low immunity to SARS COV (despite recent vaccination) with suggestion of vaccine unresponsiveness / immune dysfunction, inverse association of SARS-CoV-2 antibody levels with disease severity, possible immune dysfunction. No etiology noted for the event, which had features consistent with both ADEM and meningitis (fever, CSF findings). Investigations indicate a neuro inflammatory process in central nervous system (CNS). MRI show CNS lesions. Explosive cellular CSF response found following vaccine and steroid tapering suggests a pre-existing sensitizing condition. Hence, the company assessed the causality as **'Possible with confounders'**.

Rapporteur assessment comment:

The MAH's clarification is noted. **The overall conclusion on ADEM remains unchanged.**

AstraZeneca clarification response for Rinaldi et al 2022: The case [redacted] was suppressed as it was a duplicate case. The case [redacted] captures the information from Rinaldi et al (2022) article. The BCC classification of BCC1 based on neurological symptoms, time to onset of 12 days, MRI findings of large poorly marginated hyperintensities, in the brain; however also noted were several non-responsive, non-enhancing dorsal cord lesions The **BCC 1 classification is complicated however by the fact that the spinal MRI shows older spinal lesions, non-enhancing, and which non-enhancing lesions did not at all resolve with the treatment of the subject**. The case shows evidence of prior lesions in the spinal cord, which remained after treatment of the neurological events discovered post vaccine treatment. The pre-existing lesions form a diagnostic feature inconsistent with ADEM and consistent with MS or neuromyelitis optica spectrum disorder (NMOsd) (multiple lesions over time) or MOGAD. Atypical ADEM presentation, could be consistent with multiple sclerosis. There was spontaneous resolution of initial neurological events after a events after a events after a week, including the initial symptoms of numbness, reduced visual acuity, dysarthria, dysphagia, clumsy right hand movements, and urge incontinence. It is not clear whether the course of the disease is monophasic. The company is of the opinion that **WHO causality would be 'possible with limited information' as there is insufficient information on prior infections and prior medical history** of any cardiac disorders, vasculitis, migraine, embolism, thrombosis), family neurological history, like MS, neuropathy.

There is no mention of the pathology of the condition. Anti-SARS-CoV-2 IgG titre was low, and no IgM. It is not specified whether these were antibodies against spike or core antigens. There is no information on COVID-19 polymerase chain reaction (PCR) tests. **Infectious workup was done but was incomplete**. Besides the poorly marginated T2-weighted hyperintensities, brain MRI showed a thalamic lesion and a single dorsal spinal area, gadolinium enhancement on T1-weighted images and several non-enhancing dorsal cord lesions which stayed static. There are no past imaging investigations to indicate whether these were pre-existing lesions.

Rapporteur assessment comment:

The MAH's clarification is noted. **The overall conclusion on ADEM remains unchanged.**

Rapporteur assessment comment:

Overall conclusion: the MAH provided the requested clarification as well as an update cumulative review of cases and literature, as well as a discussion on the need to update the EU-PI and/or RMP. ADEM is discussed in Section 2.3.6.3. of the AR. The previous conclusion on ADEM remains unchanged. ADEM will continue to be monitored as part of the monitoring of the important potential risk of Immune-mediated neurological conditions.

Issue resolved

Request 2. Menstrual disorders

The MAH is requested to provide and discuss an updated literature review of Menstrual disorders. Besides, the MAH is requested to further discuss the serious cases requiring hospitalization and the cases resulting in death.

AstraZeneca response: Please refer to Section 15.2.2 in the PBRER (reporting period 29 June 2022 to 28 December 2022).

Rapporteur assessment comment:

Data were provided and discussed as requested (see Section 2.3.17. of the AR).

Issue resolved

Request 3. Glomerulonephritis and nephrotic syndrome including IgA nephropathy

The MAH is requested to further search for literature on GN/SN following COVID-19 vaccination, with a special focus to Adeno-vectored vaccines, relapse and flare up, and measured kidney alterations after vaccination.

AstraZeneca response: Please refer to Section 15.2.3 in the PBRER (reporting period 29 June 2022 to 28 December 2022).

Rapporteur assessment comment:

Data were provided and discussed as requested (see Section 2.3.19. of the AR).

Issue resolved

Request 4. Venous Thromboembolism

The MAH is requested to further investigate venous thromboembolism by providing an updated literature review, with a focus on new relevant epidemiological studies.

AstraZeneca response: Please refer to Section 15.2.4 in the PBRER (reporting period 29 June 2022 to 28 December 2022).

Rapporteur assessment comment:

Data were provided and discussed as requested (see Section 2.3.4.2. of the AR).

In conclusion, a re-assessment of the observational studies reporting VTE, focusing on the studies including a large number of Vaxzevria vaccinees was conducted. Using a variety of study designs, this demonstrates a consistent increase in VTE among the younger age-groups. The PRAC Rapporteur considers that there is sufficient evidence to conclude there is a reasonable possibility that Vaxzevria is causally related to VTE.

A regulatory action is proposed, with updates of the SmPC section 4.4 and 4.8 to include Venous thromboembolism; the PIL should be updated accordingly. See section 3 for suggested wording [Request for a variation].

The RMP should be updated at the next regulatory opportunity with upgrading of 'thrombosis' from important potential risk to important identified risk. [RSI]

Issue not resolved

Request 5. Thrombosis

The MAH is requested to provide a tabular summary of the fatal cases reporting a thrombotic event after dose 3 (or dose 4) of the vaccine.

AstraZeneca response: Please refer to Section 15.2.5 in the PBRER and Section 2.1.1 in Appendix R3 in the PBRER (reporting period 29 June 2022 to 28 December 2022).

Rapporteur assessment comment:

Data were provided as requested (see Section 2.3.4.1. of the AR).

Issue resolved

Request 6. Use in immunocompromised patients

The MAH is requested to verify the PTs reported in fatal cases, especially regarding TTS and Thrombocytopenia.

AstraZeneca response: Please refer to Section 15.2.6 in the PBRER (reporting period 29 June 2022 to 28 December 2022).

Rapporteur assessment comment:

The MAH confirmed the PTs reported in fatal cases. (see Section 2.3.11. of the AR).

Issue resolved

Request 7. Severe cutaneous adverse reactions (SCAR)

Following a potential signal of SCAR identified by WHO-UMC, the MAH is requested to provide a cumulative review of cases reported with VAXZEVRIA together with a review of literature. A discussion on the need to update the PI should be included.

AstraZeneca response: Please refer to Section 15.2.7 in the PBRER (reporting period 29 June 2022 to 28 December 2022).

Rapporteur assessment comment:

Data were provided and discussed as requested (see Section 2.3.20. of the AR).

Considering the SCAR cases: The MAH stated that 19 literature case reports were discussed in the previous review of ICSRs retrieved from the AstraZeneca Global Patient Safety Database. However the PRAC rapporteur was unable to find a discussion on these cases from previous PSUR. Therefore these cases and any new literature reports on SCARs should be reviewed and presented in next PBRER. [Request for the next PBRER].

Considering Erythema multiforme cases, the MAH should present:

- a cumulative review of erythema multiforme (at PT level) based on data from all available sources;

- a causality assessment of the cases (using the WHO-UMC causality assessment) and discuss the cases assessed as WHO Possible, Probable or Certain;

- relevant literature data;

-a discussion on the need for updating product information and/or risk management plan, and submit proposal as required. [Request for the next PBRER].

Issue partially resolved

Request 8. Hearing loss

The MAH is requested to provide and discuss an updated review of hearing loss cases with a recovered with sequelae or not recovered outcome.

AstraZeneca response: Please refer to Section 15.2.8 in the PBRER (reporting period 29 June 2022 to 28 December 2022).

Rapporteur assessment comment:

Data were provided and discussed as requested (see Section 2.3.18. of the AR).

Issue resolved

Request 9. New daily persistent headache

The MAH is requested to provide a cumulative review of cases of new daily persistent headache in association with VAXZEVRIA, including spontaneous reports and data from the literature and clinical trials. The analysis should include an overall discussion of the cases, as well as an individual causality assessment of each cases.

AstraZeneca response: Please refer to Section 15.2.9 and Appendix 13 in the PBRER (reporting period 29 June 2022 to 28 December 2022).

Rapporteur assessment comment:

Data were provided and discussed as requested (see Section 2.3.21. of the AR).

Issue resolved

Responses following Other requests

Request 1. Myositis

On January 13th, 2023, AstraZeneca received the below request from EMA (EPITT 19882).

The MAH of VAXZEVRIA should perform a cumulative review of all cases of idiopathic inflammatory myopathies (IIM)/myositis from all sources including, but not limited to, available data from clinical trials, scientific literature and post marketing exposure. The search strategy should include, but not be limited to the following PTs: Anti-melanoma differentiation-associated protein 5 antibody positive, Anti-SRP antibody positive, Antisynthetase syndrome, Autoimmune myositis, Dermatomyositis, Focal myositis, Idiopathic inflammatory myopathy, Immune-mediated myositis, Inclusion body myositis, Juvenile polymyositis, Lupus myositis, Myositis, Necrotising myositis, Orbital myositis, Overlap syndrome, Polymyositis. The discussion should include considerations on whether the identified cases of IIM/myositis are considered "new onset" or "flare". The MAH should use a data lock point as recent as possible.

The MAH should submit in the next PSUR (data lock point 28 December 2022) answers to the below List of Questions.

1. **The MAH should perform a causality assessment of all cases of IIM/myositis using the WHO-UMC causality assessment criteria per case, including a clear breakdown of all cases identified. Justification of causality category should be given for each case. A discussion of cases assessed as WHO Possible, Probable or Certain should be presented. Case narratives should be provided in an annex. Information of severity and if possible, on long term outcome should be described and discussed. In a tabulated overview of all cases sorted by causality, at least the following data should be presented for each case report: Case ID (EV no. if possible); Age/gender; Time to onset (TTO) and dose number(s) after which IIM/myositis occurred; Medically confirmed (or not); Associated clinical signs/co-reported PTs; Ascertainment of diagnosis/diagnostic work-up; Confounding comorbidities, other medical confounders or risk factors present (including latency/TTO as applicable); Confounding medications (including latency/TTO as applicable); Response to re-challenge, if applicable Seriousness and outcome; WHO-UMC causality assessment, including a justification of the causality category.**

2. **The review should explore possible risk factors, considering gender, age, relevant medical history, and dose distribution of reported cases. The MAH should discuss whether any patterns or trends can be identified concerning these risk factors.**
3. **The MAH should ensure that all identified literature cases have been submitted to EudraVigilance and efforts should be made to follow up on other spontaneous cases which are currently subject to limited information.**
4. **The MAH should discuss the plausibility and possible mechanism(s) of action for the occurrence of IIM/myositis following administration of the vaccine. The MAH should discuss the timing of development of clinical symptoms in relationship to the proposed mechanism of action.**
5. **The MAH should provide an observed to expected (O/E) analysis for all cases identified in EU and UK of myositis and related conditions with risk windows of 7, 14 and 30 days (including events with unknown TTO). For the calculations of the O/E analysis, the relevant and justifiable background incidence rate(s) should be used as well as exposure in EU/UK.**
6. **Considering the information from individual case reports (especially cases assessed as WHO possible, probable, or certain), literature, possible mechanism, and O/E analyses, the MAH should discuss whether a causal relationship between the vaccine and IIM/myositis can be established.**
7. **The MAH should discuss the need to update the product information and/or the risk management plan, including relevant risk minimisation measures and submit proposals as appropriate.**

AstraZeneca response: Please refer to Section 15.2.10 and Appendix 14 in the PBRER (reporting period 29 June 2022 to 28 December 2022).

Rapporteur assessment comment:

Data were provided and discussed as requested (see Section 2.3.22 of the AR).

Taking all this information into account, the MAH is requested to provide a O/E analysis specific for dermatomyositis. Optimal background incidence rates for dermatomyositis should be used. Whenever possible, it should take into account a possible change in the occurrence of dermatomyositis during SARS-CoV-2 circulation.

Based on evidence for dermatomyositis, the MAH should discuss the need to update the product information and/or the risk management plan .

Finally, the MAH is requested to consider the monitoring of this event within the ongoing PASS "Post-marketing observational study using existing secondary health data sources".

[RSI]

Issue partially resolved

Request 2. Corneal graft rejection

The MAH is requested to discuss any new data, including data from the literature on Corneal graft rejection in the next PBRER.

AstraZeneca response: Please refer to Section 15.2.11 in the PBRER (reporting period 29 June 2022 to 28 December 2022).

Rapporteur assessment comment:

Data were provided and discussed as requested (see Section 2.3.23 of the AR).

Issue resolved

Request 3. Histiocytic necrotizing lymphadenitis

On September 1st 2022, AstraZeneca received the below request from EMA.

PRAC has agreed that AstraZeneca AB should submit within the next PSUR (DLP 28 December 2022) a cumulative review of all cases concerning VAXZEVRIA associated with histiocytic necrotizing lymphadenitis from all sources, including any relevant articles from literature and to discuss probable mechanism(s) of action for the occurrence of vaccine-associated histiocytic necrotizing lymphadenitis following administration of VAXZEVRIA. The MAH should discuss the need for any potential amendment to the product information and/or the risk management plan and make accordingly a proposal for changes to the relevant sections within this discussion. The PRAC will assess the cumulative review within this PSUR.

AstraZeneca response: Please refer to Section 15.2.12 in the PBRER (reporting period 29 June 2022 to 28 December 2022).

Rapporteur assessment comment:

Data were provided and discussed as requested (see Section 2.3.24. of the AR).

Issue resolved

Appendix 02: Assessment of cases of interest of Myositis

Sr. No.	AZ Case ID / Country / Serious (S/NS)/ HCP (Y/N)/ source	Age (y) / Sex	Adverse Event PTs in Case Information	Myositis event PT / Outcome	TTO / Vaccine dose	Medical History / Concomitant Medications	WHO-UMC Causality AZ assessment	Rationale (AZ comment)	Literature Reference or EVDAS number	BE Rheumatologist Expert comment
196	[redacted] S / Y / Literature	46 / F	Antisynthetase syndrome	Antisynthetase syndrome / Unknown	7 d / Dose 2	Not Reported / Not Reported	Possible with limited information	TTO within RW (0-28 d). Limited information: Concomitant medication, medical history.	Gupta 2021	Probable: very low incidence of anti-synthetase syndrome and temporal relationship. (NB: Prescription of methotrexate despite the presence of ILD!), concomitant medication has no impact on the onset of anti-synthetase syndrome
197	[redacted] S / Y / Literature	68 / M	Dermatomyositis	Dermatomyositis / Recovering	~21 d / Dose 2	Not Reported /Not Reported	Possible with limited information	TT'0 within RW (0-28 d). Limited information on baseline health status, medical history and concomitant medications.	Ajdinaj 2021	Probable: dermatomyositis is a very rare disease. Suggestive temporal relationship. Baseline health status and concomitant medication has no impact on the onset of DM
247	[redacted] NS / Y / Literature	74 / M	Dermatomyositis	Dermatomyositis / Unknown	14 d / Dose 2	Not Reported / Not Reported	Possible with limited information	TTO within RW (0-28 d). Limited information on medical history and concomitant medications.	Cantisani 2022	Possible: Diagnosis of "Dermatomyositis like eruption" by the authors, no objective data available about muscle involvement. Unusual clinical presentation, paraneoplastic aetiology not excluded, concomitant medication could not influenced the onset of DM
227	[redacted] S / S / Y / Literature	44 / M	Multiple organ dysfunction syndrome; Sepsis; Myositis; Dermatomyositis; Vasculitis; Rhabdomyolysis; Renal failure; Compartment syndrome; Myalgia	Myositis - Dermatomyositis / Unknown - Unknown	14 d / Dose 2	Not Reported / Not Reported	Possible with limited information	TTO within RW (0-28 d). Limited information on baseline health status, medical history and concomitant medications.	Cheng 2022	Probable: fulminant presentation and TTO. Knowledge of concomitant medication is not necessary to interpretate this case

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230	[redacted] S / Y / Literature	58 / F	Dermatomyositis	Dermatomyositis / Recovering	14 d / Dose 2	Diabetes mellitus / Not Reported	Possible with limited information	TTO within RW (0-28 d). Limited information on baseline serology panel and concomitant medication	Gonzalez 2022	Possible: low incidence of dermatomyositis and the temporal relationship with the administration of the vaccine but DM as paraneoplastic syndrome was not excluded (15 to 30% of the DM) ." In addition, multiple enlarged necrotic lymph nodes were seen at the bilateral supraclavicular ,region"
249	[redacted] S / Y / Literature	27 / M	Dermatomyositis	Dermatomyositis / Unknown	Few days / Dose 2	Not Reported / Not Reported	Possible with limited information	TTO within RW (0-28 d). Limited information on baseline health status, medical history and concomitant medications.	Ranniel Guevarra 2022	Probable: but limited information
255	[redacted] S / Y / Literature	53 / F	Pelvic venous thrombosis; Pulmonary embolism; Dermatomyositis	Dermatomyositis / Recovering	30 d / Dose 1	Pericarditis; Interstitial lung disease / Not Reported	Unlikely	TTO outside the RW (0-28 d). Ongoing histories of pericarditis and Interstitial lung disease may have contributed to the event.	Gniadecki 2022	Unlikely: broad autoimmune panel positive and long TTO
175	[redacted] S / Y / Literature	74 /M	Tachycardia; Immune-mediated myositis; Vasculitis; Arthralgia	Immune-mediated myositis / Recovered	2 d / Dose 1	Not Reported / Not Reported	Possible with limited information	TTO within RW (0-28 d). Limited information: Concomitant	Maramatton 2021	Possible: the cases are well documented, atypical presentation of "classical" autoimmune myositis because negative antibody, normal CPK but abnormalities on MRI
176	[redacted] S / Y / Literature	75 /F	Tachycardia; Immune-mediated myositis; Arthralgia	Immune-mediated myositis / Recovered	2 d / Dose 1	Not Reported / Not Reported	Possible with limited information	TTO within RW (0-28 d). Limited information on concomitant medication, medical history and diagnostic evidence.	Maramatton 2021	Possible: the cases are well documented, atypical presentation of "classical" autoimmune myositis because negative antibody, normal CPK but abnormalities on MRI
177	[redacted] S/Y / Literature	80 /F	Immune-mediated myositis; Tachycardia; Pyrexia; Fatigue	Immune-mediated myositis / Recovering	2 d / Dose 2	Not Reported / Not Reported	Possible with limited information	TTO within RW (0-28 d). Limited information on concomitant medication, medical history and diagnostic evidence.	Maramatton 2021	Possible: the cases are well documented, atypical presentation of "classical" myositis because negative antibody, normal CPK but abnormalities on MRI
217	[redacted] S/Y / Literature	53 /M	Myositis	Myositis / Recovered	2 d / Dose 1	Gait disturbance / Not Reported	Possible with	TTO within RW (0-28 d). Limited information: Concomitant medication.	Bose 2022	Possible: the temporal relationship and atypical clinical presentation (no other differential

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							limited information			diagnosis could explain the symptoms)
257	[redacted] S / Y /Literature	68 / F	Myositis	Myositis / Recovered	34 weeks / Dose 2	None / None	Unlikely	TTO outside the RW (0-28 d). Limited information on family history of autoimmunity, other triggers such as infection or it can be idiopathic of unknown cause.	De Marco 2022	Unlikely
258	[redacted] S / Y / Literature	68 / F	Myositis	Myositis / Recovered	25 Weeks / Dose 2	None / None	Unlikely	TTO outside the RW (0-28 d). Limited information on family history of autoimmunity, other triggers such as infection or it can be idiopathic of unknown cause.	De Marco 2022	Unlikely
259	[redacted] S / Y / Literature	58 / F	Myositis	Myositis / Recovered	4 weeks / Dose 1	None / None	Possible with limited information	TTO within RW (0-28 d). Limited information on family history of autoimmunity, other triggers such as infection or it can be idiopathic of unknown cause.	De Marco 2022	Possible: differential diagnosis Sjögren
260	[redacted] S / Y / Literature	61 / M	Myositis	Myositis / Recovered	2 weeks / Dose 1	None / None	Possible with limited information	TTO within RW (0-28 d). Limited information on family history of autoimmunity, other triggers such as infection or it can be idiopathic of unknown cause, asthenia and weight loss could be suggestive of underlying chronic illness.	De Marco 2022	Probable: autoimmune serology negative, normal CRP, high CK: atypical presentation
261	[redacted] S / Y / Literature	76 / F	Myositis	Myositis / Recovered	5 weeks / Dose 2	None / Atorvastatin	Unlikely	TTO outside the RW (0-28 d). Confounder by concomitant use of Atorvastatin. Limited information on family history of autoimmunity, other triggers such as infection or it can be	De Marco 2022	Possible: normal CRP, high CK: atypical presentation but relative long TTO

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								idiopathic of unknown cause.		
262	[redacted] S / Y / Literature	37 / F	Myositis	Myositis / Recovered	4 weeks / Dose 1	Systemic lupus erythematosus (CK normal, no clinical myositis) / None	Possible with confounders	TTO within RW (0-28 d). Confounded by history of Systemic lupus erythematosus. Limited information on family history of. autoimmunity, other triggers such as infection or it can be idiopathic of unknown cause.	De Marco 2022	Possible: no lupus flare because of normal CRP
263	[redacted] S / Y / Literature	78 / F	Myositis	Myositis / Recovered	2 weeks / Dose 1	None / None	Possible with limited information	TTO within RW (0-28 d). Limited information on family history of autoimmunity, other triggers such as infection or it can be idiopathic of unknown cause.	De Marco 2022	Possible

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264	[redacted] / United Kingdom / S / Y /Literature	67 / M	Myositis	Myositis / Died	6 weeks / Dose 2	None / Atorvastatin	Unlikely	TTO outside the RW (0-28 d). There is limited information on the clinical course, chronology of events, medical history and autopsy report in this patient which limits complete medical assessment. The time to onset of myositis was reported as 6 weeks which suggests unlikely causal association. The case is further confounded by concomitant statin (no details on indication and duration). The additional reported symptoms of anuria (renal failure haemodialysis-dependant), respiratory arrest (dependent on intensive care support), suspected myocarditis and multiple supra-infections could be contributory to the fatal outcome.	De Marco 2022	Unlikely: TTO is long; differential diagnosis sepsis
265	[redacted] S / Y /Literature	83 / F	Myositis	Myositis / Recovering	6 weeks / Dose 2	Giant Cell Arteritis / None	Unlikely	TTO outside the RW (0-28 d). Confounded by history of Giant cell arteritis. Limited information on family history of autoimmunity, other triggers such as infection or it can be idiopathic of unknown cause, asthenia and weight loss could be suggestive of underlying chronic illness.	De Marco 2022	Unlikely: TTO is to long
199	[redacted]	62 / M	Myopericarditis; Myositis;	Myositis / Recovered	5 weeks / Dose 1	Occupational exposure to	Unlikely	ITO outside the RW (0-28 d). Limited information on	Farooq 2022	Possible but missing information (exposure)

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	[redacted] / S / Y / Literature		Pneumonitis; Respiratory symptom			dust; Asymptomatic COVID-19 / Not Reported		concomitant medication, circumstances leading to condition.		
209	[redacted] NS / Y / Literature	20 / Unk	Myositis	Myositis / Unknown	1 d / Dose 1	Not Reported / Glucocorticoids	Possible with limited information	TTO within RW (0-28 d). Limited information on medical history and diagnostic evidence.	Hocevar 2022	Unclassified: very few information available, only "myositis"; TTO 1 day!
251	[redacted] / Australia / S / Y / Literature	76 / M	Autoimmune hepatitis; Myositis; Renal failure; Hepatic failure	Myositis / Died	12 d / Dose 1	Hypertension; Diabetes mellitus / Not Reported	Possible with confounders	TTO within RW (0-28 d). The assessment of this case is complicated by the coreported event of preceding severe liver inflammation. It is unknown if the patient was taking any concomitant herbal medications. The patient's medical history of diabetes mellitus could be the confounder. The fatal outcome in this case is more likely due to the subsequent progressive liver failure. Limited information on baseline laboratory data including LFTs further limits the assessment of this case.	Nguyen 2022	Probable: time relationship, fulminant disease, no other evident differential diagnosis
94	[redacted] / NS / Y / Literature	37 / F	Arthritis; Muscular weakness; Neuralgia; Polymyositis; Oedema peripheral; Rash	Polymyositis / Unknown	Approx 6.5 weeks / Dose 1	None /Not Reported	Unlikely	TTO outside the RW (0-28 d). Limited information on concomitant medication, circumstances leading to condition.	Capassoni 2021	Possible: Skin rash after 4 days
67	[redacted] / France / S / Y / Regulatory	64 / M	Myositis; Spontaneous haematoma	Myositis / Died	14 d / Dose 1	Hypertriglyceridaemia; Thyroid cancer; Glaucoma;	Possible with confounders	TTO within RW (0-28 d). The onset of event from the vaccine was reported as 14 days (diagnostic evidence was not	[redacted]	Possible: temporal relationship and negative autoimmune serology, but as mentioned by the authors of this case is a

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						Cholecystectomy; Thyroidectomy / Levothyrox; Fenofibrate; Ganfort; Sotalol (Chlorhydrate De); Citicoline		provided). The patient died approximately 3.5 months later. Cause of death was reported as sepsis (no further details) and myositis. Autopsy was not performed. This case is confounded by concomitant fenofibrate and history of thyroid cancer. Limited information on baseline labs, diagnostic work-up, details of sepsis and autopsy report preclude complete medical assessment.		paraneoplastic disease not excluded

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121	[redacted] / Brazil / S / NS / N / Spontaneous	65 / F	Cardiac arrest; Dermatomyositis; Arthralgia; Muscular weakness; Immobile; Post vaccination syndrome; Myositis; Incorrect route of product administration; Incorrect dose administered; Motor dysfunction; Dysphagia; Myalgia; Myopathy; Rash erythematous; Dyspnoea exertional; Asthenia; Eye swelling	Dermatomyositis / Myositis / Died / Unknown	63 d / Dose 1	Not Reported / Not Reported	Unlikely	TTO outside the RW (0-28 d). Patient presented initial symptoms including muscular weakness and total immobility about 54 days from first dose of vaccine which suggests unlikely causal association. Dermatomyositis was suspected 63 days from first dose. Subsequently on an unknown date the patient experienced cardiac arrest and died about 5 months from the initial symptoms. It was reported that autopsy was performed with a cause of death of cardiac arrest. It was unclear from the reported details if dermatomyositis was a confirmed cause of death at autopsy. This case is poorly documented missing important details for full medical assessment including concomitant medications, medical history, diagnostic details and full details of the autopsy report.	[redacted]	Unlikely

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194	[redacted] / Brazil / S / N / Spontaneous	44 / F	Dermatomyositis	Dermatomyositis / Died	54 d / Dose 1	Nicotine dependence; Tobacco user / Not Reported	Unlikely	TTO outside the RW (0-28 d). Patient was initially diagnosed with motor deficit syndrome about 54 days from first dose of vaccine which suggests unlikely causal association, subsequently dermatomyositis was suspected. Patient was a smoker. Details of muscle biopsy or myositis specific antibodies were not provided. Patient had a cardiac arrest about 5 months from initial symptoms and died. Limited information on baseline health status, concomitant mediations and autopsy report among others preclude complete medical assessment of this case.	[redacted]	Unlikely: TTO too long
95	[redacted] S/N / Spontaneous	48 /F	Antisynthetase syndrome; Urinary tract infection	Antisynthetase syndrome / Recovering	40 d / Dose 2	Not Reported / Not Reported	Unlikely	TTO outside the RW (0-28 d). Limited information on medical history and concomitant medications.	[redacted]	Possible: first symptoms begin within suggestive TTO
218	[redacted] / S / Y / Regulatory	55 / F	Oral dysaesthesia; Autoimmune arthritis; Ageusia; Headache; Hypoaesthesia; Autoimmune myositis	Autoimmune myositis / Not recovered	91 d / Dose 2	Anaemia / Not Reported	Unlikely	TTO outside the RW (0-28 d). Limited information on concomitant medications, circumstances leading to the condition.	[redacted]	Unlikely
70	[redacted] / S / Y / Regulatory	59 / F	Dermatomyositis	Dermatomyositis /Not recovered	20 d / Dose 1	Hypothyroidism / Not Reported	Possible with confounders	TTO within RW (0-28 d). Confounder: history of ongoing Hypothyroidism.	[redacted]	Probable: DM is a rare disease, suggestive temporal relationship. But was a paraneoplastic aetiology excludes (15 intil 40%

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										of DM)? Hypothyroidism is not a confounder (no increased risk for DM)
86	[redacted] S / Y / Regulatory	73 / M	Dermatomyositis	Dermatomyositis / Not recovered	1 d / Dose 2	Hypertension; Hyperlipidaemia; Type 1 diabetes mellitus; Transient ischaemic attack / Not Reported	Possible with confounders	TTO within RW (0-28 d). Confounder: history of type 1 diabetes mellitus. Insufficient information on concomitant medication, biopsy confirmation, clinical course, etiological workup for a further comprehensive assessment.	[redacted]	Possible: bacterial infection also possible (fever, acute onset, partial response to antibiotic), diabetes is not a confounder, diagnose poor documented
108	[redacted] S / N / Regulatory	78 / M	Fatigue; Rash pruritic; Myalgia; Dermatomyositis	Dermatomyositis / Not recovered	14 d / Dose 2	Neoplasm malignant / Not Reported	Possible with confounders	TTO within RW (0-28 d). Confounder: History of Neoplasm malignant.		Unlikely: underlying neoplasm (DM as paraneoplastic syndrome)
208	[redacted] S / N / Regulatory	58 / F	Dermatomyositis	Dermatomyositis / Not recovered	47 d / Dose 2	Diabetes mellitus / Cyclophosphamide ; Prednisolone	Unlikely	TTO outside the RW (0-28 d). Confounder: history of Diabetes mellitus.		Unlikely: It is not clear why the patient is taking prednisolone and cyclophosphamide. Is de myositis a flare of an underlying autoimmune disease?
213	[redacted] S / Y / Regulatory	67 / M	Immune-mediated myositis	Immune-mediated myositis / Recovering	2 d / Dose 1	Hypertension; Dyslipidaemia; Type 2 diabetes mellitus / Alopurinol; Perindopril/Indapamide; Ezetimibe; Empagliflozin; Rosuvastatine ; Carvedilol; Metformin	Possible with confounders	TTO within RW (0-28 d). Possible Confounders: history of type II Diabetes Mellitus / Rosuvastatin (unspecified dates and any action taken with it).		Possible: but evolution to chronic disease resistant to immunosuppressive therapies are not expected in vaccine induced myositis
33	[redacted]	25 / F	Blood creatine phosphokinase	Myositis / Recovering	5 d / Dose 1	Chronic myeloid	possible with	TTO within RW (0-28 d). Confounders: history of		Possible: confounders not relevant, missing data: CRP and

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	/ S / Y / Regulatory		increased; Palpitations; Hypotension; Myositis; Thrombocytopeni a; Asthenia; Nausea; Decreased appetite; Dizziness; Myalgia			leukaemia; Bacterial infection; Bone marrow transplant / Dydrogesterone, estradiol; Levothyroxine sodium; Pantoprazole.	confounders	Chronic myeloid leukaemia, Bacterial infection.		WBC, COVID Ag (differential diagnosis viral infection)
46	[redacted] S / Y /Regulatory	41 / F	Metabolic acidosis; Sepsis; Myocarditis; Myositis; Muscle necrosis; Pain in extremity	Myositis / Not recovered	33 d / Dose 1	Personality disorder; Obesity; Bipolar disorder / Azithromycin; Ceftriaxone; Clindamycin	Unlikely	TTO outside the RW (0-28 d). Limited information on baseline labs and details to exclude other possible risk factors.	[redacted]	Unassessable: Not enough information
106	[redacted] S / N / Regulatory	Unk / F	Gastrooesophagea 1 reflux disease; Post viral fatigue syndrome; Thyroid pain; Dizziness postural; Osteitis; Myositis; Post viral fatigue syndrome; Musculoskeletal disorder; Cognitive disorder; Dyspnoea; Lymphadenopath y, Neck pain; Musculoskeletal chest pain;	Myositis / Not recovered	76 d / Dose 1	Post viral fatigue syndrome; Hypermobility syndrome; Pectus excavatum; Cholelithiasis; Infectious mononucleosis; Uterine polypectomy; Abortion spontaneous; Hyperreflexia; Spinal disorder; Deformity thorax; Post viral fatigue syndrome; Varicella;	Unlikely	TTO outside the RW (0-28 d). History of post viral fatigue syndrome could be the confounder.		Unlikely: cognitive/psychiatric history, patient not reliable

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			Asthenia; Lymph node pain			Tonsillectomy; Bladder neck operation; Cystoscopy / Turmeric; Zinc				
117	[redacted] S / Y / Regulatory	47 / M	Myositis	Myositis / Recovering	Between day 44 to day 60 / Dose 1	Spinal cord operation / Not Reported	Unlikely	TTO outside the RW (0-28 d). Limited information on further details regarding 'Leucocyte and result was increased.'.	[redacted]	Unassessable: diagnosis not enough documented
144	[redacted] S / N / Regulatory	39 / M	Cerebral artery occlusion; Pulmonary embolism; Blood pressure increased; Rhabdomyolysis ; Troponin T increased; Muscle disorder; Type 2 diabetes mellitus; Essential hypertension; Aortic aneurysm; Troponin T increased; Blood glucose increased; Blood creatine phosphokinase increased; Transaminases abnormal; Chromaturia; Oedema peripheral; Peripheral swelling; Oedema	Myositis / Unknown	26 d / Dose 1	Hospitalisation ; Aortic valve stenosis; Aortic aneurysm; Hypertension; Type 2 diabetes mellitus; Attention deficit hyperactivity disorder; Depression; Adverse event; Hospitalisation ; Bicuspid aortic valve; Osteoarthritis; Abstains from alcohol; Drug abuse; Tobacco abuse; Tendon disorder; Personality disorder; Carpal tunnel syndrome / Atomoxetine;	Possible with confounders	TTO within RW (0-28 d). Confounders: history of Type 2 diabetes mellitus,Osteoarthrits, Drug abuse, Tobacco abuse, Tendon disorder, Carpal tunnel syndrome.		Possible: with many confounders

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			peripheral; C-reactive protein increased; Peripheral swelling; Limb discomfort; Lymphoedema; Musculoskeletal stiffness; Pain in extremity; Rash; Erythema; Arthralgia; Arthralgia; Myalgia; Arthralgia; Asthenia; Swelling; Aortic aneurysm; Cardiovascular disorder; Myositis; Myalgia; Pain in extremity; Pain in extremity; Transaminases increased; Muscular weakness; Erythema; Movement disorder; Dyspnoea; Rash; Peripheral swelling; Peripheral swelling; Peripheral swelling; Weight decreased; Peripheral vascular			Candesartan; Metformin; Venlfalaxin				

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			disorder; Dizziness; Fatigue; Pyrexia; Palpitations; Cyst; Stress; Mitral valve thickening; Aortic stenosis; Diastolic dysfunction							
80	[redacted] S / Y / Regulatory	Unk / F	Polymyositis	Polymyositis / Not recovered	31 d / Dose 1	Steroid therapy; Polymyositis / Beclomethasone dipropionate; Clopidogrel; Lansoprazole; Prednisolone	Unlikely	TT'0 outside the RW (0-28 d). Ongoing Polymyositis needing steroid treatment is a possible confounder, however, there is insufficient information on previous clinical course, any action taken with steroids prior to vaccination and biopsy information for a further comprehensive assessment.	[redacted]	Possible: with confounders
102	[redacted] S / N / Regulatory	33 / F	Polymyositis; Colitis ulcerative; Arthritis	Polymyositis / Recovered with sequelae	7 d / Dose 1	Colitis ulcerative / Cortisone	Possible with confounders	TTO within RW (0-28 d). Confounder: History of acute ulcerative colitis.		Unassessable: diagnosis not enough documented
128	[redacted] S / Y / Regulatory	71 / M	Polymyositis	Polymyositis / Recovering	121 d / Dose 1	Peripheral arterial occlusive disease; Angina pectoris; Dyslipidaemia; Hypertension / Isosorbide dinitrate; Paracetamol; Aspirin; Bisoprolol;	Unlikely	TTO outside the RW (0-28 d). Limited information on baseline health condition, circumstances leading to the condition, Covid test details.		Unlikely: long TTO and evolution to chronic disease resistant to immunosuppressive therapies are not expected in vaccine induced myositis

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						Ramipril; Lormetazepam ; Esomeprazole				
250	[redacted] S / Y / Regulatory	83 / F	Polymyositis	Polymyositis / Not recovered	121 d / Dose 2	Hypertensive nephropathy; Ex- tobacco user; Myocardial ischaemia; Hypertension; Angioplasty; Peripheral arterial occlusive disease; Diabetic eye disease; Aplasia pure red cell; Renal failure / Rosuvastatin	Unlikely	TTO outside the RW (0-28 d). Confounders: Elderly age (above 80 years), history of Peripheral arterial occlusive disease, Diabetic eye disease, Renal failure / Rosuvastatin.	[redacted]	Unlikely

Periodic Safety Update Report	
Medicinal Product	VAXZEVRIA (ChAdOx1-S [recombinant])
Date	17 February 2023

Periodic Safety Update Report

for

VAXZEVRIA™ (AZD1222)

ATC Code(s): J07BX03

Note: The format and content of the PSUR are based on those for the Periodic Benefit-Risk Evaluation Report (PBRER) as described in the ICH E2C(R2) guideline – the term PBRER is used within the report itself.

Medicinal Products Covered:

Invented name of the medicinal product(s)	Marketing authorisation number(s)	Date(s) of authorisation[a]	Marketing authorisation holder
VAXZEVRIA	EU/1/21/1529/001-002	29 January 2021	AstraZeneca AB

[a] International Birth Date is underlined. This footnote is particularly applicable if there are numerous authorisation dates; if the list of authorisations is presented separately this footnote may be deleted.

Authorisation procedure in the European Union (EU):	Centralised
International Birth Date (IBD):	29 December 2020
EU Reference Date (EURD):	29 December 2020
Period covered:	29 June 2022 to 28 December 2022
Date of report:	17 February 2023
Marketing authorisation holder's name and address:	AstraZeneca AB 151 85 Södertälje Sweden E-mail address: [redacted]
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The content of this Periodic Safety Update Report has been reviewed and endorsed by:	Magnus Ysander Qualified Person for Pharmacovigilance in the EU	Electronic signature is available at the end of the document

This PSUR is submitted according to the guidance:

User Guidance for Marketing Authorisation Holders (MAHs) for PSUR Repository

Periodic Benefit-Risk Evaluation Report	
Medicinal Product	VAXZEVRIA (ChAdOx1-S [recombinant])
Date	17 February 2023

VAXZEVRIA™(AZD1222)

Periodic Benefit-Risk Evaluation Report

Period covered: 29 June 2022 to 28 December 2022

International birth date: 29 December 2020 (United Kingdom)

Note: This report contains unblinded clinical trial adverse event data.

VAXZEVRIA™(AZD1222)

Periodic Benefit-Risk Evaluation Report

Period covered:	29 June 2022 to 28 December 2022
International birth date:	29 December 2020 (United Kingdom)

The content of this Periodic Benefit-Risk Evaluation Report has been reviewed and endorsed by:	Magnus Ysander Qualified Person for Pharmacovigilance in the EU	Electronic signature is available at the end of the document

EXECUTIVE SUMMARY

- **Introduction:** This Periodic Benefit-Risk Evaluation Report (PBRER) for VAXZEVRIA™ (AZD1222) summarises safety and efficacy/effectiveness data received and evaluated by AstraZeneca from 29 June 2022 to 28 December 2022 and places it in the context of the cumulative data and the overall benefit-risk profile.
- **Medicinal product:** VAXZEVRIA is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of the Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2). Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralizing antibody and cellular immune responses. VAXZEVRIA is indicated for active immunization of individuals ≥ 18 years old for the prevention of coronavirus disease 2019 (COVID-19). VAXZEVRIA is supplied as a vial containing either 8 doses or 10 doses per vial, 0.5 mL per dose for intramuscular (IM) injection. The VAXZEVRIA primary vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks after the first dose. It is recommended that individuals who receive a first dose of VAXZEVRIA complete the vaccination course with VAXZEVRIA. A booster dose (third dose) of 0.5 ml may be given to individuals who completed the primary vaccination course with VAXZEVRIA or another authorised COVID-19 vaccine at least 3-months after completing the primary vaccination course. The approval and dosing interval of booster dose for VAXZEVRIA may vary according to the countries of authorisation.
- **Marketing approvals:** As of 28 December 2022, VAXZEVRIA has been granted either full marketing authorisation, conditional marketing authorisation or emergency use authorisation in more than 90 countries managed by AstraZeneca and its partners – Serum Institute of India (SII), R-pharm and Fiocruz.
- **Actions taken or proposed for safety reasons:** No significant actions related to safety were taken or proposed during the reporting period.
- **Safety changes to Reference Safety Information:** During this reporting period, the VAXZEVRIA Core Data Sheet (CDS) was updated to include the following safety-related changes:

  CDS Section 4.8 – Undesirable side effects was updated with addition of tinnitus (frequency uncommon), cutaneous vasculitis (frequency not known), and immune thrombocytopenia (frequency not known).

  Also, CDS Section 4.4 - Special warnings and special precautions for use was updated with addition of text pertaining to immune thrombocytopenia.
- **Estimated cumulative exposure of clinical trial subjects:** Approximately 60597 participants have been enrolled into the clinical development programme, of which approximately 35942 have received VAXZEVRIA.
- **Estimated cumulative and reporting period patient exposure from post-approval (marketing) experience:** AstraZeneca is working directly with health departments in individual countries to determine the number of doses administered. Presently, administration data is available from the European Union, United Kingdom, Afghanistan, Argentina, Australia, Bangladesh, Brazil, Canada, Chile, Colombia, Ecuador, Guatemala, India, Iran, Iraq, Japan, Lebanon, Malaysia, Mexico, Nepal, New Zealand, Peru,

Philippines, Saint Lucia, South Korea, Taiwan, Thailand and Uruguay. The cumulative number of doses administered in these territories/regions was confirmed as being over 2.35 billion doses. The number of doses distributed globally are over 3.02 billion doses cumulatively.

- **Late-breaking information:** Post data lock point (DLP) of this PBRER, based on the final pooled analysis of COV001, COV002, COV003 and COV005 studies AstraZeneca decided to update the VAXZEVRIA CDS section 4.8 with inclusion of adverse drug reaction (ADR) "Decreased appetite" with the frequency as "Uncommon", and frequency categories for other adverse events ie, Dizziness, Abdominal pain in VAXZEVRIA group and Vomiting, Pain in extremity and Urticaria in the control group.

  Immunocompromise study D8111C00010 was discontinued due to recruitment challenges. This was agreed by EMA Pharmacovigilance Risk Assessment Committee (PRAC) and Committee For Medicinal Products For Human Use (CHMP).

- **Summary of overall benefit-risk evaluation:** During the covering period of this PBRER, safety concerns were reclassified in Core Risk Management Plan (RMP) Version 8.0 with removal of the important potential risk of Vaccine-associated enhanced disease (VAED)/ vaccine-associated enhanced respiratory disease (VAERD) and the missing information of "Use of AZD1222 with other vaccines" from the list of safety concerns. The clinical benefit demonstrated in clinical trials, combined with the overall safety profile of VAXZEVRIA has established a positive benefit-risk profile for the approved indication.

  The data received during the reporting period do not indicate a change in the positive benefit-risk profile for the approved indication.

- **Conclusions and actions**: It is AstraZeneca's opinion that the information in the current document and the CDS accurately reflects the known benefit-risk profile for VAXZEVRIA.

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LIST OF ABBREVIATIONS

The following abbreviations are used in this Periodic Benefit-Risk Evaluation Report.

Abbreviation or special term	Explanation
AAN	Aristolochic Acid Nephropathy
AAV	Anca Associated Vasculitis
ACE	Angiotensin Converting Enzyme
ADAMTS	A Disintegrin And Metalloproteinase With A Thrombospondin Motif
ADEM	Acute Disseminated Encephalomyelitis
ADR	Adverse Drug Reaction
AE	Adverse Event
AEFI	Adverse Event Following Immunization
AESI	Adverse Event Of Special Interest
AGEP	Acute Generalised Exanthematous Pustulosis
AIH	Autoimmune Hepatitis
AIN	Acute Interstitial Nephritis
AKI	Acute Kidney Injury
ANA	Antinuclear Antibody
ANCA	Antineutrophil Cytoplasmic Antibodies
ANE	Acute Haemorrhagic Necrotizing Encephalopathy
APLS	Antiphospholipid Syndrome
APO	Apolipoprotein
ARDS	Acute Respiratory Distress Syndrome
ARI	Acute Respiratory Infection
ARS	Agenzia Regionale Di Sanità
AUB	Abnormal Uterine Bleeding
AZ	AstraZeneca
BAU	Binding Antibody Units
BC	Brighton Criteria
BCC	Brighton Collaboration Criteria
BG	Background
BKT	Biokangtai
BMI	Body Mass Index
BPH	Benign Prostatic Hyperplasia
BSA	Business Services Authority

Abbreviation or special term	Explanation
CDC	Centres For Disease Control And Prevention
CDS	Core Data Sheet
CG	Collapsing Glomerulopathy
ChAdOx1	Chimpanzee Adenovirus
CI	Confidence Interval
CK	Creatine Kinase
CKD	Chronic Kidney Disease
CLL	Chronic Lymphocytic Leukaemia
CM	Chronic Migraine
CMA	Conditional Marketing Authorisation
CMBD	Minimum Basic Data Set
CNBG	China National Biotec Group
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
COVAX	Covid-19 Vaccines Global Access
COVID-19	Coronavirus Disease Of 2019
CPRD	Clinical Practice Research Datalink
CRP	C-Reactive Protein
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
CT	Computed Tomography
CTACK	Cutaneous T Cell Attracting Chemokine
CV	Cardiovascular
CVA	Cerebrovascular Accident
CVD	Cardiovascular Disease
CVST	Cerebral Venous Sinus Thrombosis
CVT	Cerebral Venous Thrombosis
DEC	Drug Event Combination
DIAL	Dialysis
DIBD	Development International Birth Date
DIC	Disseminated Intravascular Coagulation
DIF	Direct Immunofluorescence
DLP	Data Lock Point
DM	Dermatomyositis

Abbreviation or special term	Explanation
DMSA	Dimercaptosuccinic Acid
DNA	Deoxyribonucleic Acid
DRESS	Drug Reaction With Eosinophilia And Systemic Symptoms
DSUR	Development Safety Update Report
DVT	Deep Vein Thrombosis
EAR	Auricular
EBNA	Epstein-Barré Nuclear Antigen
EBV	Epstein–Barr Virus
ECDC	European Centre For Disease Prevention And Control
EDTA	Ethylenediaminetetraacetic Acid
EEA	European Economic Area
EEG	Electroencephalography
eGFR	Estimated Glomerular Filtration Rate
EGPA	Eosinophilic Granulomatosis With Polyangiitis
ELISA	Enzyme-Linked Immunosorbent Assay
EMA/EMEA	European Medicines Agency
EPITT	European Pharmacovigilance Issues Tracking Tool
ERA	European Renal Association
ESR	Erythrocyte Sedimentation Rate
ETE	Embolic And Thrombotic Event
EU	European Union
EUA	Emergency Use Authorizations
EUL	Emergency Use Listing
EUVAS	European Vasculitis Society
EVDAS	Eudravigilance Data Analysis System
FANA	Fluorescent Antinuclear Antibody
FBC	Full Blood Count
FLAIR	Fluid-Attenuated Inversion Recovery
FSGS	Focal Segmental Glomerulosclerosis
FSI	First Subject In
FU	Follow-Up
FVS	Fully Vaccinated Analysis Set
GBM	Gomerular Basement Membrane
GBS	Guillain-Barre Syndrome

Abbreviation or special term	Explanation
GDPPR	General Practice Extraction Service Data for Pandemic Planning and Research
GE	Gastroenteral
GI	Gastrointestinal
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titer
GMTR	Geometric Mean Titer Ratio
GN	Glomerulonephritis
GP	General Practitioner
GPES	General Practice Extraction Service
HBV	Hepatitis B Virus
HCP	Healthcare Professional
HCV	Hepatitis C Virus
HDL	High-Density Lipoprotein
HES	Hospital Episode Statistics
HIT	Heparin-Induced Thrombocytopenia
HIV	Human Immunodeficiency Virus
HL	Hearing Loss
HLA	Human Leukocyte Antigen
HLT	High Level Term
HMG-CoA	Hydroxymethylglutaryl-Coenzyme A
HNL	Histiocytic Necrotizing Lymphandenitis
HPF	High-Power Field
HPO	Hypothalamo-Pituitary-Ovarian
HPV	Human Papillomavirus
HR	Hazard Ratio
HSV	Herpes Simplex Virus
IB	Intravesical
IBD	International Birth Date
IBM	International Business Machines Corporation
IC	Intracardiac
ICD	International Classification Of Diseases
ICH	International Council For Harmonisation Of Technical Requirements For Pharmaceuticals For Human Use
ICHD	International Classification Of Headache Disorders

Abbreviation or special term	Explanation
ICMR	Indian Council Of Medical Research
ICP	Immunocompromised Person
ICS	Intracavernous
ICSR	Individual Case Safety Reports
ICVT	Intracranial Venous Thrombosis
IF	Infiltration
IFN	Interferons
IgAN	Immunoglobulin A Nephropathy
IH	Respiratory (Inhalation)
IIM	Idiopathic Inflammatory Myopathies
IJ	Intra-Articular
IL	Interleukin
IM	Intramuscular
IMEN	Intrameningeal
IMGT	International Immunogenetics Database
IMKD	Immune Mediated Kidney Diseases
IOC	Intraocular
IPCI	Integrated Primary Care Information
IQR	Interquartile Range
IR	Incidence Rate
IS	Intradiscal (Intraspinal)
ISN	International Society Of Nephrology
ISTH	The International Society On Thrombosis And Haemostasis
ISYN	Intrasynovial
ITP	Immune Thrombocytopenia
IV	Intravenous
IWG	Immunonephrology Working Group
KFD	Kikuchi-Fujimoto Disease
LD	Low Dose
LDL	Low-Density Lipoprotein
LDSD	1 Low Dose And 1 Standard Dose
LFT	Liver Function Test
LLT	Lowest Level Terms
LMIC	Low- And Middle-Income Countries

Abbreviation or special term	Explanation
LOC	Level Of Certainty
LPD	Longitudinal Patient Data
LSO	Last Subject Out
LT	Life Threatening
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MC	Medically Confirmed
MCD	Minimal Change Disease
ME	Myalgic Encephalomyelitis
MedDRA	Medical Dictionary For Regulatory Activities
MENACWY	Meningococcal Vaccine
MEST	Mesenteric Thrombosis
MHRA	Medicines And Healthcare Products Regulatory Agency
MI	Myocardial Infarction
MMII	Multimodal Image Integration
MN	Membranous Nephropathy
MOA	Mechanism of Action
MPGN	Membranoproliferative Glomerulonephritis
MPO	Myeloperoxidase
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MST	MedDRA Search Term
NA	Neuralgic Amyotrophy
NDPH	New Daily Persistent Headache
NEC	Necrotizing Enterocolitis
NHS	National Health Service
NIMS	National Immunisation Management System
NMOSD	Neuromyelitis Optica Spectrum Disorder
NS	Non-Serious
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
OBS	Observational Study
OE	Observed-To-Expected
OHDSI	Observational Health Data Science And Informatics
PAHO	Pan American Health Organization

Abbreviation or special term	Explanation
pANCA	Antimyeloperoxidase Antibodies
PAR	Parenteral
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PCR	Polymerase Chain Reaction
PE	Pulmonary Embolism
PEDW	Patient Episode Dataset For Wales
PEG	Polyethylene Glycol
PF4	Platelet Factor 4
PI	Prescribing Information
PIL	Patient Information Leaflet
PM	Polymyositis
PO	Oral
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
PVFS	Post Viral Fatigue Syndrome
PVT	Portal Vein Thrombosis
PY	Person Years
RBC	Red Blood Cell
RBD	Receptor-Binding Domain
RHS	Regional Health Service
RMP	Risk Management Plan
RNA	Ribonucleic Acid
ROR	Reporting Odds Ratio
ROW	Rest Of The World
RPS	Renal Pathology Society
RR	Relative Risk
RT	Randomised Trial
RT-PCR	Reverse Transcription Polymerase Chain Reaction
RW	Risk Window
SA	South Africa
SAB	Spontaneous Abortion
SAE	Serious Adverse Event

Abbreviation or special term	Explanation
SAIL	Secure Anonymized Information Linkage
SARS	Severe Acute Respiratory Syndrome
SCAR	Severe Cutaneous Adverse Reactions
SCCS	Self-Controlled Case Series
SCGF	Stem Cell Growth Factor
SCON	Subconjunctival
SD	Standard Dose
SDSD	2 Standard Doses
SII	Serum Institute Of India
SJS	Stevens-Johnson Syndrome
SLE	Systemic Lupus Erythematosus
SMQ	Standardised MedDRA Query
SNAM	Statin-Induced Necrotizing Autoimmune Myopathy
SNDS	French Administrative Health Care Database
SNHL	Sensorineural Hearing Loss
SNOMED	Systematized Nomenclature Of Medicine Clinical Terms
SOC	System Organ Class
SOT	Solid Organ Transplantation
SQ	Subcutaneous
SRP	Signal Recognition Particle
SSAR	Suspected Serious Adverse Reactions
SUS	Secondary Uses Service
SVT	Splanchnic Venous Thrombosis
TCP	Thrombocytopenia
TE	Thromboembolism
TEN	Toxic Epidermal Necrolysis
TGA	Therapeutic Goods Administration
THIN	The Health Improvement Network
TM	Transverse Myelitis
TMA	Thrombotic Microangiopathy
TNCC	Test-Negative Case-Control Design
TNF	Tumor Necrosis Factor
TPL	Transplacental
TTO	Time To Onset

Abbreviation or special term	Explanation
TTS	Thrombosis With Thrombocytopenia Syndrome
UK	United Kingdom
UKTHIN	United Kingdom The Health Improvement Network
UMC	Uppsala Monitoring Centre
UNICEF	United Nations Children's Fund
UNK	Unknown
US	United States
USA	United States Of America
USG	Ultrasonogram
UTI	Urinary Tract Infection
VACTERL	Vertebral Defects, Anal Atresia, Cardiac Defects, Tracheo-Esophageal Fistula, Renal Anomalies, And Limb Abnormalities
VAED	Vaccine Associated Enhanced Disease
VAERD	Vaccine-Associated Enhanced Respiratory Disease
VAERS	Vaccine Adverse Event Reporting System
VDRL	Venereal Disease Research Laboratory Test
VE	Vaccine Efficacy
VIPER	Vaccines International Pregnancy Exposure Registry
VITT	Vaccine-Induced Thrombotic Thrombocytopenia
VTE	Venous Thromboembolism
WHO	World Health Organization
WLGP	Welsh Longitudinal General Practice Dataset

1 INTRODUCTION

This Periodic Benefit-Risk Evaluation Report (PBRER) prepared by AstraZeneca for VAXZEVRIA™ (AZD1222) summarises the safety and efficacy/effectiveness information received and evaluated by AstraZeneca from worldwide sources between 29 June 2022 and 28 December 2022. It is compiled in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E2C(R2) PBRER guideline and EU Good Pharmacovigilance Practices Module VII (Revision 1); the terms/terminology used in this report are consistent with this guidance, and applicable international regulatory requirements.

The VAXZEVRIA International Birth Date (IBD) is 29 December 2020.

VAXZEVRIA is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of the Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2). Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralizing antibody and cellular immune responses.

VAXZEVRIA is indicated for active immunisation of individuals ≥18 years for the prevention of Coronavirus Disease 2019 (COVID-19).

VAXZEVRIA is supplied as a vial containing either 8 doses or 10 doses per vial, 0.5 mL per dose for intramuscular (IM) injection. VAXZEVRIA primary vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks after the first dose. It is recommended that individuals who receive a first dose of VAXZEVRIA complete the primary vaccination course with VAXZEVRIA. The core data sheet (CDS) indicates that a booster dose (third dose) of 0.5 ml may be given to individuals who completed the primary vaccination course with VAXZEVRIA or another authorised COVID-19 vaccine. The third dose should be administered at least 3 months after completing the primary vaccination course. The status of approval and the recommendation in national prescribing information (PI) documents relating to the booster dose vary.

The inclusion of any information relating to a validated signal, important potential risk, or missing information within this PBRER should not be taken to imply that a causal association with the use of VAXZEVRIA has been established.

The frequency of submission of PBRER in the EU is changed from 6 month to annual at the first possibility with the data lock point (DLP) of 28 December 2023 at the request of Pharmacovigilance Risk Assessment Committee (PRAC) (Procedure no.: EMEA/H/C/PSUSA/00010912/202206).

2 WORLDWIDE MARKETING APPROVAL STATUS

VAXZEVRIA was first approved for active immunisation in individuals 18 years of age and older for the prevention of COVID-19 in United Kingdom (UK) on 29 December 2020. It received CMA in the EU on 29 January 2021.

VAXZEVRIA has been approved either as Marketing Authorisation (MA), Conditional Marketing Authorisation (CMA), or emergency use authorisation in more than 90 countries managed by AstraZeneca and its partners – Serum Institute of India (SII), R-pharm and Fiocruz. A summary of the worldwide marketing approval status applicable to VAXZEVRIA, with AstraZeneca as the MAH is provided in Table 1.

Table 1 Summary of worldwide marketing authorisation status applicable to VAXZEVRIA

Country	Date of Authorisation
Argentina	30 December 2020
Australia	15 February 2021
Brazil	12 March 2021
Brunei	27 May 2021
Canada	26 February 2021 (4 ml) 19 November 2021 (5 ml)
Chile	27 January 2021
Colombia	23 February 2021
Dominican Republic	30 December 2020
El Salvador	30 December 2020
European Union/European Medicines Agency (includes Norway, Lichtenstein & Iceland)	29 January 2021
Great Britain	24 June 2021 (Conditional Marketing Authorisation)
Guatemala	21 June 2021
Honduras	05 February 2021
Hungary	21 January 2021
Indonesia	23 April 2021
Japan	21 May 2021
Korea, Republic of (South)	10 February 2021 (Domestic Supply) 21 May 2021 (Overseas Supply)
Malaysia	02 March 2021
Maldives	20 June 2021
Mexico	04 January 2021
Montenegro	05 March 2021

Table 1 Summary of worldwide marketing authorisation status applicable to VAXZEVRIA

Country	Date of Authorisation
New Zealand	29 July 2021
Panama	05 February 2021
Peru	07 September 2021
Philippines	28 January 2021
Serbia	05 March 2021
Thailand	20 January 2021
Ukraine	20 April 2021
Vietnam	21 October 2021
World Health Organization	15 February 2021 (South Korea supply) 16 April 2021 (European Union supply) 09 July 2021 (Japan supply) 09 July 2021 (Australian supply) 27 August 2021 (Canadian supply)

3 ACTIONS TAKEN IN THE REPORTING PERIOD FOR SAFETY REASONS

No significant actions related to safety were taken or proposed during the reporting period.

4 CHANGES TO REFERENCE SAFETY INFORMATION

AstraZeneca's reference safety information is the Core Data Sheet (CDS). The CDS covers material relating to safety, indications, dosing, pharmacology, and other information concerning the medicinal product (providing the medical and scientific information AstraZeneca believes is necessary for the safe and effective use of a product); it serves as the master document for regular implementation of material changes in national or local authorised product information.

The VAXZEVRIA CDS in effect at the beginning of the reporting period was dated 11 May 2022 (version 18.0).

During this reporting period, the VAXZEVRIA CDS was updated to include the changes summarised in Table 2.

Table 2 Summary of safety-related changes to the VAXZEVRIA CDS during the reporting period.

CDS version date	CDS Section Number – CDS Section Title Detail of the safety-related change	PBRER Section cross-reference, where applicable
01 July 2022	**CDS Section 4.8 – Undesirable effects** Addition of tinnitus under "ear and labyrinth disorders" with the frequency "uncommon"	16.2.5.1
31 August 2022	**CDS Section 4.8 – Undesirable effects** Addition of cutaneous vasculitis with the frequency "not known".	16.2.5.2
08 November 2022	**CDS Section 4.4 – Special warnings and special precautions for use** Addition of text pertaining to Thrombocytopenia including immune thrombocytopenia. Re-organised the content under medical concept of Coagulation disorders with the following sub-topics: -Thromboembolism in combination with thrombocytopenia - Cerebrovascular venous and sinus thrombosis without thrombocytopenia - Thrombocytopenia **CDS Section 4.8 – Undesirable effects** Addition of immune thrombocytopenia in summary of post-authorisation data, with the frequency "not known".	16.2.5.3

CDS Core Data Sheet, PBRER Periodic Benefit-Risk Evaluation Report

A copy of the VAXZEVRIA CDS in effect at the end of the reporting period is presented in Appendix 1. For the purpose of this PBRER, this CDS dated 08 November 2022 (version 21.0), is the reference for both the benefit and risk sections. Post the DLP of PBRER, it was decided to update the CDS to include "Decreased appetite" as an Adverse Drug Reaction (ADR) and Number and percentage of solicited and unsolicited events were updated based on the final pooled analysis from COV studies (COV001, 002, 003 and 005: 31 December 2021). See section 14.

5 ESTIMATED EXPOSURE AND USE PATTERNS

5.1 Cumulative subject exposure in clinical trials

Estimates of overall cumulative subject exposure are provided in Table 3, based on actual enrolment/randomisation schemes for trials.

Table 3 Estimated cumulative subject exposure from clinical trials

Treatment	Number of subjects
VAXZEVRIA	35942
AZD2816[a]	1523
MenACWY	10960
Rabies vaccine	200
Placebo	11972

Cumulative numbers from initiation of the first clinical trials up to 28 December 2022. Participants rolled over from COV001 and COV002 into COV009, no additional dosing in COV009. COV009 excluded to avoid double-reporting.

[a] AZD2816 is a discontinued vaccine developed from AZD1222 targeting Beta variant of SARS-CoV-2. AZD2816 is used in Study D7220C00001 which is further described in Section 7.2.1.

Cumulative summary tabulations of exposure to both VAXZEVRIA and AZD2816 by age/sex and by racial group are presented in Table 4 and Table 5, respectively.

Table 4 Estimated cumulative subject exposure to VAXZEVRIA and AZD2816 from ongoing clinical trials by age and sex

	Number of subjects		
Age range (years)	**Male**	**Female**	**Total**
1-11	56	55	111
12-17	76	74	150
18-64	24906	25091	49997
>=65	5868	4372	10240
Missing	70	29	99
Total	30976	29621	60597[a]

Data from ongoing clinical trials as of 28 December 2022.

All dosed subjects are included. Gender is based on biological sex at birth in COV008 study.

[a] Participants rolled over from COV001 and COV002 into COV009, no additional dosing in COV009. COV009 excluded to avoid double-reporting.

Table 5 Estimated cumulative subject exposure to VAXZEVRIA and AZD2816 from ongoing clinical trials by racial group

Racial group	Number of subjects
American Indian Or Alaska Native	1289
Asian	2626
Black Or African American	5908
Native Hawaiian Or Other Pacific Islander	81
White	46022
Other	1569
Multiple Categories Checked	1907
Missing	795
Total	**60197**[a]

Data from ongoing clinical trials as of 28 December 2022. All dosed subjects are included.

Other race category includes multiple race categories.

[a] 400 subjects from Study COV004 not included since racial groups were not collected in this study. Participants rolled over from COV001 and COV002 into COV009, no additional dosing in COV009. COV009 excluded to avoid double-reporting.

Cumulative summary tabulations of exposure to VAXZEVRIA and AZD2816 by age/sex and by racial group are presented in Table 6 and Table 7, respectively.

Table 6 Estimated cumulative subject exposure to VAXZEVRIA and AZD2816 from ongoing clinical trials by age and sex

	Number of subjects VAXZEVRIA			Number of subjects AZD2816		
Age range (years)	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**
1-11	56	55	111	0	0	0
12-17	76	74	150	0	0	0
18-64	23720	24026	47746	1186	1065	2251
>=65	5538	4119	9657	330	253	583
Missing	70	29	99	0	0	0
Total	29460	28303	57763[a]	1516	1318	2838

Data from ongoing clinical trials as of 28 December 2022.

All dosed subjects are included. Gender is based on biological sex at birth in COV008 study.

[a] Participants rolled over from COV001 and COV002 into COV009, no additional dosing in COV009. COV009 excluded to avoid double-reporting.

Table 7 Estimated subject exposure to VAXZEVRIA and AZD2816 from ongoing clinical trials by racial group

Racial group	Number of subjects VAXZEVRIA	Number of subjects AZD2816
American Indian Or Alaska Native	1281	8
Asian	2569	57
Black or African American	5194	714
Native Hawaiian or Other Pacific Islander	81	0
White	44227	1795
Other	1569	0
Multiple Categories Checked	1854	53
Missing	588	207
Total	57363[a]	2834

Data from ongoing clinical trials as of 28 December 2022. All dosed subjects are included.

Other race category includes multiple race categories.

[a] 400 subjects from Study COV004 not included since racial groups were not collected in this study. Participants rolled over from COV001 and COV002 into COV009, no additional dosing in COV009. COV009 excluded to avoid double-reporting.

5.2 Cumulative and interval patient exposure from marketing experience

5.2.1 Post-approval (non-clinical trials) exposure

The post-marketing patient exposure data in this report is presented by number of doses distributed and doses administered. All exposure is intended for the same indication and route of administration.

For doses distributed, this information has been provided below in section 5.2.1.1 and it includes dose distribution information across all markets, those where AstraZeneca is the Marketing Authorisation Holder (MAH) and those supported by the licence partners (SII, R-Pharm, Fiocruz, and Verity Pharmaceuticals).

For doses administered to vaccinees, this is a more accurate measure of vaccinee exposure and provides more detailed vaccinee-level data (eg, gender and age category). Therefore, AstraZeneca is continuing to work on the collection of this information at the country level, from relevant health departments, for all countries administering the VAXZEVRIA. However, many health departments, have stopped providing the administration data due to decreased uptake of VAXZEVRIA. Exposure data based on doses administered to vaccinees in specific countries/regions is provided in section 5.2.1.2 below.

5.2.1.1 Patient exposure – doses distributed

During this reporting period, the global post-marketing patient exposure (by doses distributed) to VAXZEVRIA was estimated to be over 181 million doses (6.02% of cumulative).

The cumulative global post-marketing patient exposure (by doses distributed) to VAXZEVRIA, since launch to 31 December 2022, have been estimated to be over 3.02 billion doses.

The regional dose distribution data is presented in Table 8.

Table 8 VAXZEVRIA exposure, based on doses distributed, by Region

Region[b]	Exposure by doses distributed		Percentage (%)	
	Interval (01 July 2022 to 31 December 2022)	Cumulative (Up to 31 December 2022)	Interval	Cumulative
Europe	0	248197720	0	8.22
International	36646740	680370580	20.14	22.52
North America	14178700	33267900	7.79	1.10
Japan	57600	62720740	0.03	2.08
Serum Institute of India[a]	109067400	1745773940	59.95	57.79
Fiocruz[a]	21971750	209957440	12.08	6.95
R-Pharm[a]	0	10358700	0	0.34
BKT[a]	0	30000000	0	0.99
Total	181922190	3020647020	100	100

[a] Data from Serum Institute of India, BKT, and R-Pharm is as of 30 June 2022 and from Fiocruz is as of 31 December 2022.

[b] Where AstraZeneca (AZ) is the Marketing Authorisation Holder, dose volumes cited represent doses dispatched from AZ manufacturing sites and contracted manufacturing sites. The destinations noted 'Region' represent what is known at the time of dispatch. Country to country donations may or may not be reflected dependent on the timing and type of donation.

BKT Biokangtai

A more detailed breakdown of cumulative doses distributed across the countries within the EU can be found in Appendix 6.

5.2.1.2 Post-marketing patient exposure data for reporting period and cumulatively

AstraZeneca has obtained exposure data based on doses administered to vaccinees in EU, Afghanistan, Argentina, Australia, Bangladesh, Brazil, Canada, Chile, Colombia, Ecuador,

Ghana, Guatemala, India, Iran, Iraq, Japan, Lebanon, Malaysia, Mexico, Nepal, New Zealand, Peru, Philippines, Saint Lucia, South Korea, Taiwan, Thailand, UK and Uruguay. This information is summarised in Table 9 below and it represents the interval and cumulative exposure (by doses administered). This data has either been provided to AstraZeneca directly from Government bodies or has been sourced from country specific websites.

Administration data from the licence partners (Serum Institute of India, Fiocruz and R-Pharm) have not been provided to AstraZeneca directly.

Please note that administration in other markets where the VAXZEVRIA is authorised has not yet been made available to AstraZeneca. As such, the doses administered presented in this report is less than the doses distributed. The cumulative global post-marketing patient exposure (by doses administered) to VAXZEVRIA, since launch to 31 December 2022, have been estimated to be over 2.35 billion doses.

The vaccine administration data is provided by the health departments only in cumulative manner. Therefore, the interval data is calculated by subtracting the previous cumulative from the current cumulative data across all the countries. The weekly administered data is subject to change every week, based on the reconciliation and update provided by the individual markets. Hence, the negative values are due to a greater cumulative value from previous report in comparison to current report.

Table 9 VAXZEVRIA interval and cumulative exposure based on doses administered, by Region/Country

Region	Interval			Cumulative			Percentage (%)	
	Dose 1	Dose 2	Dose3/ Dose 4/Booster	Dose 1	Dose 2	Dose3/Dose 4/Booster	Interval	Cumulative
European Union	22490	14334	10179	38935859	29830777	31951	0.025	2.922
United Kingdom	-7439	-7973	831	24725401	24141350	59155	-0.008	2.078
Afghanistan	0			975338			0.000	0.041
Australia	-188227	-170548	386772	6710682	6644072	479167	0.015	0.588
Philippines	284777			22135134			0.149	0.940
India	165833251			1745211297			86.665	74.120
Canada	1654	1083	204	2236627	577088	1788	0.002	0.120
Argentina	7256	11021	61373	10181628	9944079	6643766	0.042	1.137
Bangladesh	220251	371169	524825 1	20769391	19503709	15968643	3.052	2.389

Table 9 VAXZEVRIA interval and cumulative exposure based on doses administered, by Region/Country

Region	Interval			Cumulative			Percentage (%)	
	Dose 1	Dose 2	Dose3/ Dose 4/Booster	Dose 1	Dose 2	Dose3/Dose 4/Booster	Interval	Cumulative
Colombia	453211	513600	456393	5761263	3886086	2039794	0.744	0.496
Ecuador	25295	50994	1172435	1764549	1470105	5039008	0.653	0.351
Iran	5006	6213	238149	5601073	5045996	3779468	0.130	0.613
Japan	-18	341	0	58689	59160	0	0.000	0.005
Brazil	35844	-988002	15505290	62269829	56441002	32863466	7.606	6.437
Chile	4	14	1130	410045	139643	2656600	0.001	0.136
Guatemala	4751	5213	18633	2038088	1612254	837482	0.015	0.191
Ghana	448113			10545038			0.234	0.448
Lebanon	2,077			722870			0.001	0.031
Iraq	0			717233			0.000	0.030
Mexico	0			49783383			0.000	2.114
Malaysia	1378	1729	12452	2047982	2027704	1631803	0.008	0.242
Nepal	131436	190873	676894	5506364	4789110	4703764	0.522	0.637
Peru	3547	10929	138128	2244579	2110451	3747778	0.080	0.344
Saint Lucia	0	0	0	37850	34810	0	0.000	0.003
Taiwan	471	1944	1070	8072530	7164623	60558	0.002	0.650
Thailand	20407	21384	53437	14098645	28682204	5923245	0.050	2.068
New Zealand	3	27	191	3317	3646	2076	0.000	0.000
South Korea	27,539			20348873			0.014	0.864
Uruguay	3	0	0	46687	44454	179	0.000	0.004
Grand Total	**191,349,237**			**2,354,582,258**			**100**	**100**

The data cut off for Iraq is 29 August 2021
The data cut off for Afghanistan is 30 April 2022
The data cut off for United Kingdom is 12 September 2022
The data cut off for Nepal is 25 September 2022
The data cut off for Mexico is 01 October 2022
The data cut off for Saint Lucia is 18 October 2022
The data cut off for Thailand is 25 November 2022
The data cut off for Philippines and Peru is 30 November 2022
The data cut off for Canada is 04 December 2022

The data cut off for New Zealand is 06 December 2022

The data cut off for Ghana is 09 December 2022

The data cut off for EU is 11 December 2022. *EU - AZ vaccine administration data for Germany is not available

The data cut off for Iran and South Koreais 17 December 2022

The data cut off for Australia is 21 December 2022

The data cut off for Brazil and Taiwan is 25 December 2022

The data cut off for Chile and India is 26 December 2022

The data cut off for Colombia and Japan is 27 December 2022

The data cut off for Argentina, Malaysia, Bangladesh, Ecuador, Guatemala, Lebanon and Uruguay is 28 December 2022

The weekly administered data is subject to change every week. The administered data for the PBRER reporting interval is derived by subtracting the previous report's cumulative from current cumulative values (Current Cumulative - Previous Cumulative = Current Interval) across all the Countries. Therefore, the negative values here is due to a greater cumulative value from previous report in comparison to current report.

A more detailed presentation of doses administered by country/states as well as vaccine administration by dose number, age and/or gender where provided for specified countries can be found in Appendix 6. However, a summary of the post-marketing patient exposure by age and gender (as currently available) is presented in Table 10 and Table 11, respectively.

Table 10 presents the vaccine doses administered by Age Group for the following specific countries:

- Australia, Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and UK.

Table 10 VAXZEVRIA Doses Administered by Age Group

Age Group	Interval				Cumulative			
	Dose 1	Dose 2	Total	Percentage (%)	Dose 1	Dose 2	Total	Percentage (%)
18-24	-984324	-952783	-1937107	570.25	1051441	897242	1948683	1.77
25-49	349069	353840	702909	-206.93	13733482	12584066	26317548	23.85
50-59	-542708	-504639	-1047347	308.32	10781550	10120269	20901819	18.94
60-69	-372036	-348893	-720929	212.23	17362817	16707499	34070316	30.88
70-79	-55502	-64660	-120162	35.37	10101101	9899019	20000120	18.12
≥80	-220803	-183952	-404755	119.15	1925813	1883574	3809387	3.45

Table 10 VAXZEVRIA Doses Administered by Age Group

Age Group	Interval				Cumulative			
	Dose 1	Dose 2	Total	Percentage (%)	Dose 1	Dose 2	Total	Percentage (%)
Unknown	1652808	1534891	3187699	-938.41	1727712	1570369	3298081	2.99
Total	-173496	-166196	-339692	100	56683916	53662038	110345954	100

The total doses administered by Age group do not reflect the total doses administered that appear in Table 9. This is due to the fact that doses administered by Age group are not available for all countries that have provided vaccine administration information.

Table 11 present the vaccine doses administered by Gender Group for UK

Table 11 VAXZEVRIA Doses Administered by Gender UK

Gender	Total doses administered		Percentage (%)
	Interval	Cumulative	Cumulative
Male	-1603894	22377923	45.74
Female	-1542544	23252503	47.53
Unspecified	3191191	3295480	6.74
Total	44753	48925906	**100**

The total doses administered by Gender group does not reflect the total doses administered that appears in Table 9. This is due to the fact that doses administered by Gender group is not available for all countries that have provided vaccine administration information.

For current reporting period UK data was available and Australia data was not available as per gender group

Exposure by doses administered is used as for Observed versus Expected (O/E) Analyses for Adverse Event Of Special Interests (AESIs)/signals and safety concerns, refer to Appendix 8 for further details.

AstraZeneca will continue efforts to obtain exposure data by gender for each EU Member State, as currently the data provided via the European Centre for Disease Prevention and Control (ECDC) does not include gender breakdown at a country level. If this data become available, it will be included in future reports. However, multiple health authorities/government agencies have stopped updating the vaccine administration data, AstraZeneca will assess the situation and consider the data cut-off for administration data and O/E analysis in the next PBRER.

5.2.2 Post-approval use in special populations

It is not possible to provide an estimate of patient numbers exposed from post-approval use in special populations.

5.2.3 Other post-approval use

AstraZeneca is not aware of any patterns of use (for example overdose, drug abuse, misuse or off-label use) of VAXZEVRIA considered to be relevant for the interpretation of safety data.

6 DATA IN SUMMARY TABULATIONS

6.1 Reference information

The Medical Dictionary for Regulatory Activities (MedDRA), version 25.1, has been used for coding adverse events (AEs). The summary tabulations are arranged in the internationally agreed order by primary MedDRA System Organ Class (SOC), and refer to the Preferred Term (PT) level.

6.2 Cumulative summary tabulations of serious adverse events (SAE) from clinical trials

A cumulative summary tabulation of SAEs from AstraZeneca-sponsored and license partner sponsored interventional clinical trials that have been reported during the VAXZEVRIA clinical development programme, from the Development International Birth Date (DIBD) to the data lock point (28 December 2022), organised by SOC, is presented in Appendix 2.

A summary of the total number of case reports with SAEs from AZD1222 (VAXZEVRIA) and AZD2816 clinical trials along with the total number of SAEs for each treatment is provided in Table 12.

There is an increase in Clinical trial SAEs/ cases in the current PBRER internal compared to the previous PBRER interval, this is because the COV Studies (001, 002, 003 and 005) were unblinded and the cases were edited to add the treatment allocation. There is no new safety concern identified from these events.

Table 12 Summary tabulation of SAE case reports received from VAXZEVRIA (AZD1222) and AZD2816 clinical trials[a]

Treatment	Previous PBRER Interval (29 December 2021 to 28 June 2022)		Current PBRER reporting interval (29 June 2022 – 28 December 2022)		Cumulative (through 28 December 2022)	
	Number of Cases	Number of Serious Adverse Events	Number of Cases	Number of Serious Adverse Events	Number of Cases	Number of Serious Adverse Events
VAXZEVRIA	480	601	1011	1130	2199	2524
AZD2816[c]	25	26	5	5	40	42
MENACWY	122	143	84	92	139	150
Meningocccal Group B Vaccine	1	1	1	1	5	6
Placebo	325	423	531	599	1614	1876
Study procedure	3	3	4	4	13	16
Total[b]	956	1197	1636	1831	2216	4614

[a] Numbers presented in this table will not match those presented in Appendix 2, Table 1 due to differences in the date that the table and appendices were generated from the AstraZeneca Global Safety database.

[b] AZD2816 is a vaccine developed from AZD1222 targeting variants of SARS-CoV-2. AZD2816 is used in Study D7220C00001 which is further described in Section 7.2.1.

[c] Cases may have more than one treatment listed. Therefore, the sum of cases and SAEs will exceed the total.

There is an increase in the CT cases, this is because the COV Studies (001, 002, 003 and 005) were unblinded and the cases were edited to add the treatment allocation. This is the reason for spike in the cases.

A review of Table 1 of Appendix 2 has been completed for the PBRER period from 29 June 2022 to 28 December 2022 and there are no noteworthy changes in the absolute frequency numbers from the previous PBRER.

6.3 Cumulative and interval summary tabulations from post-marketing data sources

Cumulative and interval summary tabulations of adverse reactions (ie, AEs considered as "a reasonable possibility of a causal relationship between the medicinal product and the event" for Table 2 Appendix 2) that have been reported from marketed experience with VAXZEVRIA, from the IBD to the data lock point, organised by SOC, are presented in Appendix 2.

A summary of the total number of VAXZEVRIA case reports and corresponding AEs/SAEs received from Spontaneous sources for both the interval and cumulative periods is provided in Table 13. Compared to the previous interval, there is a decrease in the case and event count

for the current reporting interval. This is due to decreased update in many regions, compared to the previous intervals.

Table 13 Summary tabulation of VAXZEVRIA case reports and adverse events received from spontaneous sources[a]

Case/Event Seriousness	Previous PBRER Interval (29 December 2021 – 28 June 2022)		Current PBRER Interval (29 June 2022 to 28 December 2022)		Cumulative to 28 December 2022	
	Number of Cases	Number of Adverse Events	Number of Cases	Number of Adverse Events	Number of Cases	Number of Adverse Events
Serious	36456	95064	10689	34706	264036	972096
Non-Serious	93912	393777	49237	210221	543981	2077833
Not available/ Not entered	1	0	0	0	2	0
Total	**130369**	**488841**	**59926**	**244927**	**808019**	**3049929**

[a] Numbers presented in this table will not match those presented in Appendix 2 due to differences in the date that the table and appendices were generated from the AstraZeneca Global Safety database.

In the PM experience, there is very less cases compared to last reporting interval. This is due to the administration uptake in many regions

A review of Table 2 Appendix 2 has been completed for the PBRER period from 29 June 2022 to 28 December 2022 and there are no noteworthy changes in the absolute frequency numbers from the previous PBRER.

6.3.1 Lack of efficacy from Post-Marketing

Interval Period (29 June 2022 – 28 December 2022)

A search of the AstraZeneca Global Safety database for the reporting interval using the Lack of Efficacy standardised MedDRA query (SMQ), retrieved 2716 reports with the following 2728 AEs (PTs): Vaccination failure (2381), Drug ineffective (290), Therapeutic product effect decreased (21), Therapeutic product effect incomplete (9), Therapeutic response shortened (9), Therapeutic response decreased (5), Disease progression (3), Drug resistance (2), Therapy non-responder (2), Drug ineffective for unapproved indication (1), Drug level abnormal (1), Drug level decreased (1), Therapeutic product effect delayed (1), Therapeutic product ineffective (1), and Therapy partial responder (1).

Of the 2716 reports, 2498 (92.0%) were medically confirmed (MC) and the remaining 218 (8.0%) were consumer reports. 2645 of the 2716 reports were initial and 71 were follow-ups (FU). A total of 2500 (92.0%) reports were considered serious due to the AE being considered medically important (2475), required hospitalization (47), was life threatening

(LT) (1), resulted in disability (2), and/or resulted in death (8). Cases may have met more than one criteria for seriousness. The remaining 216 (8.0%) reports were non-serious (NS). Of the 2716 reports, 2248 (82.8%) were reported from Austria. All reports from Austria were received during June, September and November 2022.

There were 8 fatal cases in the reporting interval. Age was reported in all of these 8 cases with a median age of 63 years (range 40 to 76 years) and included 6 females and 2males. Cause of death PTs (≥2) included: COVID-19 (3), COVID-19 pneumonia (3), Drug ineffective (3), Pneumonia (1), and Vaccine associated enhanced respiratory disease (1). Most fatal cases contained confounders, such as advanced age, diabetes, chronic kidney disease (CKD), immunodeficiency, cancer, heart failure/disease, and dyslipidaemia.

Of the 2708 non-fatal cases, the outcomes were as follows: Not recovered (89), Recovered (61), Recovering (58), and Unknown (2500).

Information on COVID-19 testing was available in 2384 reports; of these 2371 (99.5%) were reported as COVID-19 test positive, 5 (0.2%) were reported as COVID-19 test negative and 1 (0.04%) were reported as unknown. Further information on the 2371 reports (including 10 with first dose, 2350 with second dose, 3 with booster dose, and 8 with unknown dose) with a positive COVID-19 test is presented below:

- In 10 (0.4%) of the 2371 reports, COVID-19 test was positive after the receipt of the first dose of the vaccine; time to positive COVID-19 test was available for 8 (0.3%) cases and ranged from 281 to 555 days with a median of 380 days. In 2 (0.1%) reports, time to positive Covid-19 test after first dose of vaccine was unknown.
- In 2350 (99.18%) reports, COVID-19 test was positive after the receipt of the second dose of the vaccine; time to positive COVID-19 test was available for 2291 (96.6.5%) cases and ranged from 28 days to 483 days with a median of 151 days. In 59 (2.5%) reports, time to positive COVID-19 test after second dose of vaccine was unknown. In 1 report, the date of positive test result was before the vaccination date.
- In 3 (0.1%) reports, COVID-19 test was positive after the receipt of the booster dose of the vaccine; time to positive COVID-19 test was 0 days for 2 of the reports and unknown for 1.
- In 8 (0.3%) reports, COVID-19 test was positive after the receipt of unknown dose of the vaccine. In 7 reports, time to positive Covid-19 test after unknown dose of vaccine was unknown and in 1 report, the date of positive test result was before the vaccination date.

Cumulative Review (29 December 2020 – 28 December 2022)

A cumulative search of the Global Safety database using the Lack of Efficacy SMQ, retrieved 25335 reports with the following 25346 PTs: Vaccination failure (23779), Drug ineffective (1316), Therapy partial responder (70), Therapeutic product effect decreased (36), Therapeutic product ineffective (34), Treatment failure (21), Therapeutic product effect

incomplete (18), Disease progression (14), Therapeutic response shortened (11), Therapeutic response decreased (9), Therapy non-responder (9), Drug effect less than expected (5), Drug tolerance (4), Drug level decreased (3), Therapeutic product effect delayed (3), Drug resistance (2), Paradoxical drug reaction (2), Therapeutic reaction time decreased (2), Absence of immediate treatment response (1), Drug ineffective for unapproved indication (1), Therapeutic response changed (1), Remission not achieved (1), Drug level abnormal (1), Therapeutic response delayed (1), Device defective (1), and Diet failure (1).

Of the 25335 reports, 24109 (95.2%) were medically confirmed and the remaining 1226 (4.8%) were consumer reports. A total of 23828 (94.1%) reports were considered serious due to the AE being considered medially important (23231), the AE resulted in a congenital anomaly (1), the AE was reported to have resulted in disability (26), required hospitalization (627), was life threatening (92), and/or resulted in death (160). Cases may have met more than one criteria for seriousness. The remaining 1507 (5.9%) reports were non-serious. Of the 25335 reports, 87.2% (22099) were reported from Austria. Cumulatively, there have been 160 fatal cases.

Of the 25175 non-fatal cases, the outcomes were as follows:

Not recovered (602) Recovered (832), Recovered with sequelae (9), Recovering (513), and Unknown (23219).

Conclusion

Review of all the lack of efficacy reports did not demonstrate any specific trend or safety information associated with use of VAXZEVRIA. There was a decrease in the number of case reports for lack of efficacy during this interval (2716) compared to the previous PBRER (16964) covering the period 29 December 2021 to 28 June 2022. Cumulatively, of the 25335 lack of efficacy reports, there have been 160 fatal cases. Also noted that 82.8% of the reports (2248/2716) during the reporting interval and 87.2% (22099/25335) of the reports cumulatively were from Austria. This is due to a local reporting system where cases from the epidemiological reporting system for COVID-19 are linked with the vaccination passport and submitted to Eudravigilance/AstraZeneca in bulk.

6.3.2 Fatal events, including case reports involving Sudden Death/Sudden cardiac death

6.3.2.1 Fatal Events

Interval Review (29 June 2022 to 28 December 2022)

A total of 681 fatal cases were received during the reporting period (29 June 2022 to 28 December 2022) which includes 489 (72%) of initial case reports and 192 (28%) follow-up reports. Of the 489 initial cases, 231 (47%) of cases, reported exposure to vaccine in the

previous reporting intervals and they were received by AstraZeneca from the sources during the reporting interval and hence considered under interval data analysis. Most of these cases were reported from India (n=79, 34%), Philippines (n=46, 20%), United Kingdom (n=38, 16%) and Brazil (n=30, 13%).

Of these 681 fatal cases, in 503 (74%) cases, the vaccinees' age was reported and in 178 (26%) cases, age was unknown (See Table 14. In 201 (30%) of 503 cases, the vaccinees' were aged 65 years and above. The median age was 60 years. The gender was reported in 568 (83%) the vaccinees; 317 (56%) were male and 251 (44%) were female. Of the 681 case reports 431 (63%) were medically confirmed and 250 (37%) were consumer reports. Most of the cases were reported from Brazil (n=176, 26%), United Kingdom (n=160, 23%), India (n=91, 13%) and Philippines (n=81, 12%).

During the reporting period, in 41 cases, events with fatal outcome were reported after booster doses [Dose 3 (n=37) and Dose 4 (n=13)]. Most of the cases were reported from Brazil (n=13), United Kingdom (n=11) and Philippines (n=7). In 10 cases, patients received mRNA vaccine as booster (different booster vaccine from the primary vaccine or primary vaccination series) and in 31 cases patient received VAXZEVRIA as booster dose. Of the 31 cases, in one case, fatal outcome was confounded by underlying risk factor of chronic obstructive pulmonary disease (COPD) and hypertension. In four cases, the fatal events: myocardial infarction (MI), parkinsonism, cardiogenic shock, and chest pain were considered as unlikely based on the time to onset (TTO) (67, 122, 144 and 252 days) of events. The remaining 26 cases had limited information on relevant medical history and cause of death.

Of the 681 cases, 42 (6%) were reported with sudden Death. Case reports of Sudden Death are included in the overall number of cases with fatal outcome and are discussed in Section 6.3.2.2.

Distribution of fatal cases per age group during the reporting interval is presented in Table 14.

Table 14 Fatal cases per age group (in years)

Age group	Number of cases
18-49	163 (32)
50-59	80 (16)
60-64	59 (12)
65-74	109 (22)
>75	92 (18)
Unknown	178
Grand total	**681**

Information regarding comorbid conditions was available in 203 (30%) out of 681 cases. Important comorbid conditions included hypertension (n=72), diabetes mellitus (n=24), type 2 diabetes mellitus (n=11), coronary artery disease (n=10), asthma, myocardial ischemia, COPD and cerebrovascular accident (CVA) (n=7, each), chronic kidney disease and COVID-19 (n=6, each).

Out of 681 cases, the cause of death was not reported in 226 (33%). The reported cause of death in remaining 455 fatal case reports are presented in Table 15 (Note: In some cases, single most relevant cause of death could not be determined due to insufficient information. Also, one case might have multiple causes of death).

Table 15 Reported cause of death in Fatal Cases with VAXZEVRIA (n = 455) during the Interval period: 29 June 2022 – 28 December 2022

Cause of Death	Fatal cases
Cardiorespiratory causes (includes Sudden cardiac death, Pulmonary embolism, Myocardial Infarction, Dyspnoea, Acute respiratory failure, Acute myocardial infarction, Cardiac arrest, Cardio-respiratory arrest, Acute coronary syndrome, Respiratory failure, Coronary artery disease, Severe acute respiratory syndrome, Acute respiratory distress syndrome etc)	180
Infection [a]	72
Cerebrovascular accident without reported thrombocytopenia	45
Thrombosis with Thrombocytopenic syndrome [b] (including haemorrhage) (including cerebral venous sinus thrombosis (CVST) (including Ischaemic stroke) (including Cerebral venous thrombosis (CVT)) (including intraabdominal thrombosis) (including pulmonary embolism)	60 20 18 7 6 4 2
Cerebral haemorrhage	41
Thrombosis (without thrombocytopenia)	35
Malignancy	27
Renal dysfunction	16
Thrombocytopenia	16
CVT/CVST without thrombocytopenia	21
Seizure	11
Guillain Barre Syndrome	11
Gastrointestinal causes	8
Hepatic disorder[c]	6

Table 15 Reported cause of death in Fatal Cases with VAXZEVRIA (n = 455) during the Interval period: 29 June 2022 – 28 December 2022

Cause of Death	Fatal cases
Thrombocytopenia with haemorrhage	3
Aneurysm	3
Multiple organ failure	3
Anaphylaxis/ Hypersensitivity	3
Pancreatitis	2
Haemophagocytic lymphohistiocytosis	1
Others	63

[a] Note: The cause of death is either grouped by event and their symptoms or related diseases. In some cases, single most relevant cause of death could not be determined due to insufficient information.

[b] The 6 subsets of Thrombosis with Thrombocytopenic syndrome (TTS) were placed in the brackets

[c] Not limited to hepatic cirrhosis, hepatitis.

CVST Cerebral venous sinus thrombosis, CVT Cerebral venous thrombosis

Of the 72 case reports where infections were reported as the cause of death, 30 cases (42%) reported COVID-19 infection as the cause of death. Out of 30 COVID-19 cases, 10 cases (33%) were reported after first vaccine dose and time to death or fatal outcome ranged from 1 day to 63 days (median 5 days). In 10 cases (33%), COVID-19 infection was reported after second dose of vaccination and in two cases after second booster dose. Time to death or fatal outcome ranged from 3 days to 359 days (median 59 days) after second dose and 38 days after booster (second) dose. No trends of SAEs were noted with booster doses.

Other infections included: sepsis, septic shock, pneumonia, *Pneumocystis jirovecii* pneumonia, herpes zoster, encephalitis Japanese B, gastroenteritis, meningococcal bacteraemia (bacterial meningitis), tuberculosis, hepatitis A, and bronchial infection.

Among the cases reporting fatal outcome during the reporting interval, no specific pattern regarding underlying conditions or cause of death could be identified. In the cases reporting fatal outcome post booster dose, there was insufficient information on dates of vaccination, medical history and cause of death in many reports.

Cumulative Review (29 December 2020 – 28 December 2022)

Cumulatively through 29 December 2020 to 28 June 2022, there have been 6897 fatal cases. Out of 6897 cases, age of vaccinees was reported in 5711 cases (83%) and was unknown in 1,186 cases (17%). In 2933 (51%) of the 5711 case reports, the vaccinees were aged 65 years and above. The median age of the fatal cases was 65 years. Out of 6897 cases, gender was reported in 6510 cases (94%). There were 2945 females (45%) and 3565 males (55%).

Cumulatively, of the 6897 case reports with fatal outcome, 4237 (61%) were medically confirmed and 2660 (39%) were consumer reports. Cumulatively, 58 fatal cases were reported with booster dose, and 41 cases are already discussed under reporting period analysis. The remaining cases had insufficient information on relevant medical history and cause of death. Of the 6897 cases, 402 (6%) were reported as sudden Death. Case reports of sudden Death, see Section 6.3.2.2, are included in the overall number of cases with fatal outcome.

Cumulative O/E analyses were conducted for fatal cases and were stratified by age group and gender where administration data was available. Reference for background estimates obtained from the literature are provided in Appendix 9. The O/E analysis of fatal reports showed that observed cases occurred significantly less frequently than the expected for all the ages and by different age stratifications from European Economic Area (EEA) + UK + Brazil + and Australia. Results of the O/E analyses are presented in Table 16, Table 17, and Table 18. Conservatively, the exposure for global reports (466115644) is based on doses administered in 13 regions/markets as explained in Appendix 8.

Table 16 Observed versus expected analyses for Fatal cases overall

Medical Concept	Observed cases	Expected cases	Risk Window	Background rate/100,000 person years	Rate ratio (CI 95%)	Conclusion
Fatal Reports RW 42 [a]	3914	196040.6	42	365.75	0.02 (0.02 - 0.02)	Observed significantly < expected
Fatal Reports RW42 + Unk TTO	6259	196040.6	42	365.75	0.03 (0.03 - 0.03)	Observed significantly < expected

[a] Includes global reports irrespective of age and gender.
Global exposure was 466115644.
CI Confidence Interval, RW Risk Window, TTO Time to onset, Unk Unknown.

Table 17 Observed versus expected analyses for Fatal cases by age group from EU+UK+Brazil+Australia region

Medical Concept	Age Group	Risk Window	BG rates	Exposure	Observed cases [b]	Expected cases	Rate ratio (CI 95%)	Conclusion
Fatal Reports [a] (from EU+UK +Brazil+	18 – 49 RW 42	42	65.86	110094983	453	8337.9	0.05 (0.05 - 0.06)	Observed significantly < expected
	50 – 59 RW42	42	193.2	58336094	428	12960.2	0.03 (0.03 - 0.04)	Observed significantly < expected

Table 17 Observed versus expected analyses for Fatal cases by age group from EU+UK+Brazil+Australia region

Medical Concept	Age Group	Risk Window	BG rates	Exposure	Observed cases [b]	Expected cases	Rate ratio (CI 95%)	Conclusion
Australia)	60 – 69 RW42	42	314.82	57960860	806	20982.9	0.04 (0.04 - 0.04)	Observed significantly < expected
	70+ RW 42	42	1010.74	32376365	1256	37630.1	0.03 (0.03 - 0.04)	Observed significantly < expected
	18 – 49 RW 42 + Unk TTO	42	65.86	110094983	673	8337.9	0.08 (0.07 - 0.09)	Observed significantly < expected
	50 – 59 RW42 + Unk TTO	42	193.2	58336094	533	12960.2	0.04 (0.04 - 0.04)	Observed significantly < expected
	60 – 69 RW42 + Unk TTO	42	314.82	57960860	973	20982.9	0.04 (0.04 - 0.05)	Observed significantly < expected
	70+ RW 42 + Unk TTO	42	1010.74	32376365	1586	37630.1	0.04 (0.04 - 0.04)	Observed significantly < expected

[a] Fatal report O/E by age group is based on cases reported from EU+UK+Brazil+Australia, as corresponding exposure was only available from this region.

[b] Includes cases reported within risk window of 42 days.

BG background rate CI Confidence Interval; EU European Union, RW Risk window, UK United Kingdom.

Table 18 Observed versus expected analyses for Fatal cases by age group in UK

Medical Concept	Age Group	Risk window in days	BG rates	Exposure	Observed cases [b]	Expected cases	Rate ratio (CI 95%)	Conclusion
Fatal Reports [a] (from UK)	18-29 (RW 42) UK	42	28.22	1918869	25	62.3	0.4 (0.26 - 0.59)	Observed significantly < expected
	30-39 (RW 42) UK	42	48.8	3308256	33	185.7	0.18 (0.12 - 0.25)	Observed significantly < expected

Table 18 Observed versus expected analyses for Fatal cases by age group in UK

Medical Concept	Age Group	Risk window in days	BG rates	Exposure	Observed cases [b]	Expected cases	Rate ratio (CI 95%)	Conclusion
	40-49 (RW 42) UK	42	100.86	8954709	74	1038.6	0.07 (0.06 - 0.09)	Observed significantly < expected
	50-59 (RW 42) UK	42	193.2	12455887	134	2767.3	0.05 (0.04 - 0.06)	Observed significantly < expected
	60-69 (RW 42) UK	42	314.82	9718273	155	3518.2	0.04 (0.04 - 0.05)	Observed significantly < expected
	70-79 (RW 42) UK	42	553.23	6613249	204	4207.2	0.05 (0.04 - 0.06)	Observed significantly < expected
	80+ (RW 42) UK	42	1638.26	2655389	282	5002.4	0.06 (0.05 - 0.06)	Observed significantly < expected
	18-29 (RW 42+Unk) UK	42	28.22	1918869	37	62.3	0.59 (0.42 - 0.82)	Observed significantly < expected
	30-39 (RW 42+Unk) UK	42	48.8	3308256	57	185.7	0.31 (0.23 - 0.4)	Observed significantly < expected
	40-49 (RW 42+Unk) UK	42	100.86	8954709	105	1038.6	0.1 (0.08 - 0.12)	Observed significantly < expected
	50-59 (RW 42+Unk) UK	42	193.2	12455887	175	2767.3	0.06 (0.05 - 0.07)	Observed significantly < expected
	60-69 (RW 42+Unk) UK	42	314.82	9718273	202	3518.2	0.06 (0.05 - 0.07)	Observed significantly < expected
	70-79 (RW 42+Unk)	42	553.23	6613249	247	4207.2	0.06 (0.05 - 0.07)	Observed significantly < expected

Table 18 Observed versus expected analyses for Fatal cases by age group in UK

Medical Concept	Age Group	Risk window in days	BG rates	Exposure	Observed cases [b]	Expected cases	Rate ratio (CI 95%)	Conclusion
	80+ (RW 42+Unk)	42	1638.26	2655389	326	5002.4	0.07 (0.06 - 0.07)	Observed significantly < expected

[a] Fatal report O/E by age group is based on cases reported from UK, as corresponding exposure was only available from this region.

[b] Includes cases reported within risk window of 42 days.

BG background rate CI Confidence Interval; UK United Kingdom, Unk Unknown.

6.3.2.2 Case reports involving PT of Sudden Death

Interval Review (29 June 2022 to 28 December 2022)

During the reporting period, 42 cases of sudden death/sudden cardiac death were reported (40 (95%) initial, 2 (5%) follow-up).

Of the 42 cases with sudden death/sudden cardiac death, 39 (93%) were medically confirmed and 3 (7%) were consumer reports. Twenty-eight (72%) vaccinees were male and 11 (28%) were female. Age of vaccinees ranged from 23 to 93 years with a median age of 57 years.

Out of 42 cases, TTO was available only in 7 cases and in 5 cases the TTO was day 1 (dose unknown) and in one case patient died on Day 88 after the first dose and in the last case, patient died on Day 13 (dose unknown).

Of the 42 cases of sudden death, the causes of death or other fatal conditions were reported in 30 cases (71%) and included the following AEs (PTs): sudden cardiac death, chronic kidney disease, hypertension, coronary artery disease and aortic aneurysm. The medical history was reported in 24 cases (57%) and it includes hypertension, diabetes mellitus, coronary artery disease, acute coronary syndrome, cerebrovascular accident, chronic hepatitis C, ischaemic cardiomyopathy, myocardial ischaemia, asthma, hepatitis alcoholic and chronic myeloid leukaemia.

Among the cases reporting sudden death, no specific pattern regarding underlying conditions or cause of death could be identified. In most of reports of sudden death, information on clinical course of the event leading to death were not provided. No new safety concerns were identified.

Cumulative Review (29 December 2020 – 28 December 2022)

Cumulatively between 29 December 2020 to 28 December 2022, out of 402 cases, 222 (55.2%) cases containing the PT of sudden death (one case with AEs sudden death and sudden cardiac death), 179 (44.5%) case containing the PT of sudden cardiac death and 1 (0.25%) case reported with sudden unexplained death in epilepsy.

Of the 402 case reports with sudden death, 336 (84%) were medically confirmed and 66 (16%) were consumer reports. 152 (38%) vaccinees were female, 244 (61%) were male and 6 (1%) was unknown. Age of vaccinees ranged from 19 to 97 years with a median age of 66 years.

Of the 402 cases, TTO was available in 190 (47%) cases. Out of 190 cases, 56 cases (29%) had time to death ranged from 0 to 263 days after receiving the first dose of the vaccine and 16 cases (40%) where time to death ranged from 0 to 121 days after receiving the second dose.

Of the 402 cases of sudden death, the causes of death were identified in 255 cases (63%) and included the PTs of sudden cardiac death; dyspnoea; pulmonary embolism (PE); pyrexia; cardiac arrest; myocardial infarction; fatigue; acute myocardial infarction; cardio-respiratory arrest; hypertension; arteriosclerosis; myocardial ischaemia; malaise; arteriosclerosis coronary artery; headache; cardiac failure; loss of consciousness; coronary artery disease; chronic obstructive pulmonary disease; pneumonia; circulatory collapse; coronary artery occlusion; respiratory failure; cardiac death; thrombosis; emphysema; pulmonary oedema; cardiovascular disorder; pain in extremity; chest pain; acute pulmonary oedema; aneurysm ruptured; syncope; deep vein thrombosis (DVT); arthralgia, aortic dissection, subarachnoid haemorrhage, aneurysm ruptured, contusion, cardiomegaly, multiple organ dysfunction syndrome, acute coronary syndrome, cardiovascular disorder, visceral venous thrombosis, cor pulmonale acute, respiratory arrest, hypertension, haemorrhage intracranial, dyspnoea, cardiac fibrillation, cerebral infarction, gastrointestinal (GI) haemorrhage, cerebrovascular accident, cardiac failure chronic, petechiae, coronary artery occlusion, coronary artery disease, sudden unexplained death in epilepsy, and circulatory collapse.

The medical history was reported in 270 cases (67%) (vaccinees may have had >1 comorbidity) and it includes hypertension, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, tobacco user, type 2 diabetes mellitus, myocardial ischaemia, obesity, cerebrovascular accident, asthma, cardiac failure, myocardial infarction, atrial fibrillation, osteoarthritis, alcoholic, hypothyroidism, dyslipidaemia, essential hypertension, epilepsy, drug hypersensitivity and chronic kidney disease. The medical history was not reported in 132 (33%) cases.

In 67% of the cases, the cause of the deaths was due to pre-existing medical condition or risk factors. Upon review of the cases cumulatively, no new trend or pattern was observed in the cases reported with sudden death.

Table 19 Observed versus expected analyses for Sudden death

Medical Concept	Observed cases	Expected cases	Risk Window	Background rate/100,000 person years	Exposure	Rate ratio (CI 95%)	
Sudden death (RW7)	118	5251	7	58.78	466115644	0.02 (0.02 – 0.03)	Observed significantly < expected
Sudden death (RW7 + Unk TTO)	320	5251	7	58.78	466115644	0.06 (0.05 - 0.07)	Observed significantly < expected

Reference for sudden death IR is ACCESS Rates. Willame et al 2021 (A) (Meta-analysis IR from 2010-2013 - 2017-2019 – Sudden Death (Narrow)
CI Confidence Interval, Unk Unknown, TTO Time to onset

From the review of data available during the reporting period for all fatal case reports (including sudden death) and also taking into account the cumulative experience along with the O/E analysis of fatal cases there is no new safety information identified on this topic in association with VAXZEVRIA.

7 SUMMARIES OF SIGNIFICANT FINDINGS FROM CLINICAL TRIALS DURING THE REPORTING PERIOD

7.1 Completed clinical trials

No clinical trials completed during the reporting period.

7.2 Ongoing clinical trials

There were 11 (COV001, COV002, COV003, COV004, COV005, COV006, COV008, COV009, D8110C00001, D8110C00010 and D7220C00001) ongoing clinical trials sponsored by University of Oxford and AstraZeneca during the reporting period. There was no clinically important information that arose from ongoing clinical trials during the reporting period. The clinical trials described below have completed recruitment but final Clinical Study Reports (CSRs) had not yet been published by the end of the reporting period and therefore are not considered as completed.

7.2.1 Ongoing Clinical Trials – Study design and results obtained on safety and efficacy

This section provides summary from the 8 (COV001, COV002, COV003, COV004, COV005, COV006, D7220C00001 and D8110C00001) out of the 11 ongoing trials that were in scope for this report. As study read-outs were not scheduled during the reporting period, data analyses were not completed for two out of these 11 ongoing clinical trials (COV008 and

COV009). One out of these 11 clinical trials (D8111C00010) will be discontinued due to recruitment challenges.

Recruitment was completed for COV005. Studies COV001, COV002 and COV003 are ongoing since the University of Oxford continues to perform follow-up for some participants (eg, for third-dose objectives). The CSRs for these studies are final, as (by agreement with EMA) they report results for a 2-dose primary series with 12-month follow-up.

COV001 (A phase I/II study to determine efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19 in UK healthy adult volunteers): Phase I/II

COV001 was an Oxford-sponsored, single-blinded, multi-centre, randomised, controlled Phase I/II trial assessing the safety, efficacy and immunogenicity of ChAdOx1 nCoV-19 (VAXZEVRIA) in 1077 healthy adults 18 to 55 years of age in the UK. Trial participants were healthy and at increased risk for being exposed to the SARS-CoV-2 virus. Participants received either a single IM dose or a 2- dose IM regimen of the low dose (LD) (~2.5 x1010 vp) and/or the standard dose (SD) (~5x1010 vp) of VAXZEVRIA or the comparator, meningococcal vaccine (MenACWY). The participants were followed for 12 months from the last vaccination.

COV002 (A phase II/III study to determine the efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19): Phase II/III

COV002 was an Oxford-sponsored, single-blinded, multi-centre, randomised, controlled Phase II/III trial assessing the safety, efficacy and immunogenicity of ChAdOx1 nCoV-19 (VAXZEVRIA) in 10,812 participants in the UK. Trial participants were ≥ 18 years of age. years of age. In addition, a single arm group whereby up to 60 Human immunodeficiency virus (HIV) infected individuals who were stable on antiretroviral therapy were recruited and received VAXZEVRIA vaccination. Participants were enrolled by age groups of 18 to 55 years, 56 to 69 years, and ≥ 70 years. Recruitment for this study focused on health care professionals and other adults with high potential for exposure to COVID-19.

Participants received a single IM dose or a 2-dose IM regimen of the LD (~2.5x1010 vp) and/orthe SD (~5x1010 vp) of VAXZEVRIA or the comparator, MenACWY, depending on the study group. The participants were followed for 12 months from the last vaccination.

COV003 (A Randomised, Controlled, Phase III Study to Determine the Safety, Efficacy, and Immunogenicity of the Non-Replicating ChAdOx1 nCoV-19 Vaccine): Phase III

COV003 was an Oxford-sponsored, single-blinded, multi-centre, randomised, controlled Phase III trial assessing the safety, efficacy, and immunogenicity of ChAdOx1 nCoV-19 Vaccine (VAXZEVRIA) in 10416 participants in Brazil. Trial participants were ≥ 18 years of age, who were healthy or have medically stable chronic diseases and were at increased risk for being exposed to the SARS COV- 2 virus. Participants were randomised to receive either a 2-dose regimen of the SD (~5x1010 vp) of VAXZEVRIA or, MenACWY or the MenACWY as the prime dose and saline placebo as boost dose by means of an IM injection. In the main study, the participants would followed for 12 months from the last vaccination.

An optional fourth dose of ChAdOx1 nCov-19 vaccine was offered to a subgroup of 350 (+/-10%) participants who previously received three doses of ChAdOx1 nCov-19 within the trial, randomly selected, and regardless of interval after the third dose. Participants in this booster sub-study were followed for 6 months from the booster vaccination.

COV004 (A phase Ib/II single-blinded, randomised, controlled study to determine safety, immunogenicity and efficacy of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19 in adults in Kenya): Phase Ib/II

COV004 was an Oxford-sponsored, phase Ib/II trial single-blinded, randomised, controlled study of the SD (~5x1010 vp) of ChAdOx1 nCoV-19 (VAXZEVRIA) in comparison to the rabies control vaccine in Kenya. The primary endpoints of the trial was vaccine safety and immunogenicity of VAXZEVRIA vaccine as compared to the rabies control vaccine, with vaccine efficacy (VE) against COVID-19 evaluated as a secondary endpoint. Approximately 400 healthy adults ≥ 18 years of age (approximately 40 participants in Phase Ib and 360 participants in Phase II) with high potential exposure to SARS-CoV-2 were randomised. In the phase Ib part of the study the participants receive 1 IM dose of the SD (~5x1010 vp) VAXZEVRIA or rabies vaccine as control. In the phase II part of the study a 2-dose regimen of the SD (~5x1010 vp) of VAXZEVRIA or rabies vaccine will be distributed at day 84 (3 months).. The primary endpoints of the trial will be vaccine safety and immunogenicity of VAXZEVRIA vaccine as compared to the rabies control vaccine, with vaccine efficacy (VE) against COVID-19 evaluated as a secondary endpoint.

Approximately 400 healthy adults ≥ 18 years of age (approximately 40 participants in Phase Ib and 360 participants in Phase II) with high potential exposure to SARS-CoV-2 will be randomised. In the phase Ib part of the study the participants receive 1 IM dose of the SD (~5x1010 vp) VAXZEVRIA or rabies vaccine as control. In the phase II part of the study a 2-dose regimen of the SD (~5x1010 vp) of VAXZEVRIA or rabies vaccine will be distributed at day 84 (3 months). The participants will be followed for 12 months from the first vaccination.

During the reporting period, data from a manuscript in preparation for peer review publication became available. In their paper, the authors reported that a total of

400 volunteers were enrolled and randomised for vaccination with ChAdOx1 nCoV-19 (n=200) or rabies vaccine (n=200) and received at least one vaccination. As expected, headache and fatigue were the most common adverse events reported in VAXZEVRIA arm. As observed in these previous trials, ASTRAZENECA COVID-19 VACCINE was safe with most adverse events being mild or moderate and no serious adverse events related to vaccination. Vaccination generated strong humoral and cellular immune responses whose kinetics matched those in other populations.

COV005 (An adaptive phase I/II randomised placebo-controlled trial to determine safety, immunogenicity and efficacy of non-replicating ChAdOx1 SARSCoV-2 vaccine in South African adults living without HIV; and safety and immunogenicity in adults living with HIV): Phase I/II

COV005 was a double-blind, multi-centre, randomised, placebo-controlled Phase I/II trial assessing the safety, efficacy, and immunogenicity of ChAdOx1 SARSCoV-2 vaccine (VAXZEVRIA) in 2130 participants with and without HIV in South Africa (SA). Trial participants aged 18-65 years were received a 2-dose IM regimen of the SD (5-7.5 x1010 vp) of VAXZEVRIA or saline placebo. The phase I study consists of two groups (HIV-uninfected adults; n=70, and HIV-infected adults; n=100), will be evaluated for safety and immunogenicity. The phase II part of the study was targeted 1900 participants (HIV uninfected) and was evaluated for immunogenicity and efficacy. The total duration of the study was 12 months from the day of enrolment for all participants.

Efficacy, safety, and immunogenicity results from pooled analyses including data from COV001, COV002, COV003 and COV005 studies:

The evaluation of the efficacy, immunogenicity and safety of VAXZEVRIA for prevention of COVID-19 was based on the pooled data from 4 ongoing clinical studies COV001 (UK), COV002 (UK), COV003 (Brazil), and COV005 (South Africa). The primary efficacy analysis demonstrated effective protection of VAXZEVRIA against COVID-19 with a VE of 66.73% (95% confidence interval [CI]: 57.41%, 74.01%) ($p< 0.001$) from 15 days after the second dose in seronegative participants receiving two standard doses (SDSD) or 1 low dose and 1 standard dose (LDSD). The pooled analyses demonstrated that VAXZEVRIA provides complete protection against COVID-19 hospital admission ≥ 22 days after the first SD dose in the seronegative analysis set. For the SDSD regimen, it was demonstrated that vaccine protection begins from 22 days after the first dose and extends at least until 12 weeks, allowing the second dose to be given in a flexible window between 4 to 12 weeks. VAXZEVRIA elicited a strong induction of humoral immunogenicity, as measured by different serological assays following the first dose and the second dose of VAXZEVRIA regardless the presence of co-morbid conditions at baseline, country, and age at screening. In summary, pooled analyses of the 4 ongoing University of Oxford-sponsored studies

demonstrated a low incidence of SAEs in both the AZD1222 and control groups, with no difference in either frequency or type between the treatment groups The vaccine was well tolerated in pooled safety analyses. There was not a significant change in the safety profile during the reporting period.

COV006 (A single-blind, randomised, phase II study to determine safety and immunogenicity of the Coronavirus Disease (COVID-19) vaccine ChAdOx1 in UK healthy children and adolescents [aged 6-17]): Phase II

COV006 was an Oxford-sponsored, Phase II, single-blinded, active-controlled, randomized study in approximately 300 healthy children and adolescents aged 6-17 years in the UK, of 2 doses 4 or 12 weeks apart of ChAdOx1 nCoV-19 (VAXZEVRIA) or active control (licensed Meningococcal B vaccine) administered IM. The study will assess safety, tolerability and immunogenicity of a SD dose (~5x1010 vp) of ChAdOx1 nCoV-19. The total duration of the study was 12 months from the day of enrolment for all participants.

A manuscript has been in preparation for submission to peer reviewed scientific publication and a summary is provided below:

The study demonstrated that participants who were seropositive at baseline had stronger immunogenic responses 28 days after first dose than at 28 days after the second dose of the VAXZEVRIA in the seronegative participants, suggesting that, in this population, a single dose of VAXZEVRIA may be able to offer protection against SARS-COV-2 in previously infected individuals. The authors also found that immune response in younger age groups (6-11 years old) was stronger when compared to older age groups (12–17 years) after both a first and second dose of vaccine with a 112-day interval.

Overall, VAXZEVRIA was well tolerated. As expected, fatigue and headache were the most commonly reported systemic solicited adverse events. The most common local solicited adverse events were pain and tenderness for all the ASTRAZENECA COVID-19 and capsular group B meningococcal groups following both doses. The proportion of participants reporting moderate to severe local reaction up to 7 days after vaccination was higher in those receiving the meningococcal vaccine than in those receiving the ASTRAZENACA COVID-19 vaccine. Even though more solicited systemic adverse events were reported in AZD1222 arm in comparison with the meningococcal vaccine arm, they were resolved within 48 hours following vaccination (Li et al 2022).

COV008 (A Phase I study to determine safety, tolerability and immunogenicity of intranasal administration of the COVID vaccine ChAdOx1 nCOV-19 in healthy UK adults): Phase I

COV008 was an Oxford-sponsored, Phase I, open label, dose escalation study in up to 54 healthy adults in the UK. In group 1a adults aged 18-40 years were eligible, the other groups included healthy adults aged 30-40 years. The study was investigated safety, tolerability and immunogenicity of one or two doses of intranasal ChAdOx1 nCOV-19 (5x109 vp, 2x1010 vp or 5x1010 vp), with randomisation between one and two dose groups. The total duration of the study was 10 months from the day of enrolment for all participants.

This study demonstrated that, when administered via intranasal route, VAXZEVRIA had and acceptable tolerability, but weak immune response against SARS--COV-2 (Madhavan et al 2022).

COV009 (Post-approval follow-up for the COV001 and 002 trials, to determine the longterm safety and character of immunological response to the ChAdOx1 nCoV-19 coronavirus vaccine): Long-term follow-up

COV009 was an Oxford-sponsored, follow-up study of participants previously enrolled on the phase I/II (COV001) and phase II/III (COV002) trials to determine the long-term safety and character of immunological responses to the ChAdOx1 nCoV-19 vaccine. Up to 1,077 participants were eligible for enrolment for the COV001 cohort and up to 10,812 participants for the COV002 cohort. No treatment will be given during this Study. Study duration is 12 months.

D8110C00001 (A Phase III Randomised, Double-blind, Placebo-controlled Multicentre Study in Adults to Determine the Safety, Efficacy, and Immunogenicity of VAXZEVRIA, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19): Phase III

D8110C00001 was an AstraZeneca-sponsored, Phase III randomised, double-blind, placebocontrolled, multi-centre study assessing the safety, efficacy, and immunogenicity of VAXZEVRIA compared to saline placebo for the prevention of COVID-19. Participants are adults ≥ 18 years of age who are healthy or have medically stable chronic diseases and were at increased risk for SARS-CoV-2 acquisition and COVID-19. A total of 32451 participants were randomised in a 2:1 ratio to receive 2 IM doses of either the SD (~5x1010 vp) of VAXZEVRIA or saline placebo 4 weeks apart. Randomization was stratified by age (18-65 years, and ≥ 65 years), with at least 25% of participants enrolled in the older age stratum. Safety will be assessed for the duration of the study. All participants will remain on study for 2 years following administration of first dose of study intervention (Day 730).

Efficacy and safety results from study D8110C00001

No new information has become available during the reporting period.

D7220C00001 (A Phase II/III Partially Double-Blinded, Randomised, Multinational, Active-Controlled Study in Both Previously Vaccinated and Unvaccinated Adults to Determine the Safety and Immunogenicity of AZD2816, a Vaccine for the Prevention of COVID-19 Caused by Variant Strains of SARS-CoV-2): Phase II/III

This is an AstraZeneca-sponsored, multi-country Phase II/III study to evaluate the safety and immunogenicity of AZD2816 as single-dose vaccination in previously vaccinated adult participants and as a 2-dose primary vaccination in previously unvaccinated adult participants. The participant population includes adults ≥18 years of age. years of age. A total of approximately 2590 SARS-CoV-2 nucleocapsid seronegative participants that have been screened and judged to be eligible for the study will be enrolled across these 2 populations with the goal of 1300 previously vaccinated participants receiving single-dose vaccination and 1290 unvaccinated participants receiving 2-dose primary vaccination. In addition, seropositive participants were enrolled (with a cap of 10% of the seronegative population or 225 participants) to support exploratory analysis is these participants.

In both the single-dose booster treatment regimen and the 2-dose primary vaccination treatment regimen, participants will receive study intervention consisting of IM administration of either AZD1222 (5×1010 vp) or AZD2816 (5 ×1010 vp). Participants receiving a 2-dose primary vaccination will be dosed at intervals of 4 weeks (for AZD1222 and AZD2816) or 12 weeks (AZD2816 only). All study participants will be followed for safety for 180 days after administration of their last vaccination dose.

AZD2816-D7220C00001.

Summary of immunogenicity results

The non-inferiority of AZD2816 was demonstrated for the co-primary and first key secondary endpoints. The Geometric Mean Titer (GMT) ratio for the comparison of the AZD2816 treatment group (4-week interval) against the Beta variant versus the VAXZEVRIA treatment group against the Wuhan-Hu-1 strain was 1.19 (95% CI 1.08, 1.32) and the seroresponse difference was 1.7 (95% CI -3.1, 6.5). The GMT ratio for the comparison of the AZD2816 treatment group (4-week interval) against the Beta variant versus the VAXZEVRIA treatment group against the Beta variant was 3.21 (95% CI 3.06, 3.36). Moreover , in this study the responses following booster doses of VAXZEVRIA and AZD2816 to the Delta and Omicron BA.1 variants were generally consistent with those observed for the Wuhan-Hu-1 strain and Beta variant.

The safety (through Day 29) and reactogenicity (through Day 8) of booster doses of VAXZEVRIA or AZD2816 in participants previously vaccinated with either VAXZEVRIA or a messenger ribonucleic acid (mRNA) vaccine, including for those in the Seronegative Safety Analysis Set, was consistent with the known safety profile of VAXZEVRIA

administered as a 2-dose primary series. No emergent safety issues were identified. There were no clinically meaningful differences between the safety profiles of booster doses of VAXZEVRIA and AZD2816. Analyses of data through to data cut-off, up to a maximum of 107 days after booster dose, did not identify any emergent safety issues. Across both parts of the study there was one death due to acute myocardial infarction, assessed as unrelated to study intervention by the investigator and another death after Day 29 due to pancreatic adenocarcinoma (VAXZEVRIA cohort boosted with AZD2816).

D8111C00010 (A Phase IV Open-Label, Non-Randomized, Multi-Cohort, Multi-centre Study in Previously Unvaccinated Immunocompromised Adults to Determine the Immunogenicity and Safety of AZD1222 Vaccine for the Prevention of COVID-19): Phase IV

This is an AstraZeneca-sponsored, Phase IV open-label, non-randomized, multi-cohort, multicentre study to evaluate the immunogenicity and safety of AZD1222 for the prevention of COVID-19 in previously unvaccinated immunocompromised adults ≥18 years. Approximately 360 SARS-CoV-2 spike and nucleocapsid seronegative participants will be enrolled. Immunocompromised participants will receive primary vaccination with 3 IM doses of AZD1222 separated by 4 weeks and will continue to be followed to the end of the study. Immunocompetent participants will receive a third dose booster 6 months after dose 1 and will continue to be followed to the end of the study. The total duration of the study is 12 months. The first participant was enrolled in January 2022 and as of 28 June 2022 there have been 34 participants enrolled in the study.

There has been extreme difficulty in recruiting unvaccinated immunocompromised participants into the study given the global increase in vaccination rates particularly for the immunocompromised population (only 9 participants recruited out of a planned total of 300 ie, 3.0% of the target from study start to in February 2022 to September 2022).In addition, there has been increased infection rates due to the Omicron variant wave, reducing the number of COVID-19 naive patients in the target population. This has resulted in an almost complete lack of recruitment, with no probability of improvement in the situation Given this and the projection of zero recruitment rate by October 2022.

7.2.2 Overall Safety, Efficacy and immunogenicity

The safety, efficacy and immunogenicity of a two-dose regimen of VAXZEVRIA has been currently investigated in 11 ongoing clinical trials. The initial VE against symptomatic disease of 66.7% (95% CI: 57.4%, 74.0%) ($p < 0.001$) demonstrated in a pooled analyses of four trials (COV001, COV002, COV003, COV005) was confirmed in a large study conducted mainly in the United States of America (USA) (VE=74%; 95CI: 65.34, 80.47). The vaccine has also shown to be highly immunogenic after a single dose, with increase in seroconversion after a second dose. Moreover, adults (including those over the age of 65 years) with

preexisting comorbidity showed similar VE and immune responses when compared to the general population. The safety of VAXZEVRIA has been evaluated in ongoing clinical trials.

Final analyses for AZD2816 programme were conducted at the end of year 2022. The final results will be included in next PBRER when the CSRs will have been completed. There were no safety concerns identified and the lack of efficacy against omicron following primary immunization in a naïve population while maintenance of immune response in a previously vaccinated population was confirmed as already described in a previous PBRER.

7.3 Long-term follow-up

Participants completing VAXZEVRIA clinical trials are not subject to longer-term follow-up beyond the 12-24 months as mentioned in the study protocols.

7.4 Other therapeutic use of medicinal product

There were no other AstraZeneca programmes that follow a specific protocol with solicited reporting for VAXZEVRIA.

7.5 New safety data related to fixed-combination therapies

This section is not applicable as VAXZEVRIA is not approved or under development as part of a fixed-combination product or a multi-drug regimen.

8 FINDINGS FROM NON-INTERVENTIONAL STUDIES

No relevant safety information or information with potential impact on the benefit or risk evaluations arose from AstraZeneca sponsored non-interventional studies of VAXZEVRIA during the reporting period.

A listing of AstraZeneca sponsored non-interventional Post-Authorisation Safety Studies (PASS) completed or ongoing during the reporting period is provided in Appendix 4.

9 INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

9.1 Other clinical trials

R-pharm is the sponsor of three studies investigating the safety and immunogenicity of a heterologous prime-boost immunization with AZD1222 and another adenoviral vector, the recombinant rAd26 (CV03872097, formerly known as D8111C00003, CV03872091 and CV03872092), which were ongoing during the reporting period.

Another study was sponsored by the Serum Institute of India (Indian Council Of Medical Research (ICMR)/SII-COVISHIELD). and was completed during the reporting period

Results from the COVISHIELD study (Phase II/III) show that COVISHIELD is highly immunogenic and induces both humoral and cell-mediated immune responses in adults.

No information relevant to the benefit-risk assessment of AZD1222 or AZD2816 have been identified from studies known to be performed by other sponsors (Fiocruz, R-Pharm and Serum Institute of India) during the reporting period.

9.2 Vaccination errors

Case reports of medication errors where no other AEs have been reported do not fulfil the criteria for inclusion in the tabulation in Appendix 2 but are included in the searches below.

The search strategy for vaccination errors includes following PTs:

- PTs in the SMQ Medication errors and
- PT's: Device failure; Device deployment issue; Prescription drug used without a prescription; Device delivery system issue; Product advertising issue; Counterfeit product administered; Device mechanical issue; Device safety feature issue; Device environmental compatibility issue; Device data issue; Device temperature issue; Device user interface issue; Device signal transmission issue; Device wireless communication issue; Unevaluable device issue; Prosthetic cardiac valve malfunction; Device calibration failure; Product sterility issue.

Interval Period (29 June 2022 – 28 December 2022)

A total of 2900 case reports (2658 initial and 242 follow up), including 2963 vaccination error AEs, have been identified during the reporting period, which represents 13.92% cases of the cumulative (20820 case reports). Of those 2900 case reports, 396 were reported as serious (191 case reports were medically confirmed and 205 were consumer reports). In 2280 (78.62%) of the 2900 cases reports no other AEs were reported in connection with the vaccination error. AEs were reported in the remaining 620 (21.37 %) case reports.

The frequently reported (>50) vaccination errors were Expired product administered (938), Interchange of vaccine products (681), Wrong product administered (525), Product administered to patient of inappropriate age (498), Inappropriate schedule of product administration (360), Incorrect dose administered (244), Poor quality product administered (104), Medication error (64) and Accidental exposure to product (53). Out of the 620 cases with other AEs, 343 (55.32 %) cases were serious and 277 (44.67%) were non-serious. Of the 620 cases, 220 (35.48%) were medically confirmed and 400 (64.51%) were non-medically confirmed. Out of 343 serious cases, the reported seriousness criteria were fatal/death in 19 case reports, hospitalisations in 105 cases and the remaining were medically important.

A review of all the cases with seriousness fatal/death received during the reporting period suggested fatal outcome in 22 cases (19 cases with AE and 3 cases without AE) in association with vaccination error.

Out of 620 case reports there were 4218 events (1721 serious and 2505 non-serious). Most of the AE's were reported from the SOC of General disorders and administration site conditions (Table 20).

Table 20 Distribution of Serious Adverse Events Associated with Vaccination Errors with VAXZEVRIA by MedDRA System Organ Class (SOC) from 29 December 2021 to 28 June 2022

MedDRA (SOC)	Events Count	Serious	Non-Serious	Percentage
General disorders and administration site conditions	745	276	473	17.66
Injury, poisoning and procedural complications	584	217	367	13.85
Nervous system disorders	489	218	272	11.59
Surgical and medical procedures	435	74	361	10.31
Musculoskeletal and connective tissue disorders	328	126	202	7.78
Infections and infestations	239	125	114	5.67
Investigations	179	85	94	4.24
Respiratory, thoracic and mediastinal disorders	178	95	83	4.22
Gastrointestinal disorders	163	67	97	3.86
Skin and subcutaneous tissue disorders	160	59	101	3.79
Psychiatric disorders	150	53	97	3.56
Cardiac disorders	101	57	44	2.39
Vascular disorders	96	50	46	2.28
Eye disorders	65	31	34	1.54
Immune system disorders	53	27	26	1.26
Blood and lymphatic system disorders	50	38	14	1.19
Ear and labyrinth disorders	43	18	25	1.02
Metabolism and nutrition disorders	35	19	16	0.83
Renal and urinary disorders	23	18	5	0.55
Pregnancy, puerperium and perinatal conditions	22	14	8	0.52

Table 20 Distribution of Serious Adverse Events Associated with Vaccination Errors with VAXZEVRIA by MedDRA System Organ Class (SOC) from 29 December 2021 to 28 June 2022

MedDRA (SOC)	Events Count	Serious	Non-Serious	Percentage
Reproductive system and breast disorders	20	10	10	0.47
Hepatobiliary disorders	18	13	5	0.43
Social circumstances	14	6	8	0.33
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11	10	1	0.26
Endocrine disorders	10	9	1	0.24
Product issues	4	3	1	0.09
Congenital, familial and genetic disorders	3	3		0.07
Total	**4218**	**1721**	**2505**	**100**

MedDRA Medical Dictionary for Regulatory Activities, SOC System Organ Class

The reported vaccination error AEs are presented in Table 20. The reported vaccination error AEs have been grouped according to specific vaccination error groups suggested in the literature (Hibbs et al 2015), see Table 22.

Most commonly reported AEs (≥50) in the 620 vaccination error cases were COVID-19 (107), Fatigue (95), Headache (89), Pyrexia (84), Pain in extremity (81), Pain (53).

During the reporting period there was one case each reported with Cutaneous (CU), Intradermal (ID), Subcutaneous (SQ) routes of administration that were associated with AE and one case was reported with Intraperitoneal (IP) route without AE. There were 2 cases each reported with Transmammary (TM) route without AE. Seven cases were reported with Transplacental (TPL) route that were associated with AE. There were 8 cases reported with Intravenous (not otherwise specified) that were associated with AE. 2877 cases were reported with intramuscular (600 with AE and 2277 without AE). Additionally, there were 2 cases where the route of administration was unspecified of these and were associated with AE.

Review of events associated with these inappropriate route of administration events did not identify any safety issues. These cases do not indicate any trends of systemic substantial errors or a need for additional risk mitigation activity.

Cumulative Review (29 December 2020 – 28 December 2022)

A total of 20820 case reports, including 22292 vaccination error AEs, have been identified during the cumulative period. Of those 20820 case reports, 1950 were considered serious (592

case reports were medically confirmed and 1358 were consumer reports). In 15159 (72.8 %) of the 20820 cases reports no other AEs were reported in connection with the vaccination error. Adverse events were reported in the remaining 5661 (27.2 %) case reports.

The frequently reported (>50) vaccination errors were Interchange of vaccine products (4359), Wrong product administered (3791), Expired product administered (3673), Inappropriate schedule of product administration (2876), Product administered to patient of inappropriate age (2020), Incorrect dose administered (1777), Medication error (1520), Incorrect route of product administration (819), Product dose omission issue (543), Incomplete course of vaccination (536), Product storage error (487), Product temperature excursion issue (402), Product administration error (382), Vaccination error (355), Intercepted medication error (316), Accidental exposure to product (302), Underdose (298), Circumstance or information capable of leading to medication error (267), Intercepted product storage error (228), Product administered at inappropriate site (203), Overdose (186), Poor quality product administered (153), Incorrect product formulation administered (148), Contraindication to vaccination (126), Product use issue (99), Extra dose administered (88) and Wrong technique in product usage process (76).

Out of the 5661 cases with adverse events, 1822 (32.2%) cases were serious and 3839 (67.8%) were non-serious. Of the 5661 cases, 1763 (31.14 %) were medically confirmed and 3898 (68.9%) were non-medically confirmed. Out of 1822 cases, the seriousness criteria were fatal/death in 75 case reports, hospitalisations in 576 cases and the remaining were medically important.

Out of 5661 case reports there were 30708 events (7423 serious and 23345 non-serious). Most of the AE's were reported from the SOC of General disorders and administration site conditions (Table 21).

Table 21 Distribution of Serious Adverse Events Associated with Vaccination Errors with COVID-19 VACCINE ASTRAZENECA by MedDRA System Organ Class (SOC) through 28 June 2022

MedDRA (SOC)	Events Count	Serious	Non-Serious	Percentage
General disorders and administration site conditions	7279	1351	5946	23.70
Injury, poisoning and procedural complications	6013	815	5202	19.58
Nervous system disorders	3836	1330	2520	12.49
Musculoskeletal and connective tissue disorders	2594	613	1990	8.45
Surgical and medical procedures	1925	171	1754	6.27
Gastrointestinal disorders	1347	367	982	4.39

Table 21 Distribution of Serious Adverse Events Associated with Vaccination Errors with COVID-19 VACCINE ASTRAZENECA by MedDRA System Organ Class (SOC) through 28 June 2022

MedDRA (SOC)	Events Count	Serious	Non-Serious	Percentage
Investigations	1342	244	1099	4.37
Respiratory, thoracic and mediastinal disorders	972	367	606	3.17
Skin and subcutaneous tissue disorders	909	257	656	2.96
Infections and infestations	872	327	546	2.84
Psychiatric disorders	681	165	517	2.22
Vascular disorders	526	289	238	1.71
Eye disorders	399	153	246	1.30
Cardiac disorders	384	217	167	1.25
Ear and labyrinth disorders	249	91	159	0.81
Reproductive system and breast disorders	244	90	155	0.79
Blood and lymphatic system disorders	216	131	87	0.70
Immune system disorders	214	89	125	0.70
Metabolism and nutrition disorders	190	65	125	0.62
Renal and urinary disorders	127	75	52	0.41
Social circumstances	121	46	75	0.39
Pregnancy, puerperium and perinatal conditions	89	74	15	0.29
Product issues	59	6	53	0.19
Hepatobiliary disorders	45	30	15	0.15
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	45	36	9	0.15
Endocrine disorders	21	15	6	0.07
Congenital, familial and genetic disorders	9	9	0	0.03
Total	**30708**	**7423**	**23345**	**100**

MedDRA Medical Dictionary for Regulatory Activities, SOC System Organ Class

The reported vaccination error AEs are presented in Table 21. The reported vaccination error AEs have been grouped according to specific vaccination error groups suggested in the literature (Hibbs et al 2015), see Table 22.

Most frequently reported AEs ≥ 50 within the 5661 case reports of vaccination error were Pyrexia (1422), Headache (1415), Fatigue (762), Pain (754), Chills (715), Pain in extremity (697), Myalgia (540), Arthralgia (461), Asthenia (446), Malaise (445), Dizziness (394), Nausea (363), COVID-19 (320), Injection site pain (276), Paraesthesia (237), Dyspnoea (227), Vomiting (205), Diarrhoea (202), Hypoaesthesia (196), Feeling abnormal (182), Cough (137), Application site pain (131), Chest pain (131), Back pain (130), Tremor (130), Rash (127), Pruritus (125), Vaccination site pain (119), Hyperhidrosis (111), Influenza like illness (104), Insomnia (103), Abdominal pain (102), Peripheral swelling (102), Thrombosis (102), Limb discomfort (101), Decreased appetite (98), Erythema (97), Hypersensitivity (95), Illness (94), Somnolence (94), Feeling cold (89), Muscular weakness (89), Tinnitus (88), Contusion (86), Nasopharyngitis (84), Gait disturbance (81), Oropharyngeal pain (79), Syncope (79), Muscle spasms (78), Maternal exposure during pregnancy (75), Heart rate increased (74), Vision blurred (73), Anxiety (72), Body temperature increased (70), Hypertension (69), Abdominal pain upper (68), Tachycardia (68), Eye pain (67), Migraine (67), Palpitations (66), Urticaria (66), Neck pain (65), Chest discomfort (62), Discomfort (61), Influenza (61), Feeling hot (60), Injection site erythema (60), Burning sensation (58), Lymphadenopathy (58), Blood pressure increased (57), Fall (56), Rhinorrhoea (56), Therapy partial responder (55), Inflammation (54), Seizure (52), Vertigo (52), Condition aggravated (50).

During the cumulative period, there was one case each reported with Gastroenteral (GE), Infiltration (IF), Intracardiac (IC), Intradiscal (intraspinal) (IS), Intravesical (IB), Respiratory (inhalation) (IH), Subconjunctival (SCON) routes that were associated with AE and Intraperitoneal (IP) was reported without AE. 2 cases each were reported with Auricular (otic) (EAR), Intra-articular (IJ), Intravenous bolus (PU), Nasal (IN), Other (OTHER) routes of administration which were associated with AE's and 2 cases were reported with Intrasynovial (ISYN) route (1 with AE and 1 without AE). There were 3 cases reported Intrameningeal (IMEN) (1 with AE and 2 without AE). 4 cases with Subdermal (SD) which were associated with AE. 5 cases were reported with Transmammary (TM) route (3 with AE and 2 without AE) and Intraocular (IOC) route (1 with AE and 4 without AE). 7 cases were reported with Parenteral (PAR) route which were associated with AE. 11 cases were reported with Oral (PO) route which were associated with AE. 12 cases were reported with Intracavernous (ICS) route and 13 cases were reported with Cutaneous (CU) route which were associated AE. 17 cases with Transplacental (TPL) route of administration that were associated with AE. 20 cases with Intradermal (ID) route of administration that were associated with AE. 131 cases with Intravenous (not otherwise specified) (IV) route (128 with AE and 3 without AE) and 230 cases with subcutaneous (SQ) route (222 with AE and 8 without AE). There were 20280 cases reported with intramuscular route of administration (5185 with AE and 15095 without AE). Additionally, there were 37 cases where the route of administration was unspecified of these, 15 were associated with AE and 22 without AE.

Table 22 Summary tabulation of Vaccination Error Adverse Events (interval and cumulative)

Vaccination error group	Adverse Event (MedDRA PT)	With AE				Without AE				Total Cumulative
		Interval		Cumulative		Interval		Cumulative		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
Accidental	Accidental exposure to product	0	5	21	25	0	48	7	249	302
	Accidental exposure to product packaging	0	0	0	1	0	0	0	0	1
	Accidental underdose	0	0	1	4	0	0	0	16	21
	Exposure to contaminated device	0	0	1	0	0	0	0	0	1
	Intercepted accidental exposure to product by child	0	0	0	0	0	0	0	1	1
Administration errors	Counterfeit product administered	0	0	0	0	0	0	0	1	1
	Drug administered in wrong device	0	0	0	0	0	0	1	1	2
	Drug monitoring procedure not performed	0	0	0	1	0	0	0	0	1
	Drug titration error	2	0	2	1	0	0	0	0	3
	Duplicate therapy error	0	0	0	0	0	0	0	3	3
	Inadequate aseptic technique in use of product	0	0	1	1	0	0	0	0	2
	Incorrect product administration duration	1	0	1	6	0	0	0	13	20
	Incorrect product formulation administered	0	0	0	1	4	17	7	140	148
	Incorrect route of product administration	6	15	57	669	0	5	0	93	819

Table 22 Summary tabulation of Vaccination Error Adverse Events (interval and cumulative)

Vaccination error group	Adverse Event (MedDRA PT)	With AE				Without AE				Total Cumulative
		Interval		Cumulative		Interval		Cumulative		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
	Lack of vaccination site rotation	0	0	1	0	0	0	0	0	1
	Product administered at inappropriate site	1	3	49	81	0	33	3	70	203
	Product administered to patient of inappropriate age	6	17	13	153	1	474	9	1845	2020
	Product administration error	1	13	19	214	0	0	1	148	382
	Product administration interrupted	0	0	0	2	0	0	0	0	2
	Product monitoring error	0	0	1	3	0	0	0	2	6
	Wrong route	0	0	0	2	0	0	0	0	2
	Wrong technique in device usage process	0	0	0	2	0	0	0	0	2
	Wrong technique in product usage process	1	1	10	27	0	19	1	38	76
Contraindication	Contraindicated product administered	0	0	3	4	0	0	0	2	9
	Contraindicated product prescribed	0	0	8	3	0	0	0	0	11
	Contraindication to medical treatment	0	0	0	1	0	0	0	0	1
	Contraindication to vaccination	0	2	6	16	0	6	3	101	126

Table 22 Summary tabulation of Vaccination Error Adverse Events (interval and cumulative)

Vaccination error group	Adverse Event (MedDRA PT)	With AE				Without AE				Total Cumulative
		Interval		Cumulative		Interval		Cumulative		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
	Documented hypersensitivity to administered product	0	0	0	0	0	0	0	2	2
	Labelled drug-drug interaction issue	2	0	2	1	0	0	0	0	3
	Labelled drug-drug interaction medication error	1	0	2	0	0	0	0	0	2
Equipment	Device connection issue	0	0	0	0	0	0	0	3	3
	Device delivery system issue	0	0	0	1	0	0	0	0	1
	Device maintenance issue	0	0	0	0	0	0	0	1	1
	Device use confusion	0	0	0	1	0	0	0	0	1
	Device use error	0	0	0	1	0	0	0	1	2
	Device use issue	0	0	1	0	0	0	0	0	1
	Injury associated with device	1	0	9	7	0	0	1	3	20
	Medical device monitoring error	0	0	0	0	0	0	0	1	1
	Needle issue	1	0	2	9	0	0	1	9	21
	Syringe issue	0	0	0	4	0	0	0	9	13
	Wrong device used	0	0	0	2	0	0	0	0	2
General error	Medication error	49	13	141	514	0	2	3	862	1520
	Occupational exposure to product	0	0	3	4	0	0	0	8	15
	Product use issue	8	1	17	63	0	0	0	19	99

Table 22 Summary tabulation of Vaccination Error Adverse Events (interval and cumulative)

Vaccination error group	Adverse Event (MedDRA PT)	With AE				Without AE				Total Cumulative
		Interval		Cumulative		Interval		Cumulative		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
	Vaccination error	0	4	11	74	0	4	0	270	355
Inappropriate schedule	Inappropriate schedule of product administration	49	51	70	970	0	260	3	1833	2876
	Wrong schedule	0	0	0	5	0	0	0	19	24
Incorrect dose	Accidental overdose	1	0	4	13	2	0	3	17	37
	Booster dose missed	0	0	0	9	0	0	0	23	32
	Dose calculation error	0	0	2	8	0	0	0	2	12
	Extra dose administered	0	1	3	18	0	0	0	67	88
	Incomplete course of vaccination	0	8	11	221	0	6	2	302	536
	Incorrect dosage administered	0	0	0	11	0	0	0	30	41
	Incorrect dose administered	2	3	18	204	40	199	47	1508	1777
	Incorrect dose administered by device	0	0	0	1	0	0	0	1	2
	Incorrect dose administered by product	0	0	0	1	0	1	0	1	2
	Incorrect product dosage form administered	0	0	1	1	0	0	0	0	2
	Overdose	0	0	54	97	0	0	0	35	186
	Prescribed overdose	0	0	0	1	0	0	0	0	1
	Prescribed underdose	2	0	3	4	0	0	0	0	7
	Product dose omission in error	0	1	0	18	0	0	0	11	29

Table 22 Summary tabulation of Vaccination Error Adverse Events (interval and cumulative)

Vaccination error group	Adverse Event (MedDRA PT)	With AE				Without AE				Total Cumulative
		Interval		Cumulative		Interval		Cumulative		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
	Product dose omission issue	24	11	30	277	0	4	0	236	543
	Underdose	1	2	2	26	0	10	4	266	298
Off-Label	Product use in unapproved indication	1	0	3	6	0	0	0	0	9
	Drug ineffective for unapproved indication	1	0	1	0	0	0	0	0	1
Potential errors	Circumstance or information capable of leading to device use error	0	0	0	0	0	0	0	2	2
	Circumstance or information capable of leading to medication error	0	2	4	91	0	0	1	171	267
	Intercepted medication error	0	0	1	15	0	0	0	300	316
	Intercepted product administration error	0	0	1	4	0	0	0	10	15
	Intercepted product dispensing error	0	0	0	0	0	0	0	1	1
	Intercepted product preparation error	0	0	0	0	0	0	0	6	6
	Intercepted product storage error	0	0	0	1	0	0	0	227	228
Preparation error	Prescription drug used without a prescription	0	0	3	0	0	0	0	0	3
	Product preparation error	0	0	0	4	0	0	0	23	27
	Product preparation issue	3	0	3	7	0	0	0	14	24

Table 22 Summary tabulation of Vaccination Error Adverse Events (interval and cumulative)

Vaccination error group	Adverse Event (MedDRA PT)	With AE				Without AE				Total Cumulative
		Interval		Cumulative		Interval		Cumulative		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
	Product reconstitution quality issue	0	0	0	4	0	0	0	2	6
Prescribing error	Transcription medication error	0	0	0	4	0	0	0	2	6
Product labelling/packaging	Product barcode issue	0	0	1	0	0	0	0	0	1
	Product confusion	0	0	0	1	0	0	0	2	3
	Product identification number issue	0	0	0	0	0	0	0	2	2
	Product label confusion	0	0	0	1	0	0	0	3	4
	Product label issue	0	0	0	2	0	0	0	1	3
	Product lot number issue	0	0	0	0	0	0	0	6	6
	Product name confusion	0	0	1	1	0	0	0	2	4
	Product packaging confusion	0	0	0	3	0	0	0	0	3
	Product packaging issue	0	0	0	0	0	0	0	1	1
Product quality	Poor quality product administered	0	0	4	2	0	104	0	147	153
	Product use complaint	0	1	0	1	0	0	0	2	3
Storage/dispensing	Device dispensing error	0	0	0	1	0	0	0	2	3
	Expired product administered	0	6	23	178	0	932	11	3461	3673
	Product communication issue	0	0	0	3	0	0	0	7	10
	Product dispensing error	0	0	12	8	0	0	0	25	45
	Product dispensing issue	0	0	0	0	0	0	0	1	1

Table 22 Summary tabulation of Vaccination Error Adverse Events (interval and cumulative)

Vaccination error group	Adverse Event (MedDRA PT)	With AE				Without AE				Total Cumulative
		Interval		Cumulative		Interval		Cumulative		
		Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	Serious	Non-Serious	
	Product prescribing error	1	0	2	6	0	0	0	16	24
	Product prescribing issue	0	0	0	1	0	0	0	2	3
	Product selection error	0	0	0	0	0	0	1	2	3
	Product storage error	6	0	6	41	0	0	0	440	487
	Product substitution error	0	0	0	0	0	0	0	1	1
	Product temperature excursion issue	4	0	4	7	0	0	0	391	402
Wrong vaccine	Interchange of vaccine products	89	513	174	2360	2	77	8	1817	4359
	Unintentional use for unapproved indication	0	0	0	0	0	0	0	1	1
	Wrong dosage form	0	0	0	1	0	0	0	0	1
	Wrong dose	0	0	0	2	0	0	0	1	3
	Wrong drug	0	0	0	0	0	0	0	5	5
	Wrong patient received product	0	0	0	1	0	0	0	0	1
	Wrong product administered	1	6	7	124	6	512	25	3635	3791
Other	Exposure via direct contact	0	0	0	2	0	0	0	0	2
	Exposure via partner	0	0	1	0	0	0	0	0	1
	Exposure via unknown route	0	0	0	1	0	0	0	0	1
Grand Total		265	679	831	6666	55	2713	142	18993	26632

Seriousness was evaluated at the event level, which may differ from the seriousness assigned to the report level.

Cases with no reported AEs are also included.

In the above table 85 events were not included as these were considered invalid during interval period.

Case reports may include more than one vaccination error AE.

AE Adverse Event; MedDRA Medical Dictionary for Regulatory Activities; PT Preferred Term

Most frequently (>1000) reported vaccination error PTs were Interchange of vaccine products, Wrong product administered, Expired product administered, Inappropriate schedule of product administration, Product administered to patient of inappropriate age, Incorrect dose administered and Medication error; most of the reports (72%) were not associated with other AEs apart from these medication errors. The above medication errors related to interchange, wrong product administered is related to interchange of vaccine (heterologous administration) for Dose1, Dose 2 and Dose 3 in many countries; and inappropriate schedule may be related to vaccine doses given at spacing intervals not aligned with the product information. Most of the reports were received from Brazil (56%), UK (10%), France (5%) and Germany (4%).

A review of the PT Interchange of vaccine products found that these medications errors were received mainly from following countries Brazil (42%), France (16%), Germany (10%), United Kingdom (7%) and Mexico (3%).

The vaccines most often interchanged with VAXZEVRIA included mRNA-PFIZER, CoronaVac, mRNA-Moderna, Janssen, mRNA-unspecified, Sputnik and Covaxin Vaccine.

CoronaVac, mRNA PFIZER, Janssen, and mRNA Moderna. vaccines were most often used in reports of the PT Wrong product administered. However, there was limited information available in narrative to interpret whether the vaccinees received wrong product/vaccine voluntarily or by mistake.

9.2.1 Fatal Cases Associated with Vaccination errors

A review of interval vaccination error case reports with case level outcome of death/fatal, the Interchange of vaccine products (n=12) and off label use (n=11) were most frequently reported vaccination error events in these reports.

Most frequently reported AEs (≥2) in these reports were: COVID-19 (3), Death (3), Sudden death (3), Constipation (2), COVID-19 pneumonia (2) and Pulmonary embolism (2).

Reported causes of death in these cases were Death (3), Sudden death (3), COVID-19 pneumonia (2), Pulmonary embolism (2), Adverse drug reaction (1), Asthma (1), Cerebral haemorrhage (1), Cerebral venous thrombosis (CVT) (1), Cerebrovascular accident (1), COVID-19 (1), Cystic fibrosis (1), Deep vein thrombosis (1), End stage renal disease (1), Lung transplant (1), Lymphoma (1), Malignant neoplasm progression (1), Pneumonia (1), Product dose omission issue (1), Pulmonary thrombosis (1), Renal disorder (1), Respiratory failure (1), Somnolence (1), Thrombocytopenia (TCP) (1) and Thrombosis with thrombocytopenia syndrome (TTS) (1).

Review of these fatal cases did not identify safety issues in relation to type of vaccination errors.

Summary and Conclusion

Most frequently reported vaccination errors along with other AEs included Inappropriate schedule of product administration, Incorrect route of product administration, Product administered to patient of inappropriate age, Wrong product administered, Interchange of vaccine products, Medication error, Product dose omission issue , Incorrect dose administered, Incomplete course of vaccination , and Expired product administered . Most of the AEs reported for these vaccination errors were related to the reactogenicity events such as Pyrexia, Headache, Chills, Fatigue, Pain, Pain in extremity, Myalgia, Arthralgia, and Malaise. There was no clustering of AEs or AESI's with any of the vaccination error types.

Review of these fatal cases did not identify safety issues in relation to type of vaccination errors.

A review of all the vaccination error AE reports received during interval and cumulative period did not demonstrate any medication error-emergent safety pattern associated with VAXZEVRIA. No new relevant patterns of vaccination errors or new safety concerns were identified during the reporting period.

Reports related to VAXZEVRIA vaccination errors will continue to be monitored by AstraZeneca through standard surveillance activities.

10 NON-CLINICAL DATA

No AstraZeneca-sponsored non-clinical in vivo and in vitro studies of AZD1222/AZD2816 were ongoing or completed during the reporting period.

11 LITERATURE

AstraZeneca has reviewed the published nonclinical scientific literature relevant to VAXZEVRIA. No relevant new nonclinical safety information or information with potential impact on the benefit or risk evaluations, during the reporting period, were identified following review of literature.

AstraZeneca conducts comprehensive monitoring of peer-reviewed published scientific literature and unpublished manuscripts routinely on an ongoing basis. The search strategy includes VAXZEVRIA and other COVID-19 vaccines in order to identify potential class related findings.

Relevant literature articles containing new and significant safety findings relevant to VAXZEVRIA published during the review period were retrieved. Articles of interest related to event reviews completed as part of Health Authority requests, Important identified and Potential risks or Missing information have been included within the review of those safety concerns throughout section 15.2 and section 16. Other articles containing new and significant safety findings are summarized below.

Graves' disease following vaccination against SARS-CoV-2 (Triantafyllidis et al 2022**)**

Triantafyllidis et al 2022 conducted a systematic cumulative literature review of Graves' disease following COVID-19 vaccination with the objective to examine the available literature and provide an overview of the reported cases. The authors identified 21 eligible articles which included 57 patients with Graves' disease following COVID-19 vaccination. Of the 57 patients, 9 received VAXZEVRIA. Of the 9 patients with VAXZEVRIA, 6 were females and 3 were males, age ranged between 30 and 70 years, 7 developed new onset Graves' disease, 1 exacerbation and in 1 case previous history of Graves' disease was not reported. The latency in the 9 patients ranged from 1 to 14 days. Treatment was reported in 7 out of the 9 patients, outcome was reported for 3 patients, in 1 patient improvement was achieved after 3 months and in 1 after 30 days. The authors discussed various potential mechanisms for such association, although none was supported with confirmatory data. The authors concluded that Graves' disease is possibly a condition, physicians and other healthcare professionals (HCP) may expect to see in patients receiving COVID-19 vaccines.

AstraZeneca comment

The publication identified fewer number of cases of Graves' disease following COVID-19 vaccination, particularly involving VAXZEVRIA. Furthermore, the authors indicated low quality of case reports and could not exclude selection bias, and hence causality in the reported cases could not be inferred. Overall, this article does not provide sufficient evidence of an increased risk of Graves' disease in vaccinees who received VAXZEVRIA.

Cutaneous symptoms of connective tissue disease after COVID-19 vaccination (Nguyen et al 2022 [A]**)**

Nguyen et al 2022 [A] conducted a systematic review of literature on cutaneous symptoms of connective tissue diseases (including lupus, systemic sclerosis, scleroderma, sclerotic skin, dermatomyositis (DM), morphea) after COVID-19 vaccination. Thirty articles were selected, including 22 single case reports, 3 case series, 2 cohort studies, 2 cross-sectional studies, and 1 clinical trial, encompassing 2020 patients, of whom 93 patients developed post-vaccine cutaneous symptoms of connective tissue diseases, such as skin thickening, and ulceration, erythematous macules, and papules, Raynaud's phenomenon. The majority of affected patients had pre-existing autoimmune disease, 72/93 (77.4%); new diagnosis of connective tissue disease after COVID-19 vaccination was established in 21/93 (22.6%) patients. The most common vaccines administered were Pfizer - 60.5%, Sinovac - 19.6% and Moderna - 10.8%; AstraZeneca COVID-19 vaccine was administered in 9.1% of patients. The authors concluded that only a small percentage of patients developed autoimmunity after COVID-19 vaccination, and suggested that autoimmunity may occur in genetically predisposed patients. The authors also suggested that the mechanisms could involve development of autoantibodies due to cross-reactivity of SARS-CoV-2 proteins and tissue antigens, or that mRNA-containing lipid nanoparticles (LNPs) may trigger autoimmunity by upregulating production of pro-inflammatory cytokines and chemokines, no new data was presented to substantiate the mechanisms.

AstraZeneca comment

The referenced evidence is based on diverse sources, mostly involving mRNA vaccines, with AstraZeneca COVID-19 vaccine amounting to less than 10% of included patients, it was not reported how many of them developed cutaneous symptoms of connective tissue diseases after the vaccination. No new mechanistic data was presented, while one of the suggested mechanisms is not relevant for AstraZeneca COVID-19 vaccine.

12 OTHER PERIODIC REPORTS

There have been no significant findings from other periodic reports provided by other parties during the reporting period.

13 LACK OF EFFICACY IN CONTROLLED CLINICAL TRIALS

Immune response against Omicron variant

The results of assessments on immunogenicity of AZD1222 vaccine serum (VAXZEVRIA, formerly COVID-19 Vaccine AstraZeneca) and convalescent serum from SARS-CoV-2-infected donors against the Alpha, Beta, and Gamma SARS-CoV-2 variants of concern as well as select variants of interest in an unvalidated pseudovirus neutralisation assay (EMEA/H/C/0005675/REC/048-059). Additional data have been provided on homologous and heterologous booster doses of AZD1222 against the Omicron variant (MS1222-0007).

In order to further characterise the neutralising antibody response induced by a primary series vaccination of AZD1222 and as part of an ongoing commitment to evaluate immunogenicity of AZD1222 against emerging variants, in the 2nd biannual virology study report (MS1222-0008; Experimental work completed: 31 October 2022), 21 pools of serum from 210 AZD1222 vaccinees have been assessed in validated pseudovirus neutralisation assays for the Alpha, Beta, Gamma, Delta, Lambda, Mu and Omicron variants of concern (including subvariants BA.2, and BA.4/5). Additionally, given the importance of booster vaccines on the effectiveness of COVID-19 vaccines against SARS-CoV-2 Omicron variants, 10 pools of 10 vaccinees receiving 3 doses of AZD1222 were also evaluated against Alpha, Beta, Gamma, Delta, and Omicron variants.

Collectively, these data show that 2-dose primary series immunisation with AZD1222 have limited but statistically significant reductions in neutralising antibody potency against the Alpha, Gamma, Delta, and Mu variants of concern. More substantial reductions in geometric mean titer ratio (GMTR) were observed against the Beta, Mu, and Omicron variants, with most primary series vaccination pools having no detectable neutralising antibodies to any sublineage of Omicron. A homologous booster dose of AZD1222 afforded higher levels of neutralizing antibodies (nAbs) to all SARS-CoV-2 strains. Notably, GMTs to all Omicron sublineages were similar or numerically higher after a 3rd-dose booster than GMTs to the ancestral strain after a 2-dose primary series.

14 LATE-BREAKING INFORMATION

Immunocompromise study (D8111C00010): a Type II Variation for removal of IC study was submitted to EMA. The Committee For Medicinal Products For Human Use (CHMP) opinion (received on 10 February 2023) and supported discontinuation of the category 1 study D8111C00010 and the removal from the Annex II (conditions or restrictions with regard to the safe and effective use of the medicinal product) of EU Product Information.

After the data lock point of the PBRER (28 December 2022), following the review of the safety data (solicited and unsolicited events) from the final pooled analysis (DCO3:31 December 2021) COV001, COV002, COV003, COV005 and the relevant post-market data; AstraZeneca decided update the CDS to include Decreased appetite as an ADR in Section 4.8 with a frequency of "Uncommon" along with some minor changes to frequency categories for other adverse events (Dizziness and Abdominal pain in the VAXZEVRIA group; Vomiting, Pain extremity and Urticaria in the Control group).

15 OVERVIEW OF SIGNALS (NEW, ONGOING OR CLOSED)

15.1 Overview of Validated Signals (New, Ongoing or Closed)

AstraZeneca are required to carry out pharmacovigilance on a routine basis according to the legislation. Routine pharmacovigilance is described in the pharmacovigilance system master file. However, a summary of signal identification is provided below.

Signals may be identified during:

- Review of individual case safety reports (ICSRs) arising from marketed use of the medicinal product or during clinical trials
- Regular analysis of aggregate ICSR data, including statistics of disproportionate reporting applied to the AstraZeneca global safety database and, as appropriate, publicly available databases of AEs (the US Food and Drug Administration Adverse Event Reporting System, the World Health Organisation VigiBase and the Eudravigilance Data Analysis System databases) (EVDAS)
- Regular review of published biomedical articles and conference abstracts
- Review of results arising from AstraZeneca-sponsored trials and externally-sponsored scientific research (previously referred to as investigator-sponsored trials)
- Review of reports from the product complaints management system (ie, product quality complaints)

Safety-related enquiries from Health Authorities, healthcare professionals, and consumers are also considered a source of signals. Relevant findings from preclinical trials and new safety information on products with the same or similar modes of action to the medicinal product are also considered.

The above are considered the most likely sources of signals, however relevant information from other sources is not excluded from consideration.

In the analysis of aggregate ICSRs arising from marketed use of AstraZeneca products, qualitative and pre-defined quantitative criteria are applied to the data in order to identify signals for evaluation. Quantitative analysis includes the use of algorithms to generate statistics of disproportionate reporting, including significant changes in these statistics over time. The initial evaluation of identified signals may lead to a more detailed evaluation and if a potential new risk is identified, a detailed review is undertaken by a scientific and medical forum.

A tabulation of **validated** signals that were ongoing or closed during the reporting period is presented in Appendix 3.

There were five validated signals that were either ongoing or closed during the reporting period. The validated signals are provided in Table 23 along with a cross-reference, where applicable, to the sections of the PBRER where further detail is provided.

Table 23 Summary of the validated signals that were ongoing or closed during the reporting period

Validated Signal	Ongoing or Closed at the DLP of the PBRER	Section of the PBRER where additional detail is provided	Reference Regulatory Procedure Number
Immune Thrombocytopenia	Closed	Section 16.2.5.3	NA
Cutaneous Vasculitis	Closed	Section 16.2.5.2	EMEA/H/C/PSUSA/00010912/202112
Tinnitus	Closed	Section 16.2.5.1	EMEA/H/C/PSUSA/00010912/202112
Decreased appetite[a]	Ongoing	Section 14, 16.2.1.1.	NA
Feeling hot[a]	Closed	Section 14, 16.2.1.1	NA

DLP Data Lock Point, NA Not Applicable, PBRER Periodic Benefit Risk Evaluation Report

[a] Signal of Decreased appetite was ongoing and Feeling hot was closed after the DLP on 17 January 2023

15.2 Health Authority requests

AstraZeneca received the following requests from PRAC in the Assessment Report (AR) for PBRER (Procedure no.: EMEA/H/C/PSUSA/00010912/202206; period 29 December 2021 to 28 June 2022). The PRAC requested the following Issues to be addressed in the next Periodic Safety Update Report (PSUR). The topics in question are presented in Table 24.

Table 24 List of Health Authority Requests

Topic	Section of the PBRER where additional detail is provided	Procedure no/ Health Authority
Acute disseminated encephalomyelitis (ADEM)	15.2.1	EMEA/H/C/PSUSA/00010912/202206

Table 24 List of Health Authority Requests

Topic	Section of the PBRER where additional detail is provided	Procedure no/ Health Authority
Menstrual disorders	15.2.2	EMEA/H/C/PSUSA/00010912/202206
Glomerulonephritis and nephrotic syndrome including IgA nephropathy	15.2.3	EMEA/H/C/PSUSA/00010912/202206
Venous Thromboembolism	15.2.4	EMEA/H/C/PSUSA/00010912/202206
Thrombosis	15.2.5	EMEA/H/C/PSUSA/00010912/202206
Use in immunocompromised patients	15.2.6	EMEA/H/C/PSUSA/00010912/202206
Severe cutaneous adverse reactions (SCAR)	15.2.7	EMEA/H/C/PSUSA/00010912/202206
Hearing loss	15.2.8	EMEA/H/C/PSUSA/00010912/202206
New daily persistent headache	15.2.9	EMEA/H/C/PSUSA/00010912/202206
Myositis	15.2.10	EMEA/H/C/PSUSA/00010912/202206
Corneal graft rejections	15.2.11	EMEA/H/C/PSUSA/189794/2022
Histiocytic necrotizing lymphandenitis (HNL), or Kikuchi's disease	15.2.12	PRAC request (EudraVigilance)
TGA request on Post -Marketing Exposure Data	5.2.1.2	PSUR - VAXZEVRIA - PM-2020-06115-1-2

PBRER Periodic Benefit-Risk Evaluation Reports, TGA Therapeutic Goods Administration

15.2.1 Acute disseminated encephalomyelitis (ADEM)

Background

In the assessment report received from the PRAC (EMEA/H/C/PSUSA/00010912/202206) for the VAXZEVRIA PBRER (review period 29 December 2021 to 28 June 2022), further information on ADEM was requested.

The MAH is requested to provide a discussion of ADEM, including but not be limited to:

(i) an updated cumulative review of cases of ADEM,

(ii) an updated literature review, with a focus on new relevant epidemiological studies,

(iii) a discussion on the need to update the PI and/or RMP.

Moreover, the MAH is requested to carefully review the evaluation of cases of ADEM as discrepancies regarding the BCC evaluation (eg, case [redacted] *classified as BCC Level 2 whereas a 4-month FU suggests a monophasic disease course) and World Health Organization (WHO)- Uppsala Monitoring Centre (UMC) causality assessment (eg, case* [redacted] *assessed as unlikely due to incorrect TTO) have been noticed.*"

Global Patient Safety Database

A cumulative search till 28 December 2022 of the AstraZeneca Global Safety Database for PT 'Acute disseminated encephalomyelitis' with VAXZEVRIA was performed using MedDRA version 25.1.

The search retrieved a total of 88 events of Acute disseminated encephalomyelitis' in 88 case reports. On review 05 case reports ([redacted] and [redacted] from Germany, [redacted] from Australia, [redacted] from Italy and [redacted] from United States) were identified to be potential duplicates and have been excluded from further analysis.

For the remaining 83 cases, the most frequently reported countries were 17 (20.48%) from United Kingdom (UK); 16 (19.28%) from India; 9 (10.84%) each from Germany and Australia; 5 (6.02%) each from Italy, Brazil and Spain; 2 (2.41%) each from Belgium, France and Greece; 1 (1.20%) each from Argentina, Croatia, Finland, Hungary, Ireland, Republic of Korea, Latvia, Poland, Sweden, United States (US) and Taiwan.

All 83 ADEM case reports were reported as serious.

The breakdown and overview of these 83 cases/ events is presented in the below Table 25.

Table 25 Overview of Events/Cases (cumulatively)

Parameter	Category	Values (%)
Event Count	Total	83 (100%)
	Serious	83 (100%)
Case Count	Medically confirmed	58 (69.88%)
Case Report Source	Interventional Clinical study	00 (00%)
	Non-interventional study	7 (8.43%)
	Spontaneous	12 (14.46%)
	Literature	19 (22.89%)
	Regulatory	45 (54.22 %)
Sex	Female N (%)	44 (53.01%)
	Male N (%)	37 (44.58%)
	Unknown/not reported N (%)	2 (2.41%)
Age Group	18-49	34 (40.96%)
	50-59	17 (20.48%)
	60-69	18 (21.69%)
	70-79	07 (8.43%)
	80+	02 (2.41%)
	Unk	05 (6.02%)
	Median age (range)	52.5 years (22 to 90)
	Dose 1 (%)	57 (66.67%)

Table 25 Overview of Events/Cases (cumulatively)

Parameter	Category	Values (%)
Event occurrence with dose	Dose 2 (%)	08 (9.64%)
	Dose 3 (%)	00 (00%)
	Dose 4 (%)	00 (00%)
	Dose unspecified	18 (21.69%)
Case level -TTO (days)[a]	0-2	15 (24.19%)
	3-14	31 (50.00%)
	15-28	7 (11.29%)
	29-42	4 (6.45%)
	43 and above	5 (8.06%)
	Unknown	21
	Median TTO in days (range)	09 (0 to 186)
Event Seriousness criteria[b]	Medically important	49 (35. 37%)
	Disability	17 (12.41%)
	Hospitalization	52 (37.96%)
	Congenital anomaly	00 (00%)
	Life-threatening	14 (10.22%)
	Death	05 (3.65%)
AE Outcome	Recovered	7 (8.43%)
	Recovering	21 (25.30%)
	Recovered with sequelae	1 (1.20%)
	Not recovered	25 (30.12%)
	Fatal	5 (6.02%)
	Unknown	24 (28.92%)
Duration of recovered/recovered with sequelae events	Range (days)	54-91
	Mean (days)	72.5
	Unknown duration (number of events)	6

[a] TTO was reported for 62 case reports (total number of cases) used to calculate the percentage.
Where multiple TTOs are present in a case, the most conservative TTO for the relevant event is chosen percentages for all, calculated based on known values

[b] some events reported > 1 seriousness criteria

AE Adverse Event, Unk Unknown, TTO Time to onset

The events most commonly co-reported with ADEM cumulatively are presented in Table 26.

Table 26 Distribution of most frequently co-reported events (top 10) in case reports for ADEM, cumulatively

Adverse events (PT)	Number of events	Percentage (%)
Headache	8	9.64
Pyrexia	8	9.64

Table 26 Distribution of most frequently co-reported events (top 10) in case reports for ADEM, cumulatively

Adverse events (PT)	Number of events	Percentage (%)
Asthenia	7	8.43
Gait disturbance	7	8.43
Ataxia	5	6.02
Hypoaesthesia	5	6.02
Confusional state	4	4.82
Dysarthria	4	4.82
Muscular weakness	4	4.82
Paraesthesia	4	4.82

ADEM Acute Disseminated Encephalomyelitis, PT Preferred Term

Events with fatal outcome

Of the 83 total events (*cumulatively through 28 December 2022*) reported, 05 (6.02%) events in 05 cases were reported with a fatal outcome, all of the events were medically confirmed.

The assessment of the fatal case reports identified cumulatively is presented in the below Table 27.

Table 27 Summary of case reports with fatal outcome for ADEM (N = 05) cumulatively

Case ID/ Age/Gender/ Medically confirmed (Y/N)/ Source/Country/	TTO /Dose	Relevant Medical History/ Concomitant medications (Risk factors)	Autopsy (Y/N)/ Summary of Autopsy result	Cause of Death PTs	Brighton Collaboration classification	WHO UMC Causality Assessment	Comment for BCC/WHO causality assessments
[redacted]/ 63 years/ M/ Y/ Literature/ Australia	12 days/ Dose 1	Medical history: recurrent vertiginous and non-vertiginous dizziness (after a small traumatic subarachnoid hemorrhage after a fall with head strike 3 years prior), which at times had orthostatic/head posture/exertional exacerbation. Concomitant medications: apixaban, bisoprolol, irbesartan, empagliflozin, metformin, Novomix-30 (insulin aspart-insulin aspart protamine),	Y/A brain biopsy confirmed ADEM	Acute disseminated encephalomyelitis	1	Possible with limited information	The case was assessed as BCC level 1 based on clinical features, MRI findings, ante mortem biopsy and autopsy. Ongoing evaluation of pre-existing vertiginous and non-vertiginous dizziness, (pre-existing foci in white matter) and presenting symptom of vertigo could also point to possible ongoing immune response to an unknown pre-existing brain pathology. The patient's condition and fatality thereof could also be complicated by underlying significant cardiac (heart disease with ischemic cardiac events) and metabolic issues (ketoacidosis and mitochondrial dysfunction) as increased lactate levels were seen in CSF even post ketoacidosis correction with no increased leucocytic pleocytosis. There was limited information on post-mortem autopsy of other organs. Limited etiologic work-up was presented, including infectious and cell type assessment on the biopsy sample.

Table 27 Summary of case reports with fatal outcome for ADEM (N = 05) cumulatively

Case ID/ Age/Gender/ Medically confirmed (Y/N)/ Source/Country/	TTO /Dose	Relevant Medical History/ Concomitant medications (Risk factors)	Autopsy (Y/N)/ Summary of Autopsy result	Cause of Death PTs	Brighton Collaboration classification	WHO UMC Causality Assessment	Comment for BCC/WHO causality assessments
		rosuvastatin, and pantoprazole.					
[redacted]/ 71 years/ M/ Y/ Regulatory/ Australia	49 days/ Unk	Unknown relevant risks and/or concomitant medications	Unk	Acute disseminated encephalomyelitis	2	Unlikely	The case was assessed as BCC level 2 based on pattern of initial MRI picture suggestive of several lesions scattered throughout the brain correlating with acute presentation of neurological features, Serial MRI showed resolving lesions with no evidence of new lesions. However, a comprehensive assessment of the fatal ADEM could not be made due to insufficient information on the complete clinical course especially after radiological resolution and discharge of the patient, and on any corrective therapy, any autopsy, medical history and any etiological workup. The WHO-UMC causality was assessed as unlikely based on the TTO >42 days.

Table 27 Summary of case reports with fatal outcome for ADEM (N = 05) cumulatively

Case ID/ Age/Gender/ Medically confirmed (Y/N)/ Source/Country/	TTO /Dose	Relevant Medical History/ Concomitant medications (Risk factors)	Autopsy (Y/N)/ Summary of Autopsy result	Cause of Death PTs	Brighton Collaboration classification	WHO UMC Causality Assessment	Comment for BCC/WHO causality assessments
[redacted] / 90 years/ M/ Y/ Spontaneous/ Brazil	0/Dose 1	Concomitant medications included enalapril maleate and doxasozin mesilate	Unk	Acute disseminated encephalomyelitis	4	Unlikely	The case was assessed as BCC level 4 due to limited information to assess ADEM. Additionally, due to the rapid onset on the day of vaccination, it is likely a pre-existing predisposition to ADEM was present before vaccination and the vaccine is unlikely to be the cause of the ADEM.
[redacted] / 40 years/ F/ Y/ Literature/ India	14 days/ Dose 1	Medical history: hypertension; myalgia; mechanical ventilation; endotracheal intubation/Unknown relevant concomitant medication	Unk	Acute disseminated encephalomyelitis	2	Possible with limited information	The case was assessed as BCC level 2 based on the clinical features of encephalopathy, changed mentation, upper motor neuron signs (increased reflexes, bilateral Babinski,) acute onset and multi-focal features on MRI suggesting demyelination in the cerebrum. Potential infectious and auto-immune causes were ruled out, however there was an unevaluated acute episode of self-resolving myalgia just prior to vaccination. Additionally, there was a description of anterior horn spinal cord ischemia/hypoperfusion or possible infarction on MRI suggesting a vascular/vasculitis pathology and noted paradoxical breathing was consistent with spinal cord pathology causing diaphragm paralysis. Limited or no information on any biopsy or autopsy, exact causes of death, work up for possible malignancies, paraneoplastic syndromes, and haematological investigations were not available. Hypertensive encephalopathy or acute fulminant multiple sclerosis would also be in the differential. Based on reasonable time

Table 27 Summary of case reports with fatal outcome for ADEM (N = 05) cumulatively

Case ID/ Age/Gender/ Medically confirmed (Y/N)/ Source/Country/	TTO /Dose	Relevant Medical History/ Concomitant medications (Risk factors)	Autopsy (Y/N)/ Summary of Autopsy result	Cause of Death PTs	Brighton Collaboration classification	WHO UMC Causality Assessment	Comment for BCC/WHO causality assessments
							relationship of the neurological event, onset to vaccine administration, the WHO-UMC causality was assessed as Possible with confounders of hypertension and spinal cord ischemia
[a] [redacted] 59 years/ M/ Y/ Literature/ United States	2 days/ Unk	Unk	Unk	Myelitis transverse; Acute disseminated encephalomyeliti s; Cerebellar syndrome; Sepsis	3	Possible with limited information	Conservatively assessed as BCC level 3 and possible causality with limited information. Time to onset 2 days. Patient had motor symptoms (ascending paralysis), areflexia, cerebellar symptoms. Absence of encephalopathy. CSF showed nonspecific results. There was no improvement of symptoms on treatment with methylprednisolone. Clinical course was complicated by sepsis which was fatal. No information on MRI, details of CSF investigations, infectious or neoplastic workup. Alternative diagnosis of GBS but no information on nerve conduction abnormalities, or treatment with immunoglobulins.

[a] Author's country *United states.*

ADEM-acute disseminated encephalomyelitis; BCC-Brighton Collaboration Criteria; CNS-central nervous system; F-female; ID-identification; M-male; MI-myocardial infarction; MRI-magnetic resonance imaging; N-no; TTO-Time To Onset; unk-unknown; WHO UMC-World Health Organization-Uppsala Monitoring Centre; Y-yes; CSF-cerebrospinal fluid; GBS- Guillain-Barre syndrome.

Recurrence case reports

There were no cases identified for ADEM after Dose 1, with a recurrence or worsening of ADEM with the Dose 2/Dose 3 of vaccination indicating potential recurrence/positive rechallenge.

WHO -UMC causality and Brighton Collaboration Classification Assessment

The Brighton collaboration criteria (BCC) (Law B 2021 [B]) was used for the case level of certainty (LOC) assessment based on the data available in the cases. The strongest level of certainty was 1, with levels of certainty 2 and 3 being less strong. Level of certainty 4 was reached for cases where the diagnosis was named but not supported with history, clinical findings, clinical course or diagnostic tests. Level of certainty 5 was the designation for cases where another diagnosis was noted. Based on this approach, of the 83 cases, 4 cases fulfilled level 1 criteria, 25 cases fulfilled level 2 criteria, 7 cases fulfilled level 3 criteria, 27 cases fulfilled level 4 criteria, and 20 cases fulfilled level 5 criteria. In addition to the BCC, the published Brighton Case Definition for ADEM (Law B 2021 [A]) was also referenced during the review of the cases for the assessment of evidence related to associated risk factors (eg, malignancy, infections, use of vaccines, or surgery).

The recommended risk window (RW) for ADEM as a vaccine -related reaction (Rowhani-Rahbara et al 2012) as cited in Law B 2021 [B]) for inactivated or subunit vaccines is 2 to 42 days. Causality assessment of all cases (or cases fulfilling BCC 1 to 5 - based on the topic and approach) was performed using WHO- UMC causality assessment criteria with a risk window of 2 to 42 days.

The BCC and WHO-UMC causality assessment performed for these cases is provided in the following Table 28.

Table 28 Overview of BCC and WHO-UMC Causality Assessments / for case reports of ADEM with VAXZEVRIA reported cumulatively

WHO-UMC/BCC Level	Level 1	Level 2	Level 3	Level 4	Level 5	Grand Total
Certain	0	0	0	0	0	0
Probable/Likely	0	0	0	0	0	0
Possible with risk factors/confounders	1	5	0	3	5	14
Possible with limited information	3	16	4	15	5	43
Unassessable/Unclassifiable with limited information	0	0	3	4	7	14
Unassessable/Unclassifiable with risk factors/confounders	0	1	0	1	2	4
Unlikely	0	3	0	4	1	8
Conditional /Unclassified	0	0	0	0	0	0
Total	**4**	**25**	**7**	**27**	**20**	**83**

Cases were considered to have "risk factors/confounders" *where the event could also be explained by the vaccinee's diseases, or where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.*

Amongst 83 cases for ADEM, 18 (21.69%) were identified either with relevant risk / confounding factors as presented in Table 29. These are presented into the following categories for risk / confounding factors in descending order of frequency.

Table 29 Relevant Risk factors / Confounders identified for case reports cumulatively

Relevant Risk factors/ Confounders [a]	Number of reports
Other conditions suggestive of possible symptoms of organic brain disorder, cancers, immunological conditions: anxiety, depression, psoriasis, urinary retention, overactive bladder, back pain, nystagmus, migraine, sub arachnoid hemorrhage, lymphocytic pleocytosis, breast cancer, bowel cancer	8
Chronic conditions such as hypertension, diabetes Mellitus type 1 and 2, and hypercholesterolemia	7
Autoimmune conditions, endocrine, and metabolic conditions	6
Para- or post infectious conditions and other vaccines	4
History of neurological disease	3

Table 29 Relevant Risk factors / Confounders identified for case reports cumulatively

Relevant Risk factors/ Confounders [a]	Number of reports
Personal history such as history of tobacco use, allergies, and being overweight	1

[a] Some cases have more than 1 relevant risk/confounding factors.

In the remaining 65 (78.31) cases, there was insufficient information with respect to either dose latency, medical history, or concomitant medication details for a comprehensive causal assessment.

Brighton Collaboration Criteria Level 1 (Refer Appendix 11)

Four (4) of the 83 cases fulfilled BCC level 1 according to classification by clinical course, examination features, and/or level of certainty.

Of the 4 cases, 2 cases were reported in a male vaccinee, 1 case was reported in female vaccinee and in 1 case the gender was unknown. The ages of the vaccinees were 45, 45, 49 and 63 years. The TTO for the 4 cases were the same day (dose 1), 13 days (dose 1), 18 days (dose 1), and 21 days (dose 2). The outcome in 1 case was fatal; however, the fatality was confounded by pre-existing ischemic heart disease, atrial fibrillation, recurrent vertiginous and non-vertiginous dizziness and diabetes. In the remaining 3 cases, the outcome was recovering. Of the 4 cases fulfilling BCC level 1, 3 cases were assessed as "Possible" with limited information (eg time to onset, medical history, family history, infectious work-up), and 1 case was assessed as "Possible with risk factors/confounders" per the WHO UMC causality assessment criteria.

Brighton Collaboration Criteria Level 2 (Refer Appendix 11)

Twenty-five (25) of the 83 cases fulfilled BCC level 2. The cases fulfilled this classification by clinical course, examination features, and confirmatory tests.

Fourteen (14) cases were reported in female vaccinees and 11 were reported in male vaccinees. The age range was 22 to 71 years with mean and median of 49 years and 51 years, respectively. The TTO ranged between the same day to 49 days and the median TTO was 9 days. Two cases ([redacted] and [redacted]) had a fatal outcome. The outcome was not recovered in 7 cases, recovered in 2 cases, recovering in 6 cases, and unknown in 8 cases. Eighteen (18) cases occurred after the 1st dose, 2 cases after the 2nd dose, and in 5 cases the dose information was unknown. Out of the 25 cases fulfilling BCC level 2, 16 cases were assessed as "Possible with limited information" as they occurred within the risk window of 2

to 42 days, 5 cases were assessed as "Possible with risk factors/confounders", 1 case was "Unassessable/ Unclassifiable with confounders" as the TTO was unknown, and 3 cases were "Unlikely" as they were outside the risk window per the WHO-UMC causality assessment criteria. Of the 25 cases, possible confounders or alternate explanations could be identified in 6 (24%) cases, which were infections (n=3; Borrelia infection, suspected COVID-19, and positive IgG for multiple viruses [adenovirus, herpes simplex 1, HHV6, cytomegalovirus, Epstein–Barr Virus (EBV) VCA, Epstein-Barré Nuclear Antigen (EBNA), parvovirus B19, toxoplasma, and VZV]), autoimmune conditions (n=2; autoimmune connective tissue disorder, polymyalgia rheumatica, and hypothyroidism), CNS (Central Nervous System) neoplasm (n=1), Bickerstaff encephalitis and GBS (n=1) and features suggestive of multiple sclerosis (MS) (n=2; concurrent optic neuritis and intrathecal IgM synthesis). Nineteen (19) cases had limited information regarding medical history or comorbidities, or investigations.

Brighton Collaboration Criteria Level 3 (Refer Appendix 11)

Seven (7) of the 83 cases fulfilled BCC level 3. The cases fulfilled this classification by clinical course, examination features, and confirmatory tests.

Five (5) cases were reported in female vaccinees and 02 were reported in male vaccinees. The age range was 32 to 64 years with mean and median of 51 years and 55 years, respectively. The TTO ranged between the same day to 30 days and the median TTO was 6 days. One case ([redacted]) had a fatal outcome. The outcome was not recovered in 1 case recovering in 1 case, and unknown in 4 cases. Two (2) cases occurred after the 1st dose, 1 case after the 2nd dose, and in 4 cases the dose information was unknown. Out of the 7 cases fulfilling BCC level 3, 4 cases were assessed as "Possible with limited information" as they occurred within the risk window of 2 to 42 days and 3 cases were "Unassessable/ Unclassifiable with limited information" as the TTO was unknown. Seven (7) cases had limited information regarding medical history or comorbidities, or investigations.

Brighton Collaboration Criteria Level 4

Twenty seven (27) of the 83 cases fulfilled BCC level 4. These cases did not fulfil criteria for a level 3, 2 or 1 certainty as there was insufficient information (pertaining to exclusion of alternate diagnosis for illnesses such as neoplasm, vascular disorder, infection and toxic/ metabolic encephalopathy) to confirm the diagnosis or medical assessment of the case as ADEM. Out of the 27 cases 15 were assessed as possible with limited information, 3 cases were assessed as possible with risk factors/confounders, 4 cases were assessed as unassessable/unclassifiable with limited information, 1 case was assessed as unassessable/Unclassifiable with risk factors/confounder and 4 cases were assessed as unlikely per the WHO-UMC causality assessment criteria.

Brighton Collaboration Criteria Level 5

Twenty (20) of the 83 cases fulfilled BCC level 5 and, therefore excluded due to an alternative diagnosis such as GBS, Neuromyelitis Optica Spectrum disorder (NMOSD), microhaemorrhages in brain, MS and infectious encephalitis. Out of the 20 cases, 5 were assessed as possible with limited information, 5 were assessed as possible with risk factors/confounders, 7 were assessed as unassessable/ unclassifiable with limited information, 2 were assessed as unassessable/ unclassifiable with confounders and 1 was assessed as unlikely per the WHO-UMC causality assessment criteria.

On review of the 83 cases of ADEM in the AstraZeneca global safety database, 20 (24.09%) cases had information on anti-MOG antibody status. Of the 20 cases, 8 (40.00%) cases were anti-MOG positive, 11 (55.00%) cases were anti-MOG negative and in 1 case (5.00%) the anti-MOG status was unknown.

On review of the global safety database, no specific trend with respect to MOG antibody positive status ADEM in individuals vaccinated with VAXZEVRIA was seen.

Observed Versus Expected (O/E) Analyses

An O/E analysis of 'Acute disseminated encephalomyelitis' was conducted cumulatively to 28 December 2022. The results were stratified by 3 risk windows (14, 30 and 42 days) for all global reports, stratified by age in the European Union (EU), UK, Brazil, and Australia, and by age and gender. The risk window of 2 to 42 days was included from the Brighton case definition (Law B 2021 [B]). In order to provide an accurate incidence rate (IR) for this rare event, a meta-analysis using random-effect model was performed based on data from years 2017 to 2019 from databases (ES_BIFAP_PC, ES_BIFAP_PCHOSP, ES_FISABIO, ES_SIDIAP_PC (Spain Information System for the Development of Research in Primary Care), ES_SIDIAP_PCHOSP, and IT_ARS, UK_CPRD) presented in the revised ACCESS protocol (Willame et al 2021 (A)).

The O/E analysis for the cumulative cases of 'Acute disseminated encephalomyelitis' with risk windows 14, 30, and 42 days is presented with results in Table 30. Conservatively, the exposure for global reports (466115644) is based on doses administered in 13 markets.

Table 30 Observed Versus Expected Analysis for all Reports of ADEM (Global Reports)

Adverse Events	Risk Window (Days)	Background Rates/ 100,000 PY	Exposure	Observed Number of Cases	Expected Number of Cases	O Over E Ratio (95% CI)	Conclusion
Overall (global) ACCESS IR ADEM	14	0.15	466115644	46	26.8	1.72 (1.26 - 2.29)	Observed significantly > expected
	30	0.15	466115644	55	57.43	0.96 (0.72 - 1.25)	Observed < expected
	42	0.15	466115644	57	80.4	0.71 (0.54 - 0.92)	Observed significantly < expected
Overall (global) ACCESS IR including cases with an unknown time to onset	14	0.15	466115644	67	26.8	2.5 (1.94 - 3.17)	Observed significantly > expected
	30	0.15	466115644	76	57.43	1.32 (1.04 - 1.66)	Observed significantly > expected
	42	0.15	466115644	78	80.4	0.97 (0.77 - 1.21)	Observed < expected

IR = 0.15/100,000 person years.

ADEM-acute disseminated encephalomyelitis; CI-confidence interval; E-expected; IR-incidence rate; O-Observed; PY-patient years.

Source:Willame et al 2021 (A) (Meta-analysis IR from 2017-2019 ADEM-Narrow).

An O/E analysis of cases meeting case definition according to BCC Level 1, 2, or 3, based on clinical course, examination such as brain histopathology, focal/multifocal CNS abnormalities, brain MRI or recurrence or relapse of illness since the symptomatic nadir, and no alternative etiology (Law B 2021 [B]) are presented in Table 31.

Table 31 Observed Versus Expected Analysis for Cases for ADEM Meeting BCC Level 1, 2 or 3 (Global Reports)

Adverse Events	Risk Window (Days)	Background Rates/ 100,000 PY	Exposure	Observed Number of Cases	Expected Number of Cases	O Over E Ratio (95% CI)	Conclusion
Overall (global) ACCESS IR ADEM BCC levels 1 to 3	14	0.15	466115644	24	26.8	0.9 (0.57 - 1.33)	Observed < expected
	30	0.15	466115644	30	57.43	0.52 (0.35 - 0.75)	Observed significantly < expected
	42	0.15	466115644	31	80.4	0.39 (0.26 - 0.55)	Observed significantly < expected
Overall (global) ACCESS IR ADEM BCC levels 1 to 3 including cases with an unknown TTO	14	0.15	466115644	28	26.8	1.04 (0.69 - 1.51)	Observed > expected
	30	0.15	466115644	34	57.43	0.59 (0.41 - 0.83)	Observed significantly < expected
	42	0.15	466115644	35	80.4	0.44 (0.3 - 0.61)	Observed significantly < expected

IR = 0.15/100,000 person years.
ADEM=acute disseminated encephalomyelitis; BCC=Brighton collaboration criteria; CI=confidence interval; E=expected; IR=incidence rate; O=Observed; PY=patient years; TTO=time to onset.
Source: Willame et al 2021 (A) Meta-analysis from revised ACCESS protocol IR from 2017-2019 ADEM-Narrow)

Additionally, the O/E analysis is presented with stratification by age for the EU, UK, Brazil, and Australia regions based on the available exposure data, this is presented in Table 32.

Table 32 Observed Versus Expected Analysis for ADEM Cases Stratified by Age for EU, UK, Brazil, and Australia Regions

Age group	Risk Window (Days)	IR[a] / 100,000 PY	Exposure[b]	Observed Number of Cases	Expected Number of Cases	O Over E Ratio (95% CI)	Conclusion
Age 18 to 49	14	0.15	110094983	18	6.33	2.84 (1.69 - 4.49)	Observed significantly > expected
	30	0.15	110094983	19	13.56	1.4 (0.84 - 2.19)	Observed > expected
	42	0.15	110094983	19	18.99	1 (0.6 - 1.56)	Observed > expected
Age 50 to 59	14	0.07	58336094	7	1.57	4.46 (1.79 - 9.19)	Observed significantly > expected
	30	0.07	58336094	8	3.35	2.39 (1.03 - 4.71)	Observed significantly > expected
	42	0.07	58336094	8	4.7	1.7 (0.73 - 3.35)	Observed > expected
Age 60 to 69	14	0.16	57960860	7	3.55	1.97 (0.79 - 4.06)	Observed > expected
	30	0.16	57960860	8	7.62	1.05 (0.45 - 2.07)	Observed > expected
	42	0.16	57960860	8	10.66	0.75 (0.32 - 1.48)	Observed < expected
Age over 70	14	0.08	32376365	3	0.99	3.03 (0.62 - 8.86)	Observed > expected
	30	0.08	32376365	4	2.13	1.88 (0.51 - 4.81)	Observed > expected
	42	0.08	32376365	5	2.98	1.68 (0.54 - 3.92)	Observed > expected

[a] Source:Willame et al 2021 (A) (Meta-analysis estimates of ACCESS from 2017-2019 ADEM-Narrow).

[b] Exposure till 28 December 2022.

ADEM-acute disseminated encephalomyelitis; AE-adverse events; CI-confidence interval; E-expected; EEA-European Economic Area IR-incidence rate; O-Observed; PY-Patient years, TTO-time to onset; UK-United Kingdom

An O/E analysis of cases meeting case definition according to BCC Level 1, 2 or 3 stratified by age and gender for the EU, UK, Brazil, and Australia regions based on the available exposure data, this is presented in Table 33.

Table 33 Observed Versus Expected Analysis for ADEM Cases Meeting BCC Level 1, 2 or 3 and Stratified by Age for EU, UK, Brazil, and Australia Regions

Age group BCC Level	Risk Window (Days)	IR[a] / 100,000 PY	Exposure[b]	Observed Number of Cases	Expected Number of Cases	O Over E Ratio (95% CI)	Conclusion
Age 18 to 49 ADEM BCC levels 1 to 3	14	0.15	110094983	7	6.33	1.11 (0.44 - 2.28)	Observed > expected
	30	0.15	110094983	7	13.56	0.52 (0.21 - 1.06)	Observed < expected
	42	0.15	110094983	7	18.99	0.37 (0.15 - 0.76)	Observed significantly < expected
Age 50 to 59 ADEM BCC levels 1 to 3	14	0.07	58336094	4	1.57	2.55 (0.69 - 6.52)	Observed > expected
	30	0.07	58336094	4	3.35	1.19 (0.33 - 3.06)	Observed > expected
	42	0.07	58336094	4	4.7	0.85 (0.23 - 2.18)	Observed < expected
Age 60 to 69 ADEM BCC levels 1 to 3	14	0.16	57960860	3	3.55	0.85 (0.17 - 2.47)	Observed < expected
	30	0.16	57960860	4	7.62	0.52 (0.14 - 1.34)	Observed < expected
	42	0.16	57960860	4	10.66	0.38 (0.1 - 0.96)	Observed significantly < expected
Age over 70 ADEM BCC levels 1 to 3	14	0.08	32376365	0	0.99	0 (0 - 3.73)	Observed < expected
	30	0.08	32376365	0	2.13	0 (0 - 1.73)	Observed < expected
	42	0.08	32376365	0	2.98	0 (0 - 1.24)	Observed < expected

[a] Source:Willame et al 2021 (A) (Meta-analysis estimates of ACCESS from 2017-2019 ADEM-Narrow).

[b] Exposure till 28 December 2022.

ADEM-acute disseminated encephalomyelitis; AE-adverse events; CI-confidence interval; E-expected; EEA-European Economic Area IR-incidence rate; O-Observed; PY-Patient years, TTO-time to onset; UK-United Kingdom

An O/E analysis of cases meeting case definition according to BCC Level 1, 2 or 3 stratified by age and gender for UK is presented in Table 34.

Table 34 Observed Versus Expected Analysis for ADEM Cases Meeting BCC Level 1, 2 or 3 and Stratified by Age and Sex for the UK

Age group BCC Level Sex	Risk Window (Days)	IR[a] / 100,000 PY	Exposure[b]	Observed Number of Cases	Expected Number of Cases[a]	O Over E Ratio (95% CI)	Conclusion
Age 18 to 49 (BCC 1 to 3) Female	14	0.07	7414701	2	0.2	10 (1.21 - 36.12)	Observed significantly > expected
	30	0.07	7414701	2	0.43	4.65 (0.56 - 16.8)	Observed > expected
	42	0.07	7414701	2	0.6	3.33 (0.4 - 12.04)	Observed > expected
Age 50 to 59 (BCC 1 to 3) Female	14	0.05	5944683	0	0.11	0 (0 - 33.54)	Observed < expected
	30	0.05	5944683	0	0.24	0 (0 - 15.37)	Observed < expected
	42	0.05	5944683	0	0.34	0 (0 - 10.85)	Observed < expected
Age 60 to 69 (BCC 1 to 3) Female	14	0.12	4783416	0	0.22	0 (0 - 16.77)	Observed < expected
	30	0.12	4783416	0	0.47	0 (0 - 7.85)	Observed < expected
	42	0.12	4783416	0	0.66	0 (0 - 5.59)	Observed < expected
Age 70 to 79 (BCC 1 to 3) Female	14	0.09	3475875	0	0.12	0 (0 - 30.74)	Observed < expected
	30	0.09	3475875	0	0.26	0 (0 - 14.19)	Observed < expected
	42	0.09	3475875	0	0.36	0 (0 - 10.25)	Observed < expected
Age over 80 (BCC 1 to 3) Female	14	0.02	1630324	0	0.01	0 (0 - 368.89)	Observed < expected
	30	0.02	1630324	0	0.03	0 (0 - 122.96)	Observed < expected
	42	0.02	1630324	0	0.04	0 (0 - 92.22)	Observed < expected
Age 18 to 49 (BCC	14	0.21	6766098	0	0.54	0 (0 - 6.83)	Observed < expected
	30	0.21	6766098	0	1.17	0 (0 - 3.15)	Observed < expected

Table 34 Observed Versus Expected Analysis for ADEM Cases Meeting BCC Level 1, 2 or 3 and Stratified by Age and Sex for the UK

Age group BCC Level Sex	Risk Window (Days)	IR[a] / 100,000 PY	Exposure[b]	Observed Number of Cases	Expected Number of Cases[a]	O Over E Ratio (95% CI)	Conclusion
1 to 3) Male	42	0.21	6766098	0	1.63	0 (0 - 2.26)	Observed < expected
Age 50 to 59 (BCC 1 to 3) Male	14	0.07	6510960	2	0.17	11.76 (1.42 - 42.5)	Observed significantly > expected
	30	0.07	6510960	2	0.37	5.41 (0.65 - 19.53)	Observed > expected
	42	0.07	6510960	2	0.52	3.85 (0.47 - 13.89)	Observed > expected
Age 60 to 69 (BCC 1 to 3) Male	14	0.12	4934728	0	0.23	0 (0 - 16.04)	Observed < expected
	30	0.12	4934728	0	0.49	0 (0 - 7.53)	Observed < expected
	42	0.12	4934728	0	0.68	0 (0 - 5.42)	Observed < expected
Age 70 to 79 (BCC 1 to 3) Male	14	0.09	3137304	0	0.11	0 (0 - 33.54)	Observed < expected
	30	0.09	3137304	0	0.23	0 (0 - 16.04)	Observed < expected
	42	0.09	3137304	0	0.32	0 (0 - 11.53)	Observed < expected

[a] Source: Willame et al 2021 (A) (meta-analysis estimates of ACCESS from 2017-2019 ADEM-Narrow)

[b] Exposure until 28 December 2022.

ADEM-acute disseminated encephalomyelitis; BCC-Brighton collaboration criteria; CI-confidence interval; E-expected; IR-incidence rate; O-Observed; PY-Patient years, UK-United Kingdom.

The O/E analysis of all cases of ADEM suggested that the observed cases of ADEM cases were less than the number of expected cases in the 30-day risk and the 42-day risk windows, while for the 14-day risk window the analysis suggested that the observed cases of ADEM were significantly more than the number of expected cases. As a conservative approach all cases with time to onset within 0 to 42 days and all cases with unknown time to onset were included in the O/E analysis. The vaccine exposure by doses administered for O/E analysis were only considered from few countries where the data were available. Eighteen cases were reported with the ADEM onset within 0 to 5 days of VAXZEVRIA vaccination. A latency of ADEM within 0 to 5 days of immunization is considered too short and cases less than 5 days from vaccination would be questionable in any causative association and may be possibly indicative of pre-existing infection or underlying condition. While immunization with the Semple rabies vaccine, which has a proven association with ADEM (Sejvar et al 2007; Hemachudha et al 1987 [A], has been shown to be associated with a peak interval of 1 to 2 weeks between immunization and onset of ADEM's neurologic symptoms among some vaccine recipients (Hemachudha et al 1987 [B]). Leake et al 2004, in an epidemiologic study of 64 ADEM cases also reported 93% of ADEM patients had one or more of the following symptoms or signs of infection within the preceding 21 days: fever, cough, rhinorrhea; vomiting; or diarrhoea. Of the 46 cases within 14 days TTO, there were 18 reports of ADEM reported within the risk window of 0-5 days; if the 18 reports are excluded the observed cases are less than expected Also, there is a possibility of reporting bias for increased reporting of cases with a shorter risk window for the passive event reporting of rare diseases. When cases with unknown TTO were added to the observed numbers, observed cases were significantly more than expected for the 14-day and 30-day risk windows and observed cases were less than expected for the 42-day risk window. However, an O/E analysis of cases meeting BCC levels 1 to 3 showed that the observed number ADEM cases fulfilling case definition were less and/or significantly less than number of expected cases in all risk windows except the 14-day risk window including cases with unknown TTO.

When O/E analyses are stratified by age in EU, UK, Australia, and Brazil, and different risk windows (14, 30, and 42 days), numbers of cases become very small resulting in observed as greater than expected for all age groups. The O/E analysis for cases meeting the BCC level 1, 2 or 3 and stratified by age group with different risk windows (14, 30, and 42 days) suggested that observed cases were less than expected for most age groups. Also, there is too much variability in these data to make an assessment.

When O/E analysis are stratified by age and gender in the UK for cases meeting BCC level 1, 2, or, 3 the observed numbers were significantly greater or greater than expected in females aged 18 to 49 and males aged 50 to 59 in all risk windows. The observed numbers were less than expected in other age and sex stratifications.

Further review of cases in these groups where observed were above expected showed that most cases had insufficient information to make a causality assessment. Of the 83 cases reported during the reporting period, only 36 cases met BCC level 1 to 3.

The O/E analyses provided is based on the most recent and available data, but there is a level of assumption made and any change in the data would impact the results. The following are some of the limitations/assumptions of the data used:

- Doses administered for determination of exposure: Currently only exposure data from certain countries are available, but these countries generate the majority of cases reported to AstraZeneca.
- The background incidence rate used for the calculation is the same as the population vaccinated: The identification of incidence rates can vary depending on the source of the data.
- Most of the observed events are spontaneously reported: Spontaneously reported events may only represent a fraction of the events that have actually occurred. Both under-reporting for certain events, and conversely, over-reporting for certain events could have played a role.
- The risk period reflects the period of time an event would occur post-vaccination: Over estimating the risk window would increase the "Person-Years at Risk" period and include events that are outside the actual period of time a true event would occur. Under estimating the risk window will result in reduced sensitivity making it difficult to reach statistical significance.

The O/E analyses does not account for confounding/risk factors which might be present in the cases, such as seasonal effects on the occurrence of certain events, or for example the effect of COVID which may also contribute. Also, when stratified by age/gender, there are small numbers of cases in each stratification, which should be considered when interpreting the significance of the results.

Literature

A cumulative literature search till 28 December 2022 of the databases in Embase, InsightMeme and PubMed was conducted for relevant articles on topic acute disseminated encephalomyelitis in association with VAXZEVRIA: 'acute disseminated encephalomyelitis'/exp OR 'acute disseminated encephalomyelitis' OR 'ADEM'.

The literature search resulted in 177 articles. After medical review of all the articles, 18 articles (which includes 26 cases) were considered relevant and are discussed as part of the AstraZeneca Global Patient Safety Database review. These relevant articles are as follows: Escolà et al 2022 ([redacted]); Garg et al 2022 (B) ([redacted]); Ancau et al 2022 ([redacted]); Kumar et al 2022 ([redacted]); Li et al 2022 ([redacted]); Maramattom et al 2022 ([redacted]); Mumoli et al 2021 ([redacted]); Nagaratnam et al 2022 ([redacted]); Netravathi et al 2022

[redacted]; Rinaldi et al 2022 ([redacted]); Simone et al 2021 ([redacted]); Sivji et al 2022 ([redacted]); Tapdia et al 2022 ([redacted]); Permezel et al 2022 ([redacted]); Michiles et al 2022 ([redacted]); Victor et al 2022 ([redacted]); Bastide et al 2022 ([redacted]) and an article reference that was redacted in the source document ([redacted]). A review of the remaining 159 articles did not find any new epidemiological studies concerning ADEM and VAXZEVRIA vaccination.

Mechanism of Action (MOA)

On review of the proposed mechanisms for COVID-19 vaccines, the mechanisms were discussed mainly for demyelinating events, as a whole, rather than to ADEM in particular. The various mechanisms hypothesized by the authors were:

- Molecular mimicry of viral proteins to myelin (Ismail and Salama 2022; Matsumoto et al 2022; Lee et al 2022)
- Immunological triggering or unmasking of pre-existing pathology by vaccine adjuvants, adenovirus vector, and messenger ribonucleic acid (mRNA) (acting as both antigen and adjuvant) (Ismail and Salama 2022; Lee et al 2022).
- Bystander activation eg, autoreactive lymphocytes (Fujinami et al 2006; Matsumoto et al 2022; Lee et al 2022).
- Susceptible patients (Ismail and Salama 2022, Lee et al 2022).

AstraZeneca comment for mechanisms of action

The review of mechanisms proposed by the authors suggests both vaccine-specific and patient susceptibility factors. However, no conclusive evidence linking proof of mechanism in either a mechanism-based study or further exploration of mechanism in the same case was identified. No new safety signals were identified from review of literature.

Overall comment on literature section: An updated literature review cumulatively though 28 December 2022 did not establish a definitive causal association between VAXZEVRIA and acute disseminated encephalomyelitis.

Summary

Cumulatively, a total of 83 reports of acute disseminated encephalomyelitis with the use of VAXZEVRIA have been received, and 58 of these were medically confirmed reports. All of the reported events were serious; and 05 (6.02%) had a seriousness criteria of Fatal. The case fatality rate of 6.02% is in line with previously document case fatality rates in ADEM (5% to 50%; Borlot et al 2011). The age range was 22 to 90 years with a median of 52.5 years. This

was well within the age range (19 to 61 years) mentioned by Schwarz et al 2001. Gender was reported in 81 cases, of which 44 (53.01%) cases were reported in female vaccinees suggesting no gender prevalence.

Fifty seven events occurred after 1st dose, 08 after 2nd dose and for 18 events the dose details were unknown. No events were reported after booster dose or after both dose 1 and dose 2 (recurrence).

Thirty six (43.37%) cases fulfilled BCC level 1,2 or 3. None of the cases met WHO-UMC causality criteria for Certain or Probable/Likely.

Fifty seven (68.67%) were considered as Possible, 43 (75.44%) were identified with limited information and 14 (24.56%) were identified with relevant risk/confounding factors.

Of 83 cases, there were 05 fatal cases which were assessed as [3 cases assigned causality of possible with limited information and 2 cases assigned causality of unlikely] as per WHO-UMC causality.

On review of the global safety database, no specific trend with respect to MOG antibody positive status ADEM in individuals vaccinated with VAXZEVRIA was seen.

The O/E analysis of all ADEM cases suggested that overall, the observed numbers were significantly less than the expected numbers in the 42-day risk windows. The observed numbers were greater than expected in a few sub group stratifications and may be explained by reporting bias for increased reporting of cases with a shorter risk window for the passive event reporting of rare diseases. Review of cases in these subgroups where observed numbers were above expected showed that most cases had insufficient information to make any causality assessment. AstraZeneca does not consider the trend analysis to be suggestive of increased risk due to VAXZEVRIA.

On cumulative review of the literature to 28 December 2022, there is insufficient evidence of a causal association or any conclusive mechanism leading to the development of ADEM. The review of published articles and case reports found no conclusive evidence linking proof of mechanism in either a mechanism-based study or further exploration of mechanism in the same case were identified.

Conclusion

The information from this updated cumulative review found insufficient evidence for a new or emerging signal regarding ADEM and VAXZEVRIA. No changes to the CDS or RMP are recommended. The topic 'acute disseminated encephalomyelitis' will continue to be closely monitored as part of AstraZeneca's ongoing surveillance activities for the important potential risk of nervous system disorders, including immune-mediated neurological conditions.

15.2.2 Menstrual disorders

Background

In the assessment report received from the PRAC EMA (PRAC PAR (EMEA/H/C/PSUSA/ 00010912/202206) for the VAXZEVRIA PBRER (review period: 29 December 2021 to 28 June 2022), further information on the topic of Menstrual disorders has been requested as follows:

The MAH is requested to provide and discuss an updated literature review of Menstrual disorders. Besides, the MAH is requested to further discuss the serious cases requiring hospitalization and the cases resulting in death.

AstraZeneca's response to these requests are provided in the subsections below.

Global Patient Safety Database

A cumulative search till 28 December 2022 of the AstraZeneca Global Safety Database for Menstrual disorders with VAXZEVRIA was performed using MedDRA version 25.1. The search was conducted at the level of MedDRA High Level Terms (HLTs): Menstruation and uterine bleeding NEC, Menstruation with decreased bleeding, Menstruation with increased bleeding; and MedDRA PTs: vaginal haemorrhage, uterine haemorrhage, and postmenopausal haemorrhage.

The search retrieved a total of 21651 case reports with 28063 events of Menstrual disorders. Out of 21651 cases, 423 cases with 520 events of Menstrual disorders were reported with the seriousness criteria of hospitalisation and 2 further cases with 2 events resulted in death. In 4 of 423 reports, gender was reported as male. These were considered as event coding errors upon further review of reported term and narrative. These 4 cases were received via regulatory authority and were excluded from analysis below.

Of the 419 cases with the seriousness criteria of hospitalisation, 386 (92.1%) were received from regulatory authority, 25 (6%) were spontaneous reports, 7 (1.7%) from clinical trial, and 1 (0.2%) from literature source. The two cases which resulted in death were both from regulatory authority.

The following Table 35 presents number and percentage (%) of case reports with Menstrual disorders serious cases requiring hospitalization reported after respective doses cumulatively.

Table 35 Number and percentage (%) of the case reports of Menstrual disorders serious cases requiring hospitalization reported after respective doses of VAXZEVRIA cumulatively through DLP

No. of Cases (After First Dose)	No. of Cases (After Second Dose)	No. of Cases (After both First and Second Dose)	No. of Cases (After Third Dose)
195 (46.6%)	155 (37.1%)	0	1 (0.2%)

DLP Data Lock Point

These serious case reports for Menstrual disorders requiring hospitalization were reported most frequently in the following countries: United Kingdom (270, 64.4%), Germany (36, 8.6%), Philippines (30, 7.1%), Brazil (12, 2.9%) and Italy (8, 1.9%).

The following observations were made from a review of the 419 case reports pertaining to Menstrual disorders serious cases requiring hospitalization:

- Vaccinee age was reported in 373 case reports and ranged 18 to 91 years (median: 41 years).
- A total of 77 (18.4%) case reports were medically confirmed and 342 (81.6%) were non-medically confirmed.
- A total of 28 vaccinees were pregnant at the time of reporting of menstrual disorders event; and 16 vaccinees had co-reported event of abortion.

All the reported MedDRA PTs were grouped in to 8 different menstrual disorders categories as presented in Table 36 below.

Table 36 Menstrual disorders categories

Category	MedDRA PTs
Heavy menstrual blood loss	Heavy menstrual bleeding
Less menstrual blood loss	Hypomenorrhoea
Irregular blood loss	Polymenorrhoea, Menstruation irregular
Intermenstrual blood loss	Intermenstrual bleeding
Amenorrhoea/oligomenorrhoea	Menstruation delayed, Amenorrhoea, Oligomenorrhoea
Dysmenorrhoea	Dysmenorrhoea, Premenstrual pain, Premenstrual syndrome, Menstrual discomfort
Other	Anovulatory cycle, Menstrual disorder, Menstrual headache, Vaginal haemorrhage, Uterine haemorrhage, Abnormal uterine bleeding
Postmenopausal haemorrhage	Postmenopausal haemorrhage

MedDRA Medical Dictionary for Regulatory Activities, PT Preferred Term

The distribution of the 516 events (in 419 cases) of Menstrual disorders cases requiring hospitalization, based on the Menstrual disorders categories is presented in Table 37 below in descending order of frequency:

Table 37 Distribution of events of Menstrual disorders cases requiring hospitalization based on Menstrual disorders categories and MedDRA PTs (n=516) reported with VAXZEVRIA

Menstrual disorder category MedDRA PTs	PT Count (hospitalization)
Other	**175**
Vaginal haemorrhage	109
Menstrual disorder	45
Uterine haemorrhage	14
Abnormal uterine bleeding	4
Anovulatory cycle	2
Menstrual headache	1
Heavy menstrual blood loss	**147**
Heavy menstrual bleeding	147
Amenorrhoea/oligomenorrhoea	**55**
Menstruation delayed	32
Amenorrhoea	20
Oligomenorrhoea	3
Irregular blood loss	**53**
Menstruation irregular	42
Polymenorrhoea	11
Dysmenorrhoea	**44**
Dysmenorrhoea	40
Premenstrual pain	2
Menstrual discomfort	1
Premenstrual syndrome	1
Intermenstrual blood loss	**24**
Intermenstrual bleeding	24
Postmenopausal haemorrhage	**15**
Postmenopausal haemorrhage	15
Less menstrual blood loss	**3**
Hypomenorrhoea	3

Table 37 Distribution of events of Menstrual disorders cases requiring hospitalization based on Menstrual disorders categories and MedDRA PTs (n=516) reported with VAXZEVRIA

Menstrual disorder category MedDRA PTs	PT Count (hospitalization)
Grand Total	**516**

MedDRA Medical Dictionary for Regulatory Activities, PT Preferred Term

- Out of 516 serious events requiring hospitalization, additional reported seriousness criteria were medically important event (258 [50%]), disability (115 [22.3%]), congenital anomaly (9 [1.7%]), life threatening (40 [7.7%]). An event may have met more than one criterion for seriousness.
- The menstrual disorder category of 'Other' (33.9%) was the most reported menstrual disorders category followed by Heavy menstrual blood loss (28.5%) and Amenorrhoea/oligomenorrhoea (10.7%). These 3 menstrual disorders category are discussed in detail below. Although the reported menstrual events were categorized in 8 categories, many of the reports contained multiple menstrual events and fell into multiple categories. In 335 (80%) only one menstrual disorders event was reported, in 70 reports (16.7%) 2 menstrual disorders event and in 14 (3.3%) reports 3 to 5 menstrual disorders event was reported.

Events categories by age group of Menstrual disorders serious cases requiring hospitalization are presented in below Table 38. The age group of 45-54 was the largest group (26.4%) followed by 35-44 (26%), and 25-34 (23.1%). Postmenopausal haemorrhage was reported in 55-64 (46.7%) followed by 45-54 (40%) years age group.

Table 38 Menstrual disorders category events by age group of Menstrual disorders serious cases requiring hospitalization

Menstrual disorders categories	<25 yrs N (%)	25-34 N (%)	35-44 N (%)	45-54 N (%)	55-64 N (%)	≥65 N (%)	Age unknown N (%)	Total N (%)
Other	7 (4)	44 (25.1)	38 (21.7)	43 (24.6)	11 (6.3)	18 (10.3)	14 (8)	175 (100)
Heavy menstrual blood loss	3 (2)	27 (18.4)	41 (27.9)	44 (29.9)	6 (4.1)	2 (1.4)	24 (16.3)	147 (100)
Amenorrhoea/oligomenorrhoea	8 (14.5)	17 (30.9)	12 (21.8)	11 (20)	0 (0)	0 (0)	7 (12.7)	55 (100)
Irregular blood loss	2 (3.8)	12 (22.6)	20 (37.7)	12 (22.6)	2 (3.8)	0 (0)	3 (9.4)	53 (100)

Table 38 Menstrual disorders category events by age group of Menstrual disorders serious cases requiring hospitalization

Menstrual disorders categories	<25 yrs N (%)	25-34 N (%)	35-44 N (%)	45-54 N (%)	55-64 N (%)	≥65 N (%)	Age unknown N (%)	Total N (%)
Dysmenorrhoea	5 (11.4)	14 (31.8)	12 (27.3)	10 (22.7)	0 (0)	0 (0)	3 (6.8)	44 (100)
Intermenstrual blood loss	1 (4.2)	5 (20.8)	9 (37.5)	9 (37.5)	0 (0)	0 (0)	0 (0)	24 (100)
Postmenopausal haemorrhage	0 (0)	0 (0)	1 (6.7)	6 (40)	7 (46.7)	1 (6.7)	0 (0)	15 (100)
Less menstrual blood loss	0 (0)	0 (0)	1 (33.3)	1 (33.3)	0 (0)	0 (0)	1 (33.3)	3 (100)
Grand Total	**26 (5)**	**119 (23.1)**	**134 (26)**	**136 (26.4)**	**26 (5)**	**21 (4.1)**	**54 (10.5)**	**516 (100)**

Events categories by age group of Menstrual disorders cases resulting in death are presented in below Table 39:

Table 39 Menstrual disorders category events by age group of Menstrual disorders cases resulting in death

Menstrual disorders categories	<25 yrs N (%)	25-34 N (%)	35-44 N (%)	45-54 N (%)	55-64 N (%)	≥65 N (%)	Age unknown N (%)	Total N (%)
Other	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	1 (100)
Intermenstrual blood loss	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
Grand Total	**0 (0)**	**0 (0)**	**1 (50)**	**1 (50)**	**0 (0)**	**0 (0)**	**0 (0)**	**2 (100)**

Time to onset of Menstrual disorders events and by age group of Menstrual disorders serious cases requiring hospitalization is presented in Table 40. In 5.2% of the events the time to onset after vaccination was unknown; among the events with TTO most of them (58.7%) occurred within 28 days post vaccination (0-2 days: 22.7%; 3-7 days: 14.1%; 8-14 days: 12% and 15-28 days: 9.9%).

Table 40 Time to onset for Menstrual disorders events by age group of Menstrual disorders serious cases requiring hospitalization

Menstrual disorders category/ Age group	0-2 Days N (%)	3-7 days N (%)	8-14 days N (%)	15-28 days N (%)	≥ 29 days N (%)	Unk N (%)	Grand Total N (%)
Other	40 (22.9)	16 (9.1)	24 (13.7)	11 (6.3)	68 (38.9)	16 (9.1)	175 (100)
Age - <25 Yrs	0 (0)	0 (0)	3 (42.9)	1 (14.3)	3 (42.9)	0 (0)	7 (100)
Age – 25-34 Yrs	20 (45.5)	2 (4.5)	6 (13.6)	1 (2.3)	13 (29.5)	2 (4.5)	44 (100)
Age – 35-44 Yrs	5 (13.2)	5 (13.2)	4 (10.5)	4 (10.5)	15 (39.5)	5 (13.2)	38 (100)
Age – 45-54 Yrs	9 (20.9)	6 (14)	7 (16.3)	4 (9.3)	15 (34.9)	2 (4.7)	43 (100)
Age – 55-64 Yrs	2 (18.2)	1 (9.1)	1 (9.1)	0 (0)	6 (54.5)	1 (9.1)	11 (100)
Age - ≥65 Yrs	3 (16.7)	2 (11.1)	1 (5.6)	0 (0)	11 (61.1)	1 (5.6)	18 (100)
Age Unk	1 (7.1)	0 (0)	2 (14.3)	1 (7.1)	5 (35.7)	5 (35.7)	14 (100)
Heavy menstrual blood loss	30 (20.4)	24 (16.3)	18 (12.2)	13 (8.8)	56 (38.1)	6 (4.1)	147 (100)
Age - <25 Yrs	0 (0)	1 (33.3)	0 (0)	1 (33.3)	1 (33.3)	0 (0)	3 (100)
Age – 25-34 Yrs	5 (18.5)	4 (14.8)	6 (22.2)	2 (7.4)	10 (37)	0 (0)	27 (100)
Age – 35-44 Yrs	11 (26.8)	4 (9.8)	5 (12.2)	4 (9.8)	15 (36.6)	2 (4.9)	41 (100)
Age – 45-54 Yrs	11 (25)	9 (20.5)	7 (15.9)	4 (9.1)	11 (25)	2 (4.5)	44 (100)
Age – 55-64 Yrs	0 (0)	4 (66.7)	0 (0)	0 (0)	2 (33.3)	0 (0)	6 (100)
Age - ≥65 Yrs	0 (0)	0 (0)	0 (0)	0 (0)	2 (100)	0 (0)	2 (100)
Age Unk	3 (12.5)	2 (8.3)	0 (0)	2 (8.3)	15 (62.5)	2 (8.3)	24 (100)

Table 40 Time to onset for Menstrual disorders events by age group of Menstrual disorders serious cases requiring hospitalization

Menstrual disorders category/ Age group	0-2 Days N (%)	3-7 days N (%)	8-14 days N (%)	15-28 days N (%)	≥ 29 days N (%)	Unk N (%)	Grand Total N (%)
Amenorrhoea/oligomenorrhoea	17 (30.9)	7 (12.7)	5 (9.1)	6 (10.9)	18 (32.7)	2 (3.6)	55 (100)
Age - <25 Yrs	2 (25)	3 (37.5)	0 (0)	1 (12.5)	1 (12.5)	1 (12.5)	8 (100)
Age – 25-34 Yrs	6 (35.3)	1 (5.9)	3 (17.6)	3 (17.6)	3 (17.6)	1 (5.9)	17 (100)
Age – 35-44 Yrs	4 (33.3)	1 (8.3)	0 (0)	0 (0)	7 (58.3)	0 (0)	12 (100)
Age – 45-54 Yrs	3 (27.3)	1 (9.1)	2 (18.2)	1 (9.1)	4 (36.4)	0 (0)	11 (100)
Age Unk	2 (28.6)	1 (14.3)	0 (0)	1 (14.3)	3 (42.9)	0 (0)	7 (100)
Irregular blood loss	9 (17.1)	9 (14.3)	6 (11.4)	11 (21.4)	15 (28.6)	3 (7.1)	53 (100)
Age - <25 Yrs	0 (0)	1 (50)	0 (0)	0 (0)	1 (50)	0 (0)	2 (100)
Age – 25-34 Yrs	1 (8.3)	0 (0)	1 (8.3)	3 (25)	5 (41.7)	2 (16.7)	12 (100)
Age – 35-44 Yrs	6 (30)	5 (25)	1 (5)	3 (15)	4 (20)	1 (5)	20 (100)
Age – 45-54 Yrs	1 (8.3)	2 (16.7)	4 (33.3)	1 (8.3)	4 (33.3)	0 (0)	12 (100)
Age – 55-64 Yrs	0 (0)	1 (50)	0 (0)	0 (0)	1 (50)	0 (0)	2 (100)
Age Unk	1 (20)	0 (0)	0 (0)	4 (80)	0 (0)	0 (0)	5 (100)
Dysmenorrhoea	9 (20.5)	10 (22.7)	4 (9.1)	3 (6.8)	18 (40.9)	0 (0)	44 (100)
Age - <25 Yrs	0 (0)	1 (20)	1 (20)	0 (0)	3 (60)	0 (0)	5 (100)

Table 40 Time to onset for Menstrual disorders events by age group of Menstrual disorders serious cases requiring hospitalization

Menstrual disorders category/ Age group	0-2 Days N (%)	3-7 days N (%)	8-14 days N (%)	15-28 days N (%)	≥ 29 days N (%)	Unk N (%)	Grand Total N (%)
Age – 25-34 Yrs	5 (35.7)	3 (21.4)	2 (14.3)	0 (0)	4 (28.6)	0 (0)	14 (100)
Age – 35-44 Yrs	2 (16.7)	2 (16.7)	1 (8.3)	2 (16.7)	5 (41.7)	0 (0)	12 (100)
Age – 45-54 Yrs	2 (20)	4 (40)	0 (0)	1 (10)	3 (30)	0 (0)	10 (100)
Age Unk	0 (0)	0 (0)	0 (0)	0 (0)	3 (100)	0 (0)	3 (100)
Intermenstrual blood loss	7 (29.2)	7 (29.2)	1 (4.2)	3 (12.5)	6 (25)	0 (0)	24 (100)
Age - <25 Yrs	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
Age – 25-34 Yrs	1 (20)	2 (40)	0 (0)	1 (20)	1 (20)	0 (0)	5 (100)
Age – 35-44 Yrs	1 (11.1)	1 (11.1)	1 (11.1)	1 (11.1)	5 (55.6)	0 (0)	9 (100)
Age – 45-54 Yrs	5 (55.6)	3 (33.3)	0 (0)	1 (11.1)	0 (0)	0 (0)	9 (100)
Postmenopausal haemorrhage	3 (22.2)	0 (0)	4 (22.2)	3 (22.2)	5 (33.3)	0 (0)	15 (100)
Age – 35-44 Yrs	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
Age – 45-54 Yrs	1 (16.7)	0 (0)	3 (50)	1 (16.7)	1 (16.7)	0 (0)	6 (100)
Age – 55-64 Yrs	1 (14.3)	0 (0)	1 (14.3)	2 (28.6)	3 (42.9)	0 (0)	7 (100)
Age - ≥65 Yrs	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)

Table 40 Time to onset for Menstrual disorders events by age group of Menstrual disorders serious cases requiring hospitalization

Menstrual disorders category/ Age group	0-2 Days N (%)	3-7 days N (%)	8-14 days N (%)	15-28 days N (%)	≥ 29 days N (%)	Unk N (%)	Grand Total N (%)
Less menstrual blood loss	2 (66.7)	0 (0)	0 (0)	1 (33.3)	0 (0)	0 (0)	3 (100)
Age – 35-44 Yrs	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
Age – 45-54 Yrs	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
Age Unk	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)
Grand Total	**117 (22.7)**	**73 (14.1)**	**62 (12)**	**51 (9.9)**	**186 (36)**	**27 (5.2)**	**516 (100)**

Unk Unknown, Yrs Years

Time to onset of Menstrual disorders events and by age group of Menstrual disorders cases resulting in death is presented in Table 41.

Table 41 Time to onset for Menstrual disorders events by age group of Menstrual disorders cases resulting in death

Menstrual disorders category/ Age group	0-2 Days N (%)	3-7 days N (%)	8-14 days N (%)	15-28 days N (%)	≥ 29 days N (%)	Unk N (%)	Grand Total N (%)
Other	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	1 (100)
Age – 45-54 Yrs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	1 (100)
Intermenstrual blood loss	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)
Age – 25-34 Yrs	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)
Grand Total	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**2 (100)**	**0 (0)**	**2 (100)**

Unk Unknown, Yrs Years

Other

A total of 175 (33.9% out of 516 events) 'other' Menstrual disorders category events were reported under Menstrual disorders serious cases requiring hospitalization and most of them (69.7%) were consumer reports, see Table 42. The age group of 25-34 was the largest group (25.1%) followed by 45-54 (24.6%) and 35-44 (21.7%) years. Most frequently reported MedDRA PTs was Vaginal haemorrhage (109), Menstrual disorder (45), Uterine haemorrhage (14), Abnormal uterine bleeding (4), Anovulatory cycle (2), and Menstrual headache (1). Most of the events (59.4%) were resolved/resolving/resolved with sequalae. Out of 34 events with a known duration, 24 (70.6%) had resolved within 14 days of onset, presumably within one menstrual cycle. A total of 16 of the women with cases with other menstrual disorders events where pregnant at the time of vaccination or after vaccination. In 38 (22.3%) case reports, the other Menstrual disorders were reported without any co-reported AEs. In the remaining 132 cases there were 1085 co-reported AEs along with menstrual disorder events. The events most commonly co-reported with other Menstrual disorders were headache (47, 4.3%), nausea (25, 2.3%), fatigue (25, 2.3%), pyrexia (24, 2.2%), dizziness (23, 2.1%), myalgia (17, 1.6%), pain (14, 1.3%), dyspnoea (14, 1.3%), malaise (14, 1.3%), back pain (12, 1.1%), abdominal pain (11, 1%), and chest pain (11, 1%).

Table 42 Overview of 'Other' Menstrual disorders reports after VAXZEVRIA

Other menstrual disorders	Age - <25 Yrs	Age – 25-34 Yrs	Age – 35-44 Yrs	Age – 45-54 Yrs	Age – 55-64 Yrs	Age - ≥65 Yrs	Age Unk	Grand Total
All events	7	44	38	43	11	18	14	175
Events by report type (consumer report & medically confirmed)								
Consumer report	5	27	28	36	7	12	7	122
Medically confirmed	2	17	10	7	4	6	7	53
Outcome of other Menstrual disorders events								
Not recovered	2	15	10	17	2	5	3	54
Recovered	3	15	5	11	2	6	2	44
Recovered with sequelae	0	7	3	2	0	1	1	14
Recovering	2	6	11	9	3	3	5	39
Unknown	0	1	9	4	4	3	3	24

Unk Unknown., Yrs Years.

Heavy menstrual blood loss

A total of 147 (28.5% out of 516 events) heavy menstrual blood loss events were reported under Menstrual disorders serious cases requiring hospitalization and most of them (93.2%)

were consumer reports, see Table 43. The age group of 45-54 was the largest group (29.9%) followed by 35-4 (27.9%) and 25-34 years (18.4%). Most frequently reported MedDRA Lowest Level Terms (LLT) was Heavy periods (52), followed by Heavy menstrual bleeding (22), Bleeding menstrual heavy (21), Prolonged heavy periods (15), and Menorrhagia (15). For most women the duration of the bleeding was either unknown or the woman was not recovered yet (53.1%). However, in the medically confirmed reports 50% heavy menstrual blood loss events had resolved. Out of 29 events with a known duration, 14 (48.3%) had a bleeding duration of less than 14 days. Additionally, no trend was observed in terms of concomitant medication or medical history specific to heavy menstrual blood loss events compared to overall Menstrual disorders events. In 29 (19.7%) case reports, the heavy menstrual blood loss event was reported without any co-reported AEs. In the remaining 118 cases there were 929 co-reported AEs along with Menstrual disorder events. The events most commonly co-reported with heavy menstrual blood loss event were headache (38, 4.1%), fatigue (31, 3.3%), dizziness (19, 2.1%), pyrexia (17, 1.8%), nausea (17, 1.8%), paraesthesia (15, 1.6%), anaemia (14, 1.5%), pain (13, 1.4%), vomiting (13, 1.4%), palpitations (12, 1.3%), chills (11, 1.2%), myalgia (11, 1.2%), malaise (11, 1.2%), syncope (10, 1.1%), dyspnoea (10, 1.1%), and pain in extremity (10, 1.1%).

Table 43 Overview of heavy menstrual blood loss reports after VAXZEVRIA

Heavy menstrual blood loss	Age - <25 Yrs	Age – 25-34 Yrs	Age – 35-44 Yrs	Age – 45-54 Yrs	Age – 55-64 Yrs	Age - 65+ Yrs	Age Unk	Grand Total
All events	3	27	41	44	6	2	24	147
Events by report type (consumer report & medically confirmed)								
Consumer report	3	25	38	40	6	2	23	137
Medically confirmed	0	2	3	4	0	0	1	10
Outcome of heavy menstrual blood loss events								
Not recovered	2	21	21	19	1	1	13	78
Recovered	0	1	7	6	3	1	4	22
Recovered with sequelae	1	2	5	3	1	0	3	15
Recovering	0	1	4	12	1	0	3	21
Unknown	0	2	4	4	0	0	1	11

Unk Unknown., Yrs Years.

Amenorrhoea/oligomenorrhoea

A total of 55 (10.7% out of 516 events) amenorrhoea/oligomenorrhoea events were reported under Menstrual disorders serious cases requiring hospitalization and most of them (97.2%)

were consumer reports, see Table 44. The age group of 25-34 (30.9%) was the largest followed by 35-44 (21.8%) and 45-54 years (20%). Most frequently reported MedDRA LLT was Irregular periods (23), followed by Menstrual cycle shortened (7), Menstruation irregular (7), Menstrual irregularity (6), and Frequent periods (4). For most women the duration of the bleeding was either unknown or the woman was not recovered yet (74.5%). Additionally, no trend was observed in terms of concomitant medication or medical history specific to amenorrhoea/oligomenorrhoea events compared to overall Menstrual disorders events. In 9 (16.4%) case reports, the amenorrhoea/oligomenorrhoea events were reported without any co-reported AEs. In the remaining 46 cases there were 521 co-reported AEs along with menstrual disorder events. The events most commonly co-reported with amenorrhoea/oligomenorrhoea events were fatigue (17, 3.3%), headache (15, 2.9%), chest pain (11, 2.1%), dizziness (10, 1.9%), palpitations (10, 1.9%), dyspnoea (10, 1.9%), paraesthesia (8, 1.5%), nausea (7, 1.3%), pyrexia (7, 1.3%), diarrhoea (6, 1.1%), and syncope (6, 1.1%).

Table 44 Overview of amenorrhoea/oligomenorrhoea reports after VAXZEVRIA

Amenorrhoea /oligomenorrhoea	Age - <25 Yrs	Age – 25-34 Yrs	Age – 35-44 Yrs	Age – 45-54 Yrs	Age – 55-64 Yrs	Age - 65+ Yrs	Age Unk	Grand Total
All events	8	17	12	11	0	0	7	55
Events by report type (consumer report & medically confirmed)								
Consumer report	8	16	12	10	0	0	5	51
Medically confirmed	0	1	0	1	0	0	2	4
Outcome of amenorrhoea/oligomenorrhoea events								
Not recovered	6	14	9	7	0	0	5	41
Recovered	1	1	0	3	0	0	0	5
Recovered with sequelae	1	0	0	0	1	0	0	2
Recovering	0	1	1	0	0	0	2	4
Unknown	0	1	2	0	0	0	0	3

Unk Unknown., Yrs Years.

The outcome based on the Menstrual disorders categories for serious cases requiring hospitalization has been presented in Table 45. A total of 219 events (42.4%) out of 516, had resolved/resolved with sequelae/resolving. Overall, most women had not recovered at time of reporting (246 events [47.7%]). However, in the medically confirmed reports 58% of the events were resolved/resolved with sequalae/resolving at the time of reporting.

Table 45 Outcome of the Menstrual disorders event categories for serious cases requiring hospitalization

Outcome	Not recovered N (%)	Recovered N (%)	Recovered with sequelae N (%)	Recovering N (%)	Unknown N (%)	Grand Total N (%)
Other	54 (30.9)	44 (25.1)	14 (8)	39 (22.3)	24 (13.7)	175 (100)
Heavy menstrual blood loss	78 (53.1)	22 (15)	15 (10.2)	21 (14.3)	11 (7.5)	147 (100)
Amenorrhoea/oligomenorrhoea	41 (74.5)	5 (9.1)	2 (3.6)	4 (7.3)	3 (5.5)	55 (100)
Irregular blood loss	30 (56.6)	9 (17)	3 (5.7)	6 (11.3)	5 (9.4)	53 (100)
Dysmenorrhoea	26 (59.1)	4 (9.1)	5 (11.4)	6 (13.6)	3 (6.8)	44 (100)
Intermenstrual blood loss	9 (37.5)	6 (25)	0 (0)	5 (20.8)	4 (16.7)	24 (100)
Postmenopausal haemorrhage	6 (40)	3 (20)	2 (13.3)	3 (20)	1 (6.7)	15 (100)
Less menstrual blood loss	2 (66.7)	0 (0)	1 (33.3)	0 (0)	0 (0)	3 (100)
Grand Total	**246 (47.7)**	**93 (18)**	**42 (8.1)**	**84 (16.3)**	**51 (9.9)**	**516 (100)**

N Number.

Amongst 135 events with reported outcome 'recovered' or 'recovered with sequelae,' the event duration was reported in 67 [49.6%] events. The median duration of events was 6.5 days (0-273 days), while 35 (52.2%) had resolved within 8 days of onset.

Further analysis of Menstrual disorder cases requiring hospitalization

In 419 cases, there were overall 2360 events with hospitalization.

Of these, in 86 (20.5%) out of 419 cases the Menstrual disorder event was reported without any co-reported PTs. The reason for hospitalization was attributed to the Menstrual disorder events Heavy menstrual bleeding (30), Vaginal haemorrhage (29), Menstruation irregular (8), Postmenopausal haemorrhage (6), Menstrual disorder (6), Menstruation delayed (5), Dysmenorrhoea (4), Amenorrhoea (4), Intermenstrual bleeding (3), Uterine haemorrhage (2), Abnormal uterine bleeding (2), Polymenorrhoea (2), Anovulatory cycle (1), and Oligomenorrhoea (1). The median age in these cases was 44 years. In 39 (45.3%) cases, the patient age was reported as 44 years or more. The post-menopausal age group presents as a confounder to the haemorrhage events reported. In remaining 47 cases, 7 cases reported confounders for Menstrual disorders in medical history and/or concomitant medications. The

remaining cases presented insufficient information pertaining to clinical course of events, platelet count, and blood coagulation profile.

In the remaining 333 (79.5%) cases, there were 2522 co-reported AEs along with Menstrual disorder events. The most commonly co-reported events which caused hospitalization included Headache (101, 4.8%), Fatigue (77, 3.7%), Pyrexia (58, 2.8%), Dizziness (57, 2.7%), Nausea (46, 2.2%), Dyspnoea (38, 1.8%), Pain (35, 1.7%), Malaise (33, 1.6%), Myalgia (32, 1.5%), and Palpitations (30, 1.4%). In 57 out of 333 cases, the cases reported confounders for Menstrual disorders in medical history and/or concomitant medications. The remaining cases contained insufficient information on exact reason for hospitalization, if any treatments were provided, clinical course of events, medical history, and/or concomitant medications. A further review was performed of the medically confirmed case reports requiring hospitalization for Menstrual disorders and the following observations were made:

- There were 77 medically confirmed case reports requiring hospitalization. The TTO median in these cases was 29.5 days
- Of the 77 medically confirmed case reports requiring hospitalization, 25 cases reported confounders for Menstrual disorders in medical history and/or concomitant medications. Of the remaining 52 case reports, no menstrual history was reported.
- Of the 52 case reports, in 32 (61.5%) reports the reason for hospitalization was attributed to the event vaginal haemorrhage. Of these 32, 20 reports included 60 co-reported AEs and the remaining 12 reports did not include any co-reported AEs. The most commonly co-reported AEs with vaginal haemorrhage are headache (5, 7.6%), vaccination site pain (4, 6.1%), pain (3, 4.6%), exposure during pregnancy (3, 4.6%), abortion (3, 4.6%), pyrexia (3, 4.6%), myalgia (2, 3%), back pain (2, 3%), cough (2, 3%), and abdominal pain lower (2, 3%).
- Of the 52 case reports, in 3 (5.8%) reports treatment details were provided. In two of these reports, the treatment details (hydration, blood transfusion) potentially explained course of treatment for menstrual disorder event (vaginal haemorrhage, and heavy menstrual bleeding). Of the remaining case, on further analysis alternative cause of hospitalization was noted: appendicectomy.
- The median age in the 52 case reports was 35 years.
- Of the 52 case reports, 37 (71.1%) had reported outcome recovered/recovering/recovered with sequelae. Event duration was reported in 7 (13.5%) out of 52 cases. The median duration of events was 4 days (1-30 days), while 5 (71.4%) had resolved within 8 days of onset.
- In 15 (28.8%) out of 52 case reports, the menstrual disorder event was reported without any co-reported AEs. In the remaining 37 cases there were 173 co-reported AEs along with menstrual disorder events. The most commonly co-reported AEs with Menstrual disorders are presented in Table 46 and the most co-reported AEs were systemic AEs such as pyrexia, headache, myalgia, nausea, and pain.
- A review of the medically confirmed cases requiring hospitalization with complete case details was performed and no index case was found. All cases listed confounders or had

insufficient information such as treatment details, medical history and/or concomitant medications.

Table 46 Distribution of most frequently co-reported events (n > 1) in Menstrual disorders medically confirmed cases requiring hospitalization

Adverse events (PT)	Number of events	Percentage (%)
Pyrexia	9	5.2
Headache	8	4.6
Myalgia	5	2.9
Dyspnoea	4	2.3
Fatigue	4	2.3
Exposure during pregnancy	4	2.3
Vaccination site pain	4	2.3
Nausea	4	2.3
Abortion	3	1.7
Pain	3	1.7
Dizziness	3	1.7
Palpitations	3	1.7
Abnormal uterine bleeding	3	1.7
Thrombocytopenia	3	1.7
Back pain	2	1.1
Chest pain	2	1.1
Impaired work ability	2	1.1
Vomiting	2	1.1
Diarrhoea	2	1.1
Abdominal pain lower	2	1.1
COVID-19 immunisation	2	1.1
Arthralgia	2	1.1
Nasopharyngitis	2	1.1
Cough	2	1.1
Asthenia	2	1.1
Ecchymosis	2	1.1

PT Preferred Term

Events with fatal outcome

Of the 28063 events of Menstrual disorders reported, 2 events (0.01%) in 2 cases were reported with fatal outcome cumulatively through DLP 28 December 2022, and both were consumer reports.

[redacted]: A 47 years old vaccinee with a medical history of asthma received VAXZEVRIA on an unknown date. At an unspecified time after vaccination, the vaccinee experienced pulmonary embolism and menstrual disorder (unspecified type) which had a fatal outcome. Menstrual disorder was reported with no time to onset and with limited information.

AstraZeneca Comment: This report lacks information on the nature of the menstrual disorder, patient medical history including menstrual history, contraceptives or intrauterine devices used, platelet count, smoking, immobilisation and baseline health condition before the vaccination, etiological, diagnostic work up (clotting factors, coagulation panel, CT-angiogram, chest x-ray and CT-scan, full gynaecologic work up) and autopsy report. Death was attributed to pulmonary embolism and menstrual disorder and the TTO is not provided.

[redacted]: Female vaccinee of 41 years of age with a history of diabetes had been vaccinated with VAXZEVRIA in February 2022. On 11 March 2022, approximately a month after receiving VAXZEVRIA, the patient experienced intermenstrual bleeding reported as spotting for one month, subsequently followed by blood clots in an unspecified site and died. The patient's previous history of any blood disorders is unknown. The other reported events included fatigue and abdominal pain. The cause of death was intermenstrual bleeding and thrombosis.

AstraZeneca Comment: There is limited information about the vaccinee's medical history including menstrual history, use of hormonal preparations such as contraceptives, smoking, baseline health status site of thrombosis, platelet count, anti-PF4, contraceptives, which precludes performing a complete assessment. An autopsy was not performed.

Recurrence case reports

There were no serious cases requiring hospitalization indicating a recurrence.

Literature

A cumulative literature search of the databases in Embase, InsightMeme and PubMed was conducted for relevant articles on the topic in association with VAXZEVRIA. Menstrual/Menstru*/anovul*/dysmenorrhoea/"uterine bleeding"/ vaginal haemorrhage, uterine haemorrhage and postmenopausal haemorrhage/*menorrhoea*/menorrhagia. These were derived from HLTs (MedDRA (Version 25.1) HLTs were: Menstruation and uterine bleeding NEC, Menstruation with decreased bleeding, Menstruation with increased bleeding; and MedDRA PTs: vaginal haemorrhage, uterine haemorrhage and postmenopausal).

The search yielded 190 articles of which 11 articles were considered relevant for further evaluation and presentation. All the articles considered multiple COVID-vaccines.

Edelman et al 2022 conducted a global, retrospective cohort analysis of prospectively collected menstrual cycle data among individuals who use the digital fertility awareness application. Authors report more than a quarter of a million menstrual cycles recorded by 19622 individuals aged 18-45 years with cycle lengths of 24-38 days and consecutive data for at least three cycles before, one cycle after COVID (vaccinated group; n=14936) and those with at least four consecutive cycles over a similar time period (unvaccinated group; n=4686). Two thirds (9929 (66.48%) of 14 936) of the vaccinated cohort received the Pfizer-BioNTech (BNT162b2) COVID-19 vaccine, 17.46% (n=2608) received Moderna (mRNA-1273), 9.06% (n=1353) received Oxford-ASTRAZENECA (ChAdOx1 nCoV-19) and 1.89% (n=283) received Johnson & Johnson (Ad26.COV2.S). Compared with the unvaccinated group, vaccinated individuals had an adjusted increase in menstrual cycle length of less than one day with both first and second vaccine doses. Individuals who received two doses of a COVID-19 vaccine in a single cycle had an adjusted increase in cycle length of 3.70 days compared with the unvaccinated. Additionally, a significant increase was noted in the proportion of respondents who had an increase in cycle length of more than eight days (13.5%, compared with 5.0% in the unvaccinated cohort). Cycle length changes did not remain in the cycle after vaccination, except in the group that received two vaccine doses in one cycle, where cycle length changes were attenuated but still increased compared with the unvaccinated group. Cycle length changes due to COVID-19 vaccination appear similar across the different vaccine types. Authors found no differences in menses length in any group of vaccinated individuals, compared with the unvaccinated cohort.

AstraZeneca comment: Study concluded that COVID-19 vaccination is associated with a small and likely to be temporary change in menstrual cycle length but no change in menses length. The inclusion of an unvaccinated comparison group gives a comparator. The study had a large sample size but, this was a prospective cohort study among users of a digital app and may not be representative of all menstruating women. The percentage of women vaccinated with ASTRAZENECA vaccine is relatively small at 9.06%. Data analysis for individual vaccines is not mentioned. Potential effect of COVID-19 infections has not been assessed.

Dellino et al 2022 conducted the first retrospective study on Italian patients vaccinated for SARS-CoV-2 in the period between April 2021 and April 2022, to report the onset of menstrual changes after the vaccine in order to understand: etiology, duration of possible adverse effects and the extent of the phenomenon. Authors recruited 100 women aged 18–45, vaccinated for SARS-CoV-2, who were asked to complete a questionnaire. Authors excluded patients in menopause, immune-depressed, pregnant, affected by oncological diseases or by previously recognized gynecological pathologies (fibromatosis or endometrial and ovarian anomalies, polycystic ovary syndrome), in therapy with corticosteroids or contraceptives, or

who had ongoing vaccines for Human Papillomavirus (HPV) or other vaccine prophylaxis. Forty-three (43%) participants received Pfizer/ BioNTech mRNA vaccine, 32% received Moderna mRNA vaccine and 25 % received the ASTRAZENECA recombinant viral vector vaccine. The average onset of menstrual irregularity was 13 days (1–18) from inoculation of the vaccine. Of these, 90% were after the second dose and 10% were after the third dose for an average duration of 45.5 days; 15% of the total of these women reported irregularities already after the first dose of vaccine, which reappeared after the second/third dose. Twenty-three (23%) had menstrual delay and 77% had abnormal uterine bleeding (AUB), of which 47% had metrorrhagia, 30% had menometrorrhagia and 23% had menorrhagia. For AUB the highest numbers are with ASTRAZENECA vaccine, while for delayed menstruation the numbers are less than with other vaccines. The authors reported the incidence with the general population of menstrual irregularities in women of childbearing age (in the absence of organic gynecological pathology, for which an unknown or dysfunctional problem is attributable), in which menstrual irregularities occur in an estimated 14% to 25% of women of childbearing age. Authors conclude that these are preliminary data that need further investigation.

AstraZeneca comment: The study can lend itself to bias due to retrospective collection. There was no control group. The authors have not attributed causality. They mention that the data is preliminary and further investigation is needed.

The below study found no significant association of menstrual cycle changes with COVID vaccination:

Abdel -Moneim et al 2022 conducted a questionnaire-based study in Saudi Arabia on 956 women, aged from 18 to 40 years old, to screen females who have been infected with SARS-CoV-2, regardless of their vaccinal status. Sixty-nine did not get the COVID-19 vaccine, while the remaining were vaccinated with either a single dose of ChAdOx1 vaccine (n:45) or BNT162b2 vaccine (n: 142) or two doses of the vaccine (n:700) using BNT162b2 (n:477), ChAdOx1 (n:89) or ChAdOx1/ BNT162b2 (n:134). Most respondents did not suffer from any menstrual cycle change (724/956, 75.7%) and the remaining (232/956, 24.3%) reported changes, which lasted from two to more than six months. Delayed menstrual cycle was the highest in females aged 18–20 years (42/214, 19.6%) and excessive bleeding was higher in age groups 21–30 (19/520, 3.7%) and 31–40 (7/222, 3.2%) compared to the 18 to 20-year-old group (2/214, 0.9%). Extended menstrual cycle was the highest in the 31 to 40-year-old group. The current study did not find any significant variation when using different vaccines with single or double doses. Authors conclude that there is no association between COVID-19 vaccination and the development of menstrual cycle changes. Authors propose that SARS-CoV-2 infection might be responsible for extending menstrual changes beyond six months, as detected in the current study.

AstraZeneca comment: This study found an association of menstrual cycle changes with SARS-CoV-2 infection but not COVID-19 vaccination. This study had a comparator group of unvaccinated women. This study included ASTRAZENECA vaccine, but the sample size was small. Being a questionnaire-based study, it is prone for recall and sampling bias.

Review of hypothesized mechanisms cumulatively through 28 December 2022

The proposed mechanisms from published literature are provided below:

Roncati et al 2022 propose that after vaccination, a hypercoagulative state may rarely occur and involve fenestrated capillaries in the pituitary, where the blood flow is significantly decelerated. The pre-existing interconnected small branches and the trans-sellar arterial blood supply usually are sufficient collaterals, but sometimes they could be inadequate to the high blood demand from the pituitary gland, thus promoting the onset of micro ischemic events and subsequent menstrual abnormalities.

Kurdoglu 2021 proposes that vaccine-induced thrombocytopenia, immune system activation, stress, anxiety, and depression during the pandemic could be possible mechanisms for menstrual disorders.

Wang et al 2022 [D] The immune response induced by both mRNA and adenovirus-vectored vaccines may temporarily affect the hypothalamo-pituitary-ovarian (HPO) axis, which could lead to menstrual disturbances.

Caspersen et al 2023 and Farland et al 2022 propose the effect of immune response activation on menstrual cycle driving hormone as an explanation of menstrual changes. The pathophysiological mechanisms are yet unknown.

Farland et al 2022 additionally propose that changes in their menstrual cycle following VAXZEVRIA vaccination, may be due to normal menstrual cycle variability observed in the general population. Authors mention several hypothesized mechanisms through which vaccinations may influence menstrual cycles, including inflammation, endogenous hormone levels, and/or immune cells in the endometrium.

No conclusive mechanism has been identified.

Summary of case reports

Cumulatively, a total of 419 reports of Menstrual disorders serious cases requiring hospitalization with the use of VAXZEVRIA have been received, and 2 cases resulting in death. The median age was 41 years for Menstrual disorders serious cases requiring hospitalization and 44 years for cases resulting in death.

A total 195 cases of Menstrual disorders serious cases requiring hospitalization occurred after first dose, 155 after second dose, and one case after booster dose. Amongst 125 events with reported outcome 'recovered' or 'recovered with sequelae,' the event duration was reported in 72 [57.6%] events. The median duration of events was 7 days (0-273 days), while 39 (54.1%) had resolved within 8 days of onset. Of the total number of case reports cumulatively of Menstrual disorders serious cases requiring hospitalization, 77 (18.4%) were medically confirmed.

The TTO median was 16 days and among the events with TTO most of them (58.7%) occurred within 28 days post vaccination. Most of events (54.6%) were reported in age groups 45-54 (26.4%), 35-44 (26%), and 25-34 (23.1%).

The most reported menstrual disorders category was 'other' followed by heavy menstrual blood loss, and amenorrhoea/oligomenorrhoea. Menstrual disorders can be very diverse and different per individual. Although the reported menstrual events were categorised in 8 categories, many of the reports contained multiple menstrual events and fell into multiple categories.

The most frequent co-reported AEs were known systemic and local reactions. These are very common reactions and were to be expected.

A total 47.7% of menstrual disorder events had not resolved at the time of reporting. It is possible that, women reported their complaints before they fully recovered which is understandable since menstrual disorders such as amenorrhoea and irregular menstrual cycle generally can take a longer time to recover.

From the review of the medically confirmed cases requiring hospitalization with complete case details, no index case was found. All cases listed confounders or had insufficient information such as treatment details, medical history and/or concomitant medications.

Literature summary

As pointed out in Von Woon et al 2022, Lagana et al 2022, Muhaidat et al 2022, Wang et al 2022 [D], Dellino et al 2022, Edelman et al 2022, Caspersen et al 2023, Trogstad et al 2022, Farland et al 2022,Qashqari et al 2022, Molina -López et al 2022, Zhang et al 2022 articles, there seems to be an association between COVID-19 vaccination (regardless of type) and menstrual disorders. Overall, the abnormalities were self-limiting. The study by Abdel - Moneim et al 2022 found that there was no association between menstrual disorders and vaccination.

Many of the literature available recommended future work to examine the potential biological mechanisms that may explain an association between COVID-19 vaccination and menstrual

disorders. Some authors propose the effect of immune response activation on menstrual cycle, systemic inflammatory response, stress, impact on HPO axis, hypercoagulative state and vaccine-induced thrombocytopenia.as an explanation of menstrual changes. The design of most studies reviewed did not consider control groups, hence it is impossible to make causal inferences from them. The actual incidence rate of menstrual disorders with COVID-19 vaccination is still unclear due to problems of overestimating, underestimating and biases. However, there seem to be more calls for studies designed particularly to aid the determination of causal inference and also confirm biologic mechanisms that will adequately explain the effects of COVID vaccination on menstrual disorders.

Overall Summary

Upon further review of the serious cases requiring hospitalization and the cases resulting in death, there was insufficient information on menstrual history, investigations performed, and treatment details available in these reports. These findings do not provide more insight on the possible relationship between VAXZEVRIA and menstrual disorders.

From the review of the literature, many of the literature available recommended future work to examine the hypothesized biological mechanisms that may explain an association between COVID-19 vaccination and menstrual disorders.

In summary, the review of available data from spontaneous reports and literature did not identify an index case or other evidence of a new or emerging signal.

Conclusion

The information from this updated cumulative review found insufficient evidence for a new or emerging signal regarding Menstrual disorders and VAXZEVRIA. No changes to the CDS or RMP are recommended, and Menstrual disorders will continue to be monitored as part of AstraZeneca's ongoing surveillance activities.

15.2.3 Glomerulonephritis (GN) and nephrotic syndrome including IgA nephropathy

In the assessment report received from the PRAC EMA (PRAC PAR EMEA/H/C/PSUSA/00010912/202206) for the VAXZEVRIA PBRER (review period 29 December 2021 – 28 June 2022), further information on the topic of Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy) is requested from AstraZeneca as follows:

The MAH is requested to further search for literature on GN/SN following COVID-19 vaccination, with a special focus to Adeno-vectored vaccines, relapse and flare up, and measured kidney alterations after vaccination.

Literature review strategy

In line with PRAC's request, a cumulative literature search for the approved COVID-19 vaccines, in the databases - Embase, InsightMeme and PubMed was conducted using the following search terms:

Alagille syndrome, Alport's syndrome, Anti-glomerular basement membrane disease, Anti-LRP2 nephropathy, Benign familial haematuria, C1q nephropathy, C3 glomerulopathy, Chronic autoimmune glomerulonephritis, Congenital nephrotic syndrome, Denys-Drash syndrome, Fibrillary glomerulonephritis, Focal segmental glomerulosclerosis, Frasier syndrome, Glomerulonephritis, Glomerulonephritis acute, Glomerulonephritis chronic, Glomerulonephritis membranoproliferative, Glomerulonephritis membranous, Glomerulonephritis minimal lesion, Glomerulonephritis proliferative, Glomerulonephritis rapidly progressive, Goodpasture's syndrome, Granulomatosis with polyangiitis, Henoch-Schönlein purpura nephritis, Hepatitis virus-associated nephropathy, HIV associated nephropathy, IgA nephropathy, IgM nephropathy, Immunotactoid glomerulonephritis, Membranous-like glomerulopathy with masked IgG-kappa deposits, Mesangiolipidosis, Mesangioproliferative glomerulonephritis, Microscopic polyangiitis, Nephritic syndrome, Nephritis allergic, Nephrotic syndrome, Paraneoplastic glomerulonephritis, Paraneoplastic nephrotic syndrome, Post infection glomerulonephritis, Post streptococcal glomerulonephritis, Primary coenzyme Q10 deficiency, Pulmonary renal syndrome.

Search results:

The cumulative search for literature case reports published in peer-reviewed journals with special focus to Adeno-vectored vaccines was done and identified a total of 221 relevant abstracts comprising 75 published case reports / series, and 63 conference abstracts (with limited study details such as baseline characteristics, full statistical analysis plan). Three relevant articles including systematic review and retrospective studies, are summarized in below:

Literature case reports with special focus to Adeno-vectored vaccines

A further review of complete manuscripts of literature case reports published in peer-reviewed journals with a special focus to Adeno-vectored vaccines was done. A total of 29 literature case reports in 16 articles were received for adenovector vaccines (27 for VAXZEVRIA in Table 47 and 2 for Janssen vaccine in Table 48).

Table 47 and Table 48 includes cases reported in literature until 28 December 2022 and includes MCD (5), IgAN (3), Collapsing glomerulopathy (CG) (2), ANCA associated vasculitis (Glomerulonephritis rapidly progressive) (2), IgA vasculitis with nephritis (2), Acute crescentic pauci-immune glomerulonephritis (1), Acute interstitial nephritis (AIN) (1),

AKI and C3 Glomerulonephritis (1), Chronic kidney disease with acute glomerulonephritis (1), Focal class of ANCA-associated pauci-immune glomerulonephritis (1), Focal segmental glomerulosclerosis (FSGS) (1), Glomerulonephritis (1), Glomerulonephritis minimal lesion (1), Immunoglobulin-mediated Membranoproliferative Glomerulonephritis (MPGN) (1), MCD and acute tubular injury (1), Membranous Nephropathy (MN) (1), Mesangial proliferative variant of minimal change disease (MCD) (1), MPGN (1), Pauci-immune crescentic glomerulonephritis (1), Rapid progressive glomerulonephritis and high MPO-ANCA antibody titer (1).

Table 47 Summary of literature case reports with special focus to adeno-vectored VAXZEVRIA vaccine

Authors / Age /Gender/ Country	Clinical features	Final diagnosis	Time to onset (in days) / Dose number	New onset / Relapse / Worsening / Recurrence	Previous medical history	Outcome	AZ Assessment as per WHO-UMC causality scale
Leclerc et al 2021/71 / M / [redacted]	New onset hypertension, edema	MCD	13 / Dose 1	New onset	Dyslipidaemia treated with rosuvastatin, 20 mg daily	Resolved	Possible with limited information
	Laboratory data: Clinical features included anasarca, dyselectorelia (K+, Mg+++). Vaccinee underwent to CT scan and abdominal USG, ruling out infections and neoplasm, PCR for COVID-19 was negative, HIV and Hepatitis B and C were negative. However, one day after admission, with the presence of AKI, proteinuria, hematuria, edema, and hypertension. Kidney biopsy reported acute tubular injury, diffuse podocyte foot process effacement, mononuclear infiltration, and chronic changes. Immunofluorescence for immunoglobulin A (IgA), IgG, IgM, κ and λ light chain, C3, C1q, fibrin, and albumin was performed on 10 glomeruli and did not show any specific glomerular staining. The event was managed with steroids and haemodialysis.						
	AstraZeneca comment: Hypertension and edema can be attributed to nephrogenic origin considering concurrence in presentation and concurrence in progression. Temporal plausibility to onset of symptoms (hypertension, edema) next day of 1st vaccination dose is considered less reasonable. There was insufficient information on any insult in the peri-vaccination period. No investigative correlation was available at this time point as the patient had been evaluated only after 12 days. No information on concomitant medications. Thus, the WHO-UMC causality is considered Possible with limited information. Atypical MCD presentation with acute tubular injury point to a possible multi-factorial etiology.						
Biradar et al 2022/22/M/India	Yellowish discoloration of urine, periorbital and bilateral lower limb swelling	MCD	11 / Dose 1	New onset	Unknown	Resolved	Possible with limited information

Table 47 Summary of literature case reports with special focus to adeno-vectored VAXZEVRIA vaccine

Authors / Age /Gender/ Country	Clinical features	Final diagnosis	Time to onset (in days) / Dose number	New onset / Relapse / Worsening / Recurrence	Previous medical history	Outcome	AZ Assessment as per WHO-UMC causality scale
	Laboratory data: Pre-vaccination laboratory as renal function test and urine analysis, normal. Systemic examination was unremarkable. Relevant laboratory included hypercholesterolemia (401 mg/dL) and triglyceridemia (193 mg/dL). RT-PCR for COVID-19 was negative, but IgG antibodies to Spike (S) protein was positive. Renal biopsy revealed 1 out of 15 glomeruli is globally sclerosed, while all other glomeruli appear largely unremarkable; these findings were consistent with MCD. The vaccinee started on tablet prednisolone 1 mg/kg/day dose and on follow-up after 1 week achieved biochemical remission of renal parameters.						
	AstraZeneca Comment: Presentation of yellowish discoloration of urine after 1 week and sudden onset of periorbital and bilateral lower limb swelling after 11 days following 1st dose of VAXZEVRIA in a 22-year-old male vaccinee. Previous normal renal function test and urine analysis. Systemic examination was unremarkable. Relevant laboratory findings of hypercholesterolemia (401 mg/dL) and triglyceridemia (193 mg/dL). RT-PCR testing for was negative for SARS-CoV-2 IgG. IgG antibodies to Spike (S) protein was positive. On renal biopsy 1 out of 15 glomeruli is globally sclerosed, while all other glomeruli appear largely unremarkable. Tubules, interstitium and blood vessels appear largely unremarkable. Immunofluorescence for IgA, IgG, IgM, C3, C1q and Kappa, Lambda are negative. As per the reporter, these findings were consistent with MCD. The patient was started on tablet prednisolone 1 mg/kg/day dose and on follow-up after 1 week achieved biochemical remission of renal parameters. TTO of MCD to vaccine administration is reasonable. Relevant renal markers for complement or humoral immunity were normal. No evidence of T cell immune damage was reported in renal biopsy. Dyslipidaemia may have a cause-and-effect relationship to MCD/nephrotic syndrome, however, to assess further, no information on relevant past history, family history or further monitoring. Although case had limited information, the causality is assessed as Possible based on temporal association						
Caza et al 2021/1/23/M Unk	Unknown	MCD	14 / Dose 1	New onset	Unknown	Resolved	Possible with confounders / risk factors
	Laboratory data: Creatinine 2.9, Proteinuria 14, Albumin 1.7, Hematuria positive, ANA positive, ANCA positive, Kidney biopsy reported acute tubular injury and severe foot process effacement. Immunofluorescence was not staining.						

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Authors / Age /Gender/ Country	Clinical features	Final diagnosis	Time to onset (in days) / Dose number	New onset / Relapse / Worsening / Recurrence	Previous medical history	Outcome	AZ Assessment as per WHO-UMC causality scale
	AstraZeneca comment: Time to onset with VAXZEVRIA is reasonable. ANA positivity may suggest an autoimmune association. Still, there was insufficient information on medical history, concomitant medications, and etiological workup.						
Anupama et al 2021 /19 / F / [redacted]	Generalized edema	Mesangial proliferative variant of minimal change disease	8 / Dose 1	New onset	Unknown	Resolved	Possible with confounders / risk factors
	Laboratory data: Blood tests revealed serum creatinine, 1.09 mg/dl; albumin, 2.15 g/dl; and total cholesterol, 274 mg/dl; High urine protein creatinine ratio, of 3.18 g/g. Kidney biopsy revealed global mesangial cell proliferation on light microscopy, with mesangial trapping of immunoglobulin M and C3. Vaccinee was treated with prednisone 1 mg/kg body weight.						
	AstraZeneca Comment: Presenting symptom of generalized body swelling, which started 8 days after the first dose of the COVID-19 vaccination. Additional evaluation (unspecified) for secondary causes was negative. Kidney biopsy results revealed global mesangial cell proliferation on light microscopy. There was mesangial trapping of immunoglobulin M (IgM and C3). A diagnosis of a mesangial proliferative variant of minimal change disease was made. Significant non-renal finding of hypercholesterolemia. The patient responded to oral prednisone 1 mg/kg body weight with clinical and biochemical remission. TTO of nephrotic symptoms within 8 days of Dose 1 of VAXZEVRIA is considered reasonable in this 19-years old female patient. However, on etiological workup a hypercholesterolemia was seen. Dyslipidaemia may have a cause-and-effect relationship to MCD/nephrotic syndrome, however, to assess further, no information on relevant past history, vaccination history, family history or further monitoring.						
Timmermans et al 2022/ 64 / F / [redacted]	Nephrotic syndrome	Glomerulonephritis minimal lesion	7 / Dose 1 Unk / Dose 2	New onset	Unknown	Resolved	Possible with limited information

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	Laboratory data: Serum creatinine 0.8, Serum albumin 11.8, Urine protein 6.9.						
	AstraZeneca comment: TTO of MCD within 1 week after VAXZEVRIA. Patient was started on prednisolone on an unknown date and prednisolone was postponed at the time of 2nd vaccine dose. Recurrent edema after the second dose. Thus, recurrence is confounded by prednisolone interruption. On etiological work-up, drugs and malignancies were ruled out. However, there was insufficient information on exclusion of infections (especially COVID-19) and on patient's medical history for a comprehensive causal assessment.						
Chandra et al 2022/72/F[redacted]	Foamy urine and peripheral edema	MCD and acute tubular injury	14 / Dose 1	New onset	Hypertension, Obesity and Dyslipidaemia	Resolved	Possible with confounders / risk factors
	Laboratory data: Elevated creatinine 1.8 mg/dL, serum albumin 1.5 g/dL, high cholesterol (326 mg/dL) and triglyceride levels (161 mg/dL); proteinuria (1,000 mg/dL) with unremarkable urine sediment, 24-hour urinary protein was 5.2 g; renal ultrasound suggested normal-sized kidneys with regular shape without hydronephrosis; kidney biopsy showed 12 glomeruli: light microscopy was without apparent abnormalities in all glomeruli, interstitium showed small lymphocytic infiltrates, and there was acute tubular injury. Immunofluorescence revealed mild glomerular deposits of IgM (+). EM showed diffuse podocyte foot process effacement. Vaccinee received treatment with high dose of steroids						
	AstraZeneca comment: Presenting features of foamy urine and peripheral edema 14 days after VAXZEVRIA (dose 1). No joint pains, fever, cough, haemoptysis, hematuria, or frothy urine reported. Elevated creatinine 1.8 mg/dL, serum albumin 1.5 g/dL, high cholesterol (326 mg/dL) and triglyceride levels (161 mg/dL); proteinuria (1,000 mg/dL) with unremarkable urine sediment, 24-hour urinary protein was 5.2 g; renal ultrasound suggested normal-sized kidneys with regular shape without hydronephrosis; kidney biopsy showed 12 glomeruli: light microscopy was without apparent abnormalities in all glomeruli, interstitium showed small lymphocytic infiltrates, and there was acute tubular injury. IF revealed mild glomerular deposits of IgM (+). EM showed diffuse podocyte foot process effacement. The TTO is considered reasonable, however, hypertension, obesity, and dyslipidaemia are possible confounders.						

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Krishna et al 2022 / 24 / M / [redacted]	abrupt-onset puffiness of the face followed by edema in both lower extremities 2 days post vaccination dose 1	MCD	2 / Dose 1	New onset	Unknown	Recovered	Possible with limited information
	Laboratory data: Proteinuria 4+, severe hypoalbuminemia (serum albumin 1.7 mg/dl), bland urinary sediment, 24-h urinary protein 4100 mg/day, serum total cholesterol 706 mg/dL, albumin level 1.7 g/dL, haemoglobin 13.6 g/dL, and creatinine level 0.86 mg/dL. Antistreptolysin O antibodies and complements C3 and C4 levels were within the normal range, and hepatitis B surface antigen, hepatitis C antibody, and HIV antibody were negative. USG - ascites, normal kidney anatomy. RT-PCR for SARS-CoV-2 was negative. IgG antibodies against the spike protein of SARS-CoV-2 was 554 Au/mL. Renal biopsy - consistent with MCD						
	AstraZeneca comment: Presenting features of abrupt-onset puffiness of the face followed by edema in both lower extremities 2 days post vaccination dose 1 in a 24-year-old male, which gradually progressed to anasarca (over the next 7 days). It was reported that the vaccinee had no comorbidities. Biopsy confirmed MCD. Treatment with corticosteroid therapy resulted in ongoing clinical and biochemical resolution in 7 days. TTO of symptom onset in 2 days to dose 1 of vaccination is considered short for a de novo pathology. There was insufficient information on etiologic workup on autoimmune, neoplastic conditions, family history and childhood vaccination history. The WHO-UMC causality is considered possible with limited information.						
Gautam et al 2022 / 21 / M / [redacted]	Anasarca, frothuria and oliguria	MCD	13 / Dose 2	New onset	Unknown	Recovered	Possible with limited information

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	Laboratory data: urine protein of 4+ and no RBCs, serum albumin of 1.9, serum creatinine of 1.9, increased LDL cholesterol, increased triglycerides Renal biopsy (3 weeks after vaccine dose 2) - No significant findings on glomeruli and on any chronic parenchymal damage. Tubules showed protein reabsorption granules and mild acute tubular injury. Immunofluorescence showed fine granular scattered deposits of IgG.						
	AstraZeneca comment: Presenting features of anasarca, frothuria and oliguria about 10 days post vaccination dose 2 in a 19-year-old male with no comorbidities. This was preceded by fever (sudden onset, intermittent, high grade without chills) on 3rd day post dose 2. No similar complaints after dose 1 which was received 12 weeks prior. Renal biopsy suggested minimal change in glomeruli and mild acute tubular injury. There was IgG deposits on DIF (direct immunofluorescence). A diagnosis of MCD was made and treatment with oral prednisolone at 60 mg/day and furosemide was started with complete remission after a month. TTO is considered reasonable (WHO-UMC causality Possible), however, there was insufficient information on etiologic workup (autoimmune, neoplastic), childhood vaccination history, family history in the backdrop of no similar complaints after vaccination dose 1 for a comprehensive assessment.						
Villa et al 2021/ 63 / M/[redacted]	Haemoptysis	Focal class of ANCA-associated pauci-immune glomerulonephritis	7 / Dose 1	New onset	Unknown	Resolved	Possible with confounders / risk factors
	Laboratory data: Concomitant medications included acetaminophen and acetylsalicylic acid therapy. Laboratory data reported high creatinine levels with proteinuria and mild hematuria; COVID-19 test negative, pANCA positive, as well, during chest x-ray, an infiltration in the left lower lung field was noted; kidney biopsy revealed focal extracapillary proliferation and crescent formation. Vaccinee was treated with high dose of glucocorticoids, followed by a tapering course of oral prednisone reduction and oral cyclophosphamide.						

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	AstraZeneca Comment: Presenting feature of 3 episodes of haemoptysis 7 days after his first dose of VAXZEVRIA. Concomitant acetaminophen and acetylsalicylic acid therapy. Radiologic picture of left lower lung field infiltration. SARS-CoV-2 were negative. Antimyeloperoxidase antibodies (pANCA) were positive (12 UI/ml). ANCA-associated pauci-immune glomerulonephritis on biopsy. Treatment for ANCA-associated vasculitis was initiated high-dose i.v. glucocorticoids with resolution of events. No antibody response to the SARS-CoV-2 spike protein seen 2 months after the first AZD1222 vaccine. TTO is reasonable. Although concomitant acetaminophen and acetylsalicylic acid therapy are possible confounders, any action taken with these medications was not reported. Insufficient information on infectious workup especially in the backdrop of left lower lung field infiltration.						
Zamoner et al 2022/ 58 / F / [redacted]	Fatigue, paleness, arthralgia on hands, knees, ankles, foamy urine, and elevated blood pressure	ANCA associated vasculitis (Glomerulonephritis rapidly progressive)	7 / Dose 1	New onset	Hyperthyroidism	Resolving	Possible with confounders / risk factors
	Laboratory data: Serum creatinine of 2.2 mg/dL, urea of 67 mg/dL, a significant elevation compared to a baseline creatinine of 1.0 mg/dL. Urinalysis revealed hematuria (20 to 25 red blood cells per high power field) and proteinuria (2+). The 24-h urinary protein excretion was 4.4 g. Additional investigations showed hypercholesterolemia, severe anaemia, and normal serum albumin. Ultrasound showed kidneys with 10.5 cm long and parenchyma 1.6 cm size. Antinuclear antibody test (ANA) and anti-double-stranded DNA (anti-dsDNA) were negative. C3 and C4 were within normal limits; ANCA, anti-proteinase 3, GBM and viral serologies were negative. Antimyeloperoxidase was positive at a titer of 1/80. Renal biopsy revealed crescentic glomerulonephritis with glomerular sclerosis, fibrous crescents, interstitial fibrosis, and tubular atrophy, active inflammatory lesions in glomeruli characterized by endothelial swelling, endocapillary proliferation, accumulation of macrophages, hyaline deposits and cellular fibrocellular crescents. Immunofluorescence confirmed nonspecific entrapment with C3 positive in sclerotic areas. Vaccinee started treatment with cyclophosphamide, oral azathioprine, and prednisone						

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Authors / Age /Gender/ Country	Clinical features	Final diagnosis	Time to onset (in days) / Dose number	New onset / Relapse / Worsening / Recurrence	Previous medical history	Outcome	AZ Assessment as per WHO-UMC causality scale
	AstraZeneca comment: Presenting features of fatigue, paleness, arthralgia on hands, knees, ankles, foamy urine, and elevated blood pressure 7 days after VAXZEVRIA (dose 1). Serum creatinine of 2.2 mg/dL, urea of 67 mg/dL, a significant elevation compared to a baseline creatinine of 1.0 mg/dL. Urinalysis revealed hematuria (20 to 25 red blood cells per high power field) and proteinuria (2+). The 24-h urinary protein excretion was 4.4 g. Additional investigations showed hypercholesterolemia, severe anaemia, and normal serum albumin. Ultrasound showed kidneys with 10.5 cm long and parenchyma 1.6 cm size. Antinuclear antibody test (ANA) and anti-double-stranded DNA (anti-dsDNA) were negative. The serum complement (C3 and C4) was within normal limits and testing of antineutrophil cytoplasmic antibodies (ANCA) anti-proteinase 3, anti-glomerular basement membrane (GBM) and viral serologies were negative. However, Antimyeloperoxidase was positive at a titer of 1/80. Renal biopsy done 80 days post vaccination revealed crescentic glomerulonephritis with glomerular sclerosis, fibrous crescents, interstitial fibrosis, and tubular atrophy, active inflammatory lesions in glomeruli characterized by endothelial swelling, endocapillary proliferation, accumulation of macrophages, hyaline deposits and cellular fibrocellular crescents. Immunofluorescence confirmed nonspecific entrapment with C3 positive in sclerotic areas. The TTO is considered reasonable, however, demonstration of complement pathology in renal biopsy 80 days post vaccination may point to a continued underlying etiology. Renal involvement occurs in 70% of ANCA associated vasculitis.						
Cano -Gamez et al 2022 / 51 / F / [redacted]	Incidental finding of creatinine levels of 1.3 mg/dL and urinalysis with the presence of abundant leukocytes and mild proteinuria	Rapid progressive glomerulonephritis and high MPO-ANCA antibody titer	Unk / Booster dose (3rd)	New onset	Hypothyroidism	Recovered	Unassessable / Unclassifiable with confounders / risk factors

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	Laboratory data: Cr levels of 1.3 mg/dL, urea of 39 mg/dL, abundant leukocytes in urine and mild proteinuria. Worsening of Sr Cr. 4.98 mg/dL and urea to 114 mg/dL after 7 days. Autoimmune workup - anti-myeloperoxidase (MPO) antibodies with high titers (50.89 U/mL, positive >15 U/mL). Worsening of proteinuria to 743 mg and hyaline casts (2-5 per/HPF), and >41 erythrocytes/HPF with 36% dysmorphia. Renal biopsy - Diffuse extracapillary proliferative glomerulonephritis was concluded, with segmental fibrinoid necrosis, active tubulointerstitial nephritis, multifocal acute tubular injury with moderate regenerative changes of the tubular epithelium, and grade I interstitial fibrosis.						
	AstraZeneca comment: Incidental finding of creatinine levels of 1.3 mg/dL and urinalysis with the presence of abundant leukocytes and mild proteinuria during work up of myalgia, and polyarthralgia, in a 51-year-old female vaccinee who received dose 3 of VAXZEVRIA. Medical history of secondary hypothyroidism. The TTO was not reported. No information on clinical course following primary VAXZEVRIA dose series. Rapid worsening of renal function after 7 days with renal biopsy confirmation of rapid progressive glomerulonephritis and high MPO-ANCA antibody titer. Treatment with pulse steroids and cyclophosphamide 1 g, prednisone 1 mg/kg, and mycophenolate mofetil 2 g resulted in ongoing resolution at 3 months. Autoimmune milieu (MPO-ANCA and hypothyroidism) are possible confounders. Due to insufficient information on latency of events to vaccination dose, clinical course following primary vaccination series, the WHO UMC causality was Unassessable.						
David et al 2022 - 1 / 75 / M / [redacted]	Haemoptysis	Pauci-immune crescentic glomerulonephritis	35 / Dose 1	Relapse	Renal-limited MPA previously in remission	Recovering	Possible with confounders / risk factors
	Laboratory data: Baseline creatinine 226, Creatinine at presentation 227, Peak creatinine 617, ANCA p-ANCA 40, antibody MPO Ab 3.5, Creatinine at follow up dialysis dependent						
	AstraZeneca comment: Presenting features of 3 days of haemoptysis, 5 weeks after first dose of VAXZEVRIA in a 75-year-old male vaccinee with medical history of renal-limited MPA previously in remission. Serum creatinine was consistent with baseline; however, microscopic hematuria was newly present. P-ANCA was positive, with anti-MPO antibodies, having been negative at previous review. Kidney biopsy demonstrated active, pauci-immune crescentic glomerulonephritis, consistent with AAV relapse. Methylprednisolone and rituximab were commenced, and haemoptysis resolved, however kidney function deteriorated, requiring ongoing kidney replacement therapy. TTO is reasonable. Still, there was insufficient information on concomitant medications.						

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David et al 2022 - 2 / 74 / M / [redacted]	Worsening kidney impairment	Acute crescentic pauci-immune glomerulonephritis	2 weeks / Dose 1	New onset	MPA without renal involvement	Recovered	Possible with limited information
	Laboratory data: Baseline creatinine 75, Creatinine at presentation 155, Peak creatinine 882, ANCA p-ANCA >40, antibody MPO Ab >134, Creatinine at follow up 307						
	AstraZeneca comment: Presenting featuring of worsening kidney impairment noted 2 weeks after vaccination in a 74-years-old male patient with medical history of MPA, diagnosed 19 months previously without kidney involvement. Positive p-ANCA with anti-MPO >134 U/ml was noted. Kidney biopsy demonstrated acute crescentic pauci-immune glomerulonephritis, consistent with AAV. Serum creatinine peaked at 882 umol/L, and dialysis access was organized. Intravenous methylprednisolone and cyclophosphamide were commenced, kidney function improved, and he was discharged without requiring kidney replacement therapy. TTO is reasonable. However, there is lack of information regarding concomitant medications, other etiology workup and featuring after 2nd dose of VAXZEVRIA.						
Hassani et al 2021 / 55 / F / [redacted]	vomiting, oliguria and hematuria	Immunoglobulin-mediated MPGN	7 / Dose 2	New onset	Unknown	Recovering	Possible with limited information
	Laboratory data: Cr of 10.5 mg/dL (baseline 0.9 mg/dL, one year prior) with progressive worsening, BUN of 2 g/L, potassium of 5.5 mEq/L, bicarbonate of 17 mEq/L, and haemoglobin of 12.5 g/dL with nephrotic syndrome (protein-creatinine ratio was 4 g/g). PCR for SARS-CoV-2, HIV tests, Hep B tests was negative. Renal USG was normal. C3 and C4 were low (C3 = 0.45 g/L C4 = 0.02 g/L). Immunological testing for cryoglobulinemia, Anti-GBM antibodies, ANA, and Anti-dsDNA were negative. No tumor neither infection was found in the CT, cardiac ultrasound, and blood culture. Renal biopsy - diffuse endocapillary proliferation, with double contours of GBM in 12 glomeruli and cellular segmental crescents in five glomeruli, no intra-capillary thrombi were seen with some tubular injury, mild interstitial fibrosis, and fibrous endarteritis. Immunofluorescence showed mesangial and parietal granular deposits of polyclonal Igs G, A, M, and C3. A diagnosis of immunoglobulin mediated MPGN was made.						

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	AstraZeneca comment: Presenting features of vomiting, oliguria and hematuria, 7 days following vaccination dose 2 in a 55-year-old female vaccinee. Preceded by headache from second day post vaccination (dose 2). Autoimmune, neoplastic, and infective workup was negative. A diagnosis of immunoglobulin mediated MPGN was made, and management included dialysis, pulse steroids, pulse cyclophosphamide with ongoing resolution. TTO is reasonable. Autoimmune, neoplastic, and infective workup was negative. However, there was insufficient information on medical history and pre-existing conditions, concomitant medications, clinical course post vaccine dose 1.						
Mokos and Bašić-Jukić 2022/ 73 / M / [redacted]	Edema in MMII	IgAN	35 / Dose 2	New onset	Bilateral renal transplant following AAN (aristolochic acid nephropathy), in the last 8 years, and a family history of chronic kidney disease (unknown etiopathogenesis).	Unknown	Possible with limited information
	Laboratory data: progression in proteinuria (1.9 g/24 h) and elevated serum creatinine (148 µmol/L), eGFR of 35 ml/min/1.73 m2 and 5-10 erythrocytes in the urine sediment. Pathohistological findings were consistent with IgAN. Infections were ruled out through; urine culture and viral examinations, including SARS-CoV-2 IgG and IgM.						
	AstraZeneca Comment: There was no information on medical history of donor (for renal transplant), any action taken with immunosuppressive therapy prior to vaccination, any neoplasms, genetic association in view of family history of CKD. However, the TTO of 35 days after Dose 2, can be considered prolonged for an adaptative immunity or immune complex secondary to vaccination, and may be hypothesized as well as chronic insult. Based on the insufficient information as discussed above in the backdrop of reported lack of immune response for vaccine, a comprehensive causal assessment is not possible.						

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Fenoglio et al 2022-1 / 74 / M / Italy	Renal failure and Nephrotic syndrome	IgAN	42 / Dose 1	New onset	Unknown	Fatal (heart attack, no autopsy details)	Possible with limited information
	Laboratory data: Histological diagnosis supportive of IgAN.						
	AstraZeneca Comment: De novo IgA nephropathy (with presenting features of renal failure and nephrotic syndrome) in a 74-year-old patient, 42 days after 1st dose of VAXZEVRIA. The patient was managed with steroids and dialysis; however, the event outcome was not reported. It was reported that the patient died due to heart attack after 2 months. The TTO is reasonable, however there was insufficient information on medical history, concomitant medications, etiological work-up and clinical course of the events for a comprehensive causal assessment.						
Fenoglio et al 2022-2/79/M/[redacted]	Renal failure and Nephrotic syndrome	IgAN	61 / Dose 1	New onset	Unknown	Unknown	Unlikely
	Laboratory data: Histological diagnosis supportive of IgAN.						
	AstraZeneca Comment: De novo IgA nephropathy (with presenting features of renal failure and nephrotic syndrome) in a 79-year-old patient, diagnosed 61 days after 1st dose of VAXZEVRIA. The TTO is considered unlikely. The patient was managed with steroids and rituximab; however, the event outcome was not reported. There was insufficient information on medical history (autoimmune, metabolic), concomitant medications, etiological work-up and clinical course of the events for a comprehensive causal assessment.						
Jha et al 2022-1/45/M/[redacted]	Abdominal pain intermittent, polyarthralgia	IgA vasculitis with nephritis	29 / Dose 2	New onset	Unknown	Resolved	Possible with limited information

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	Laboratory data: Laboratory data included urine proteins (2+) and red cells (10 hpf), complete blood count, liver and renal function tests including serum electrolytes normal, autoimmune markers (such as ANA, anti dsDNA, ANCA) were founded without abnormal values. Etiology workup for viral markers (HIV, HBsAg, Anti HCV) were negative. Renal biopsy confirmed IgA nephropathy on DIF, MEST C Score was M1E1S0T0C1.						
	AstraZeneca comment: Observation of sub-nephrotic proteinuria and microscopic hematuria during work-up for IgA vasculitis about 29 days after receiving the second dose of VAXZEVRIA in 45-year-old male from [redacted]. Urine proteins (2+) and red cells (10 hpf); Complete blood count, liver and renal function tests including serum electrolytes-normal, autoimmune markers (ANA, anti-dsDNA, ANCA) negative, viral markers (HIV, HBsAg, Anti HCV) Negative; Renal biopsy - IgA nephropathy on DIF, MEST-C Score was M1E1S0T0C1. Complete clinical and biochemical remission of nephrotic syndrome with oral prednisolone and Telmisartan in 8 weeks. Treatment started with oral prednisolone and Telmisartan in 8 weeks. TTO of 29 days is reasonable to vaccine administration. IgAN can be explained by preceding IgA vasculitis, however, to assess further, no information on clinical course after dose 1, medical history, concomitant medications, family history.						
Jha et al 2022- 2 / 30 / M / [redacted]	Red cutaneous lesions over both legs and hands.	IgA vasculitis with nephritis	28 / Dose 2	New onset	Unknown	Resolved	Possible with limited information
	Laboratory data: significant proteinuria and microscopic hematuria noted. Urine Proteins (3+) and red cells (15 hpf). Ureteric calculus with Grade 1 hydroureteronephrosis, negative viral markers and autoimmune markers. Skin biopsy was suggestive of leukocytoclastic vasculitis and DIF was negative for all immunoreactions. Renal biopsy - IgA nephropathy on DIF, MEST C Score was M1E1S0T0C0. Vaccine started treatment with oral prednisolone and telmisartan in 10 weeks.						

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	AstraZeneca comment: Observation of significant proteinuria and microscopic hematuria during work-up for IgA vasculitis about 28 days after receiving the second dose of VAXZEVRIA in 30-year-old male from India. Urine Proteins (3+) and red cells (15 hpf); ureteric calculus with Grade 1 hydroureteronephrosis; negative viral markers and autoimmune markers; Renal biopsy - IgA nephropathy on DIF, MEST-C Score was M1E1S0T0C0. Complete clinical and biochemical remission of nephrotic syndrome with oral prednisolone and Telmisartan in 10 weeks. TTO of 28 days is reasonable to vaccine administration. IgAN can be explained by preceding IgA vasculitis, however, to assess further, no information on clinical course after dose 1, medical history, concomitant medications, family history.						
Neves et al 2022-2/58/F/[redacted]	Pulmonary congestion, massive edema, and acute-on-chronic kidney disease	Collapsing glomerulopathy	21 / Dose 1	New onset	Multiple myeloma and CKD due to past nephropathy	Resolving	Possible with confounders / risk factors
	Laboratory data: Significant investigation CKD-kidneys on USG; immunophenotyping of bone marrow excluded a multiple myeloma relapse, Rheumatoid factor, and ANA negative; infectious workup including hepatitis B and C, HIV, VDRL, COVID-19 RT-PCR and Parvovirus RT-PCR were negative, IgG COVID-19 strongly positive. Renal biopsy revealed chronic sclerotic changes in glomeruli with hypertrophy and hyperplasia of podocyte cells with segmental collapse of the glomerular tuft.						

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	AstraZeneca Comment: Presenting features of pulmonary congestion, massive edema, and acute on CKD 3 weeks after receiving her first dose VAXZEVRIA. Significant investigation workup findings at 3 weeks post vaccination: urine sediment - bland, CKD-kidneys on USG; immunophenotyping of bone marrow excluded a multiple myeloma relapse; Rheumatoid factor - negative; ANA - negative; infectious workup (hepatitis B and C, HIV, and VDRL, COVID-19 RT-PCR, Parvovirus RT-PCR) - negative; IgG (COVID-19) - strongly positive; Renal biopsy - chronic sclerotic changes in glomeruli with also hypertrophy and hyperplasia of podocyte cells with segmental collapse of the glomerular tuft; Immunofluorescence - not reported; Genotype - APOL1 (G2/G2). Managed with haemodialysis and discharged in 1 month. TTO of 3 weeks is reasonable to vaccine administration. Insufficient information on immunofluorescence in renal biopsy, concomitant medications. High risk allele APOL1 (G2/G2) in backdrop of multiple myeloma, CKD is a possible confounder.						
Jefferis 2022/ Unk / F / [redacted]	Severe acute kidney injury and nephrotic range proteinuria with no hematuria.	Collapsing glomerulopathy (CG)	14 / Dose 2	New onset	Unknown	Ongoing	Possible with limited information

Table 47 Summary of literature case reports with special focus to adeno-vectored VAXZEVRIA vaccine

Authors / Age /Gender/ Country	Clinical features	Final diagnosis	Time to onset (in days) / Dose number	New onset / Relapse / Worsening / Recurrence	Previous medical history	Outcome	AZ Assessment as per WHO-UMC causality scale
	Laboratory data: creatinine, 533 mmol/L; baseline, 125–187 mmol/L) and nephrotic range proteinuria (urine protein creatinine ratio, 2000 g/mol, with no hematuria). Initial kidney biopsy / histochemistry - glomerulomegaly, glomerulitis, podocyte enlargement with protein droplets, and collapse of the glomerular tufts along with glomerular and interstitial immune infiltrates (Banff score, i3 t0 v0 g3 ptc0 ci1 ct1 cv0 cg1b mm0 ah3 ti3 i-IFTA3), expression of Ki-67, a marker of glomerular expansion/proliferation in CG, reduced glomerular expression of synaptopodin and podocalyxin, evidence of podocyte dedifferentiation previously associated with CG Immunofluorescence for Igs and C4d immunohistochemistry and antibodies against donor specific human leukocyte antigen and angiotensin 2R1 were absent. Treatment response for suspected antibody-mediated rejection with methylprednisolone, i.v. Ig, and plasma exchange was poor. Repeated kidney biopsy / histochemistry - absence of immune cell infiltration and features consistent with collapsing glomerulopathy (CG) with acute tubular injury and mild glomerulitis. Electron microscopy revealed the detachment of podocytes with extensive foot process effacement, microvillous hyperplasia, protein droplets in some podocytes, and normal glomerular basement membranes, with no evidence of immune complex deposition. The patient required haemodialysis at 3 months with persisting proteinuria (15 g/d). Secondary causes of CG, including cytomegalovirus, BK polyomavirus, HIV, parvovirus, and SARS-CoV-2 infection, were excluded.						
	AstraZeneca comment: Presenting features of severe acute kidney injury and nephrotic range proteinuria without hematuria about 14 days post dose 2 of VAXZEVRIA vaccination in a female (unspecified age) vaccinee with stable kidney transplant (on cyclosporine for 14 years) and medical history of IgA Vasculitis (cause of kidney failure necessitating transplant). No serum creatinine perturbations were seen post dose 1. Secondary causes of CG, including cytomegalovirus, BK polyomavirus, HIV, parvovirus, and SARS-CoV-2 infection, were excluded. Renal biopsy confirmed diagnosis of collapsing glomerulopathy (CG) with acute tubular injury and mild glomerulitis was treated with methylprednisolone, IvIg, and plasma exchange with poor response. However, a histological resolution on immune cell infiltration (unspecified) was seen. Immunofluorescence for Igs and C4d immunohistochemistry Abs against donor HLA and angiotensin 2R1 were absent. The TTO of renal symptoms to dose 2 may be reasonable in the backdrop of exclusion of viral infectious workup. 'Poor response' to steroids, IvIg and plasma exchange may point towards a local rather than systemic pathology. Moreover, no serum creatinine perturbations were seen post dose 1. There was insufficient information on medical history, complete etiologic workup (especially autoimmune, neoplastic), patient demographics, clinical and laboratory status of IgA vasculitis and duration between dose 1 and dose 2. The WHO-UMC causality considered as possible with limited information.						

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Neves et al 2022-1/63/F/[redacted]	Ankle and foamy urine	Focal segmental glomerulosclerosis	9 / Dose 1	New onset	Hypertension, Heart failure and dyslipidaemia	Resolved	Possible with limited information
	Laboratory data: Three months post vaccination: eGFR - 70 ml/min per 1.73 m2; urinalysis, proteins (3+) and red cells (2+); hypercholesterolemia (405 mg/dl); Increased LDL (294 mg/dl); HDL (75 mg/dl); and hypertriglyceridemia (216 mg/dl); infectious workup including Chagas, schistosomiasis, HIV, hepatitis B and C, VDRL, COVID-19 – negative. Renal biopsy - immunofluorescence deposits of IgM and C3, microscopy - Collapsing glomerulopathy; Genotype for APO - G1/G0. Complete Vaccine treatment include oral prednisolone.						
	AstraZeneca Comment: Presenting features of edema of the ankle and foamy urine for 3 months duration, which began 9 days after receiving the first dose of VAXZEVRIA in 63-year-old Afro descendent woman. Significant investigation workup findings at 3 months post vaccination: eGFR - 70 ml/min per 1.73 m2; urinalysis, proteins (3+) and red cells (2+); hypercholesterolemia (405 mg/dl); Increased LDL (294 mg/dl); HDL (75 mg/dl); and hypertriglyceridemia (216 mg/dl); infectious workup (Chagas, schistosomiasis, HIV, hepatitis B and C, VDRL, COVID-19 - negative; Renal biopsy - immunofluorescence deposits of IgM and C3, microscopy - Collapsing glomerulopathy; Genotype for APO - G1/G0. Complete clinical and biochemical remission of nephrotic syndrome with oral prednisolone. TTO of 9 days is reasonable to vaccine administration. Dyslipidaemia may have a cause-and-effect relationship to MCD/nephrotic syndrome, however, to assess further, no information on family history or further monitoring. Deposits of IgM and C3 after 3 months of vaccine administration is immunologically implausible for single exposure to an insult 3 months back; can be attributed to new unknown insult or underlying chronic immune disorder. Medical histories of heart failure, hypertension, dyslipidaemia in the backdrop of risk genotype heterozygous allele of G1 are possible confounders.						
Sekar et al 2022/67/M/[redacted]	Worsened weakness, edema, and chills (experienced after 1st dose)	AKI and C3 Glomerulonephritis	42 / Dose 1 70 / Dose 2	New onset and Recurrence	Psoriasis, Hyperlipidaemia, benign prostatic hyperplasia, and Hypertension	Unknown	Possible with limited information

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	Laboratory data: increased creatinine (from 1.7 to 2.0 till 3.0 mg/dL), potassium was 3.8 mmol/L (3.5-5.1), and sodium was 143 mmol/L (135-144). Urinalysis at this time showed increased proteinuria (3+) with trace red blood cells. Urine microscopy reported few hyaline casts and no dysmorphic RBCs. His haemoglobin dropped to 10.2 g/dl (12-16 g/dl). The urine spot protein to creatinine ratio was 3.6. Serologies were remarkable for elevated ANA titers, serum C3 - 91.7 mg/dl (normal >90), and C4 - 24.7 mg/dl (10-40 mg/dl). A kidney biopsy was revealed mild background interstitial inflammation with some overall proliferation in the mesangium with some expansion under light microscopy. Three glomeruli showed mesangial expansion, and two showed glomerular basement membrane thickening. Under immunofluorescence, there was moderate C3 staining in glomerular capillary walls and granular staining in blood vessel walls consistent with C3 glomerulonephritis.						
	AstraZeneca comment: Presenting features of worsening of leg edema (accompanied by sudden onset of chills) about 7 days post dose 1 of VAXZEVRIA in 67-year-old male. The edema was being managed with furosemide when it progressively worsened (serum creatinine worsening) post dose 2. A pre-existing mild symptom of weakness, pitting edema, and chills that began seven months earlier was also reported. Renal USG showed mildly increased echogenicity of both kidneys without any hydronephrosis and this was attributed to possible pre-existing hypertension. Kidney biopsy was revealed mild background interstitial inflammation with some overall proliferation in the mesangium with some expansion under light microscopy. Three glomeruli showed mesangial expansion, and two showed glomerular basement membrane thickening. Under immunofluorescence, there was moderate C3 staining in glomerular capillary walls and granular staining in blood vessel walls consistent with C3 glomerulonephritis. Congo red stain was negative. Staining for kappa and lambda light chains was negative. Under electron microscopy, there were electron-dense deposits in the mesangium but did not reveal abnormal electron-dense deposits in the basement membrane. Immunosuppressants (mycophenolate, prednisolone) were initiated with ongoing resolution at one year (one year later, his creatinine had decreased to 1.5 mg /dl, and his urine protein to creatinine ratio was 1). TTO of worsening is reasonable, however, considering pre-existing similar symptoms and ongoing resolution still at 1 year despite immunosuppressants, a confounding role of an undiagnosed renal pathology in the backdrop of psoriasis, hyperlipidaemia, benign prostatic hyperplasia (BPH), and hypertension cannot be completely excluded. There was insufficient information on clinical course of psoriasis, any pre-existing treatments (especially immunosuppressants) prior to vaccination.						
Baskaran et al 2021/ 55 / M / [redacted]	Increasing ascites and peripheral oedema	Acute interstitial nephritis (AIN)	4 weeks / Dose 2	New onset	Unknown	Recovering	Possible with limited information

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	Laboratory data: Peak creatinine 633 mmol/L, urine PCR 1631 mg/mmol, serum albumin 18 g/L						
	AstraZeneca comment: Presenting features of increasing ascites and peripheral oedema 4 weeks after 2nd dose of VAXZEVRIA in a 55-years-old male patient. During his admission vaccinee experienced oliguria, rapid deterioration in renal function. Evaluation for second causes was negative. A renal biopsy demonstrated acute tubular injury with active interstitial inflammatory and diffuse effacement of foot processes, providing the diagnosis of acute interstitial nephritis (AIN) with improvement in kidney function and proteinuria, and started treatment with high-dose prednisone (60mg/d) with improvement in kidney function and proteinuria Time to onset is reasonable, however it was noted patient had intermittent doses of NSAIDs in the 4 weeks prior event presentation, which can be associated with AIN and MCD. At the same time, there is lack of information in medical history, clinical features after 1st dose, and detailed etiology workup.						
Yaghoubi et al 2022/ 22 / F / [redacted]	Ataxia, dysphasia, paraesthesia, and acute numbness	MPGN	28 / Dose 2	New onset	No past medical history, and no concomitant medications	Resolving	Possible with confounders / risk factors
	Laboratory data: Anaemia (haemoglobin 10.8 g/dL, normal range 120-160 g/dL, reticulocyte index 3.2% >2.5%) and a low platelet count (45×109/L, normal range 150400×109/L). The erythrocyte sedimentation rate (ESR) was high (77 mm/hr, normal range 0-30 mm/hr) and D-dimer was mildly elevated (424 ng/mL), creatinine rise with thrombocytopenia and brain infarction along with hematuria and proteinuria. The kidney needle biopsy reported glomerular changes like membranoproliferative glomerulonephritis (MPGN) with obliterated small arteries consistent with thrombotic microangiopathy. Fluorescent antinuclear antibody (FANA) and lupus anticoagulant were both negative. Treatment with prednisolone, rituximab						
	AstraZeneca comment: Presenting features of hematuria and proteinuria observed during workup of aTTP with ADAMTS13 low level activity and the ADAMTS-13 positive inhibitor post unknown latency of 1st dose of COVID-19 vaccination in a female patient. A diagnosis of MPGN was confirmed on biopsy. The MPGN could be explained by sequelae of TMA associated with aTTP. ADAMTS13 low level activity and the ADAMTS-13 positive inhibitor may point to a pre-existing pathology. No information on family history, etiological work-up.						

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Authors / Age /Gender/ Country	Clinical features	Final diagnosis	Time to onset (in days) / Dose number	New onset / Relapse / Worsening / Recurrence	Previous medical history	Outcome	AZ Assessment as per WHO-UMC causality scale
Maramattom et al 2022/64/M/[redacted]	Fever and drowsiness	Glomerulonephritis	10 / Dose 1	New onset	Unknown	Unknown	Possible with limited information
	Laboratory data: Anti-SARS-CoV-2 spike protein IgG antibody positive, CSF-25 cells/mm3 (40 mg/ dl), normal glucose Serum & CSF autoimmune encephalitis/paraneoplastic panel/NMO, MOG/viral encephalitis: negative. Elevated systemic inflammatory markers as ESR, CRP, d-dimer, ferritin						
	AstraZeneca Comment: Event on glomerulonephritis reported along with subsegmental pulmonary and Limbic encephalitis. Relevant findings of Anti-SARS-CoV-2 spike protein IgG antibody positive, CSF-25 cells/mm3 (40 mg/ dl), normal glucose Serum & CSF autoimmune encephalitis/paraneoplastic panel/NMO, MOG/viral encephalitis: negative. However, no information on event latency to vaccine administration or clinical course or etiological workup.						
Al Bakr and Alaithan 2022/ 29 /M/[redacted]	Abdominal and loin pain, vomiting, diarrhoea and decreased oral intake	Chronic kidney disease with acute glomerulonephritis	1 / Unk dose	New onset	Recurrent urinary tract infections, long-term impairment of kidney function	Resolving	Possible with confounders / risk factors
	Laboratory data: Presenting symptoms of abdominal and loin pain, vomiting, diarrhoea and decreased oral intake 2 days after receiving the AstraZeneca vaccine for COVID-19. Relevant investigation workup: Abdominal CT - nephrolithiasis, bilateral renal cortical scarring, mild splenomegaly, hiatus, and left inguinal hernias; 99mTechnetium dimercaptosuccinic acid (DMSA) scan showed a relative renal function of 28% on the right side and 70% on the left side; Proteinuria; low platelets; D-dimer increased; Complement levels increased; Renal biopsy - acute and chronic changes (segmental scarring, Strong staining was observed for immunoglobulin M, kappa and lambda light chains, and complement component 1q, confirming immune complex-mediated glomerulonephritis, interstitial fibrosis tubular atrophy of 40% was observed; Infectious workup - Brucella serology positive (1:2560). The patient was diagnosed with chronic kidney disease with acute glomerulonephritis and started on doxycycline, ciprofloxacin, and ceftriaxone to treat brucellosis. TTO of immune complex-mediated glomerulonephritis may be considered possible, however chronic changes in kidney, nephrolithiasis, recurrent UTI and concurrent brucellosis are strong confounders.						

Table 47 Summary of literature case reports with special focus to adeno-vectored VAXZEVRIA vaccine

Authors / Age /Gender/ Country	Clinical features	Final diagnosis	Time to onset (in days) / Dose number	New onset / Relapse / Worsening / Recurrence	Previous medical history	Outcome	AZ Assessment as per WHO-UMC causality scale
	AstraZeneca comment: time to onset between immune complex-mediated glomerulonephritis and VAXZEVRIA vaccination is considered possible, however, chronic changes in kidney, nephrolithiasis, recurrent UTI and concurrent brucellosis are strong confounders.						

AAN Aristolochic Acid Nephropathy; AAV Anca Associated Vasculitis; ADAMTS A Disintegrin And Metalloproteinase With A Thrombospondin Motif; AIN Acute Interstitial Nephritis; AKI Acute Kidney Injury; ANCA Antineutrophil Cytoplasmic Antibodies ; APO Apolipoprotein; AZ AstraZeneca; BPH Benign Prostatic Hyperplasia; CG Collapsing Glomerulopathy; CKD Chronic Kidney Disease; COVID-19 Coronavirus Disease of 2019; CRP C-Reactive Protein; CSF Cerebrospinal Fluid; eGFR estimated Glomerular Filtration Rate; ESR Erythrocyte Sedimentation Rate; GBM Gomerular Basement Membrane; HCV Hepatitis C Virus; HDL High-Density Lipoprotein; HIV Human Immunodeficiency Virus; IgAN Immunoglobulin A Nephropathy; LDL Low-Density Lipoprotein; MCD Minimal Change Disease; MMII Multimodal Image Integration; MPGN Membranoproliferative Glomerulonephritis; MPO myeloperoxidase; pANCA Antimyeloperoxidase Antibodies; PCR Polymerase Chain Reaction; RBC Red Blood Cell; RT-PCR Reverse Transcription Polymerase Chain Reaction; SARS-CoV-2 Severe Acute Respiratory Syndrome; TTO Time To Onset; UMC Uppsala Monitoring Centre ; UTI Urinary tract infection; USG Ultrasonogram; VDRL Venereal Disease Research Laboratory; WHO World Health Organization

Table 48 Summary of literature case reports with special focus to other adeno-vectored vaccines

Authors / Age /Gender/ Country/ Vaccine	Clinical features	Final diagnosis	Time to onset (in days) / Dose number	New onset / Relapse / Worsening / Recurrence	Previous history	Outcome
Yadav et al 2022/52/F/ [redacted]/JANSSEN	Fever, joint pain, and weakness of all limbs	ANCA associated vasculitis (Glomerulonephritis rapidly progressive)	12 / Dose 1	New onset	Non/obstructive calculus, Hypertension	Unknown

Table 48 Summary of literature case reports with special focus to other adeno-vectored vaccines

Authors / Age /Gender/ Country/ Vaccine	Clinical features	Final diagnosis	Time to onset (in days) / Dose number	New onset / Relapse / Worsening / Recurrence	Previous history	Outcome
	Laboratory data: Urinalysis revealed 12 red blood cells per high-power field (HPF), 4 white blood cells/HPF, and 0.631 gm/day protein with albumin (2+). Serologic evaluation was notable for increased C-reactive protein, decreased C3 complement level, normal C4 level, positivity for p-ANCA and c-ANCA (3+). Renal ultrasound showed tiny non-obstructive calculus in both kidneys. Renal biopsy revealed necrotizing and crescentic glomerulonephritis with insignificant glomerular immune complex deposit. A serum creatinine level of 0.8 mg/dl was reported on routine laboratory evaluation few months ago. Treatment included antibiotics, NSAIDS, methylprednisolone and cyclophosphamide					
Caza et al 2021-2 / 68 / M / Unk / JANSSEN	Unknown	Membranous Nephropathy	28 / Dose 1	New onset	Unknown	Recovering
	Laboratory data: Creatinine 3.3, Proteinuria 0.6, Albumin 2.3, Hematuria negative, ANCA negative, Kidney biopsy reported segmental sclerosis, acute tubular injury, mild interstitial fibrosis / tubular atrophy, severe atherosclerosis. Immunofluorescence: 2+IgG, 2+IgM gr cap loop, with subepithelial deposits and severe food process effacement					

ANCA Antineutrophil Cytoplasmic Antibodies; HPF high-power field; NSAIDS Non-Steroidal Anti-Inflammatory Drugs

Minimal change disease (Glomerulonephritis minimal lesion) comprised 8 cases (5 males and 3 females). The age distribution varied from 19 to 72 years (mean – 40 years, median – 24 years). The presenting symptoms were clinical (swelling in legs, body; foamy urine; nephrotic syndrome). The TTO varied widely from within 2 days after dose 1 (2 new onset cases), 3-7 days after dose 1 (1 case), 8-14 days after dose 1 (4 new onset cases) and 8-14 days after dose 2 (1 case). In 3 out of 7 cases, possible confounders (recurrent UTI, ANA positivity, hypertension, obesity, hypercholesterolemia, dyslipidaemia) were identified. In the remaining 5 cases, there was limited information including medical history, childhood vaccination history, concomitant medication and etiology workup precluding a comprehensive assessment.

Antineutrophil Cytoplasmic Antibodies (ANCA) associated Glomerulonephritis (pauci-immune. rapidly progressive) comprised 6 cases – 3 females (51, 52, 58 years) and 3 males (63, 74, 75). ANCA GN increases with age, with a dramatic surge after 50 years old (Jennette et al 2017, O'Shaughnessy et al 2017). The age distribution trend in these 5 cases is similar to background trend. The cases were reported from Australia, Mexico, Brazil, Nepal, and Spain. Five cases were reported with VAXZEVRIA, and 1 case report with J&J. None of them were reported with a fatal outcome. The co-presenting features were joint/limb pain and/or fatigue, haemoptysis, acute kidney injury (AKI). MPO ANCA was positive in all the 6 cases while proteinase-3 ANCA was positive in 1 case. MPO-ANCA vasculitis is more common in Asia. Renal involvement occurs in 70% of affected patients and is manifested as rapidly progressive glomerulonephritis with pauci-immune necrotizing, crescentic glomerulonephritis on biopsy (Jones et al 2010). The latency varied widely (7 to 35 days) post dose 1 of vaccination to even new onset post vaccine booster (dose 3) to suggest any singular etiopathogenesis.

IgA Nephropathy comprised 5 cases (all males). The age distribution varied from 30 to 79 years (median - 73 years). In majority of cases, the presenting symptoms were proteinuria (sub nephrotic range proteinuria in one and nephrotic range proteinuria in 3 (associated with renal failure in 2 patients). One case was reported in a transplant kidney, however there was insufficient information on medical history of donor. The onset was reported as de novo in all 5 cases. The TTO varied widely - 42 days (dose 1), 61 days (dose 1), 29 days (dose 2), 28 days (dose 2) and 35 (dose 2). Thus, a singular etiopathogenetic mechanism is considered unlikely.

FSGS or Collapsing glomerulopathy comprised 3 cases - 2 collapsing glomerulopathy: 1 FSGS. The age distribution was 58 and 63 years (unknown in 1 case). The presenting symptoms were edema / proteinuria, acute kidney injury. The TTO varied widely from 9 days after dose 1 and 14 days for dose 2 for collapsing glomerulopathy to suggest any trend: and 21 days after dose 1 for FSGS. The events of collapsing glomerulopathy were possibly confounded by risk genotype heterozygous allele of Apolipoprotein (APO) G1/Go or APOL1 (G2/G2) in the backdrop of multiple myeloma, hypertension, and dyslipidaemia and medical history of IgA vasculitis. However, for the FSGS cases, there was insufficient etiological workup and information on medical history for a comprehensive assessment.

One case reported worsening of clinical features of C3 glomerulonephritis after 2nd dose of VAXZEVRIA in an elderly patient (67/M). However, medical history revealed pre-existing mild symptoms of weakness, pitting edema, and chills that began seven months earlier to vaccination which suggests presence of a pre-existing untreated pathology and can possibly explain the current worsening. On follow-up post immunosuppressive therapy, the renal function had still not resolved at one year, suggesting a confounding role of natural history of disease. Additional confounders were also identified in this case (psoriasis, benign prostatic hyperplasia (BPH), concomitant hydralazine, and ANA, P-ANCA and MPO titres positivity).

Singular cases each of membranous nephropathy and membranoproliferative glomerulonephritis, however these were confounded by CKD and thrombotic microangiopathy (TMA) respectively.

One article reported recurrence of clinical symptoms of MCD after both the doses Timmermans et al 2022. The first episode was seen 7 days post dose 1, however, the latency to dose 2 was unknown. However, the recurrence was confounded by interruption of prednisolone therapy at the time of dose 2 of vaccination.

Literature review of relevant articles

Bronz et al 2022 performed a systematic review of the literature aiming to determine whether COVID-19 or vaccination against SARS-CoV-2 may be temporally related to a new onset, or a flare, of an immunoglobulin A-mediated disorder. The literature search returned 2.570 potentially relevant articles, though after authors' tittle and abstract assessment, they retained 68 reports; from those, 87 cases report were identified, 47 related to Berger glomerulonephritis and 40 to Henoch-Schönlein vasculitis, between them there was no a significant difference on age and gender, however 28 cases had medical history of an immunoglobulin A-mediated disease, which was considered significantly (P=0.0001) more common in Berger glomerulonephritis (N=24, 51%) that in Henoch-Schönlein vasculitis (N=4, 10%), the pre-existing autoimmune disease were mentioned as rheumatoid arthritis, antiphospholipid syndrome (APLS), Crohn disease, Hashimoto thyroiditis or ulcerative colitis. It was notified that approximately 3 out of 4 cases were preceded by a vaccination, with a tendency common in Berger glomerulonephritis (P=0,0001) (N=44; 94%) than in Henoch-Schönlein vasculitis (N=17; 43%). During the assessment related to Berger Glomerulonephritis vaccine-associated cases, the article described that 94% of the cases (N=42) occurred after mRNA vaccination (COMIRNATY N=23; SPIKEVAX N=19). No cases of Berger glomerulonephritis were reported for Adeno-vectored vaccines (VAXZEVRIA, Ad26.COV2·S). Also, the events were noted to happen more often following 2nd dose (N=34) rather than 1st dose (N=6) of vaccine, no case was observed after the 3rd vaccine dose. Even so, 3 cases of Berger glomerulonephritis occurred after both vaccinations.

AstraZeneca comments: This systematic narrative review is prone to reporting bias based on the inclusion of only case reports in temporal association with COVID-19 infection and vaccines. Also, there is no specific information on causality assessment, etiology workup, confirmation about diagnostic workup. There was no comparison to background rates.

Ma et al 2022 article collected 37 cases related to COVID-19 vaccination and membranous nephropathy (MN) through a literature search using "membranous nephropathy", or "proteinuria", or "nephrotic syndrome" and "SARS-CoV-2" or "COVID-19", or "2019-ncov", or "novel coronavirus", and "vaccine" or "vaccination", looking after clinical information of new-onset and relapse MN post COVID-19 vaccination. In total, 20 articles were highlighted, which included a total of 37 cases reports, of which 20 of them (54.1 %) were a new diagnosis and 17 (45.9 %) were reported as relapse or worsening syndrome. The median age of onset was 53.5 years (22-84), with a higher inclination to male patients (67.6 % - N=25). In regards type of COVID-19 vaccines, 30 of the cases (78.9 %) were related to mRNA vaccines, and the remaining 5 cases (13.2 %) were linked to adenovirus vector vaccines (3 after VAXZEVRIA and 2 after JCOVEN). Authors noted that more than half of all reports were provided after 2nd dose of vaccination within 2 weeks of time to onset. The most frequent clinical presentation was edema. From the 37 cases report, 20 were defined with new-onset MN post COVID-19 vaccination, the median age of onset was 57 years (22-82), with a slight inclination to male patients; with a higher predisposition after mRNA vaccines (N=15, 71.4 %), generally after 2nd dose of vaccination (50 %); the most common clinical presentation included edema and proteinuria. The remaining 17 cases from the initial 37 cases report, were described as relapse or worsening membranous nephropathy, showing a deteriorating edema and proteinuria; again, there was a higher number of male patients (13 out of 17, 76.5 %), and the medial age was 65 years (39-84); as well, 15 cases were associated with mRNA vaccine, specifically COMIRNATY with 13 cases out of those 15 cases. Potential mechanism of action of MN after COVID-19 vaccination were discussed, included cross immune response, subepithelial deposition of circulating immune complexes, enhanced immune response, and adjuvants, however authors considered that further investigation are urgently required to have a better understanding in regards incidence, recurrence rate, pathogenesis, treatment, and prognosis.

AstraZeneca comment: The authors in this study provide a description of MN cases post COVID-19 infection and COVID-19 vaccination, however, does not provide any comparative analysis. A higher predisposition of MN after COVID-19 vaccination than with COVID-19 infections (predominantly mRNA COVID-19 vaccines, especially with COMIRNATY) is observed; however, a possibility of reporting bias to vaccines cannot be excluded. Additional limitations noted in the article are insufficient diagnostic workup to confirm the event, or etiological workup to rule out other possible triggers which preclude a causal assessment.

Canney et al 2022 provided a retrospective population-level cohort study in British Columbia, Canada, from 01 January 2020 until 14 December 2020; with the objective to identify the risk of glomerular disease relapse after COVID-19 vaccination, since some of the published cases report where a temporal relationship between vaccination and disease flare is observed, does not include or mention an appropriate control of the baseline glomerular disease, which can provide a higher detail about the risk of relapse. Inclusion criteria involved a biopsy on the index date, patient without kidney failure, or experiencing a current or recent disease relapse; two /'measurements of proteinuria and kidney function in the 12 months before the index date were also required. Five sensitivity analyses were performed

as: (1) the time window used to define vaccine exposure was increased from 30 to 45 days to account for more delayed onset relapses; (2) the analysis was repeated using the secondary outcome; (3) the primary analysis was repeated among those who received at least one vaccine dose; (4) the primary analysis was repeated among those who received at least 2 vaccine doses; and (5) the relative rate of relapse associated with vaccine exposure was assessed using a self-controlled case series (SCCS) that was conducted only in patients who experienced disease relapse. The cohort included 1105 patients with biopsy confirmed glomerular disease, 301 with IgA nephropathy, 239 with Focal segmental glomerulosclerosis (FSGS), 182 with membranous nephropathy, 154 with ANCA-Glomerulonephritis, 142 with lupus nephritis and 82 with minimal change disease. 1016 patients (92 %) out of 1105, during the 281 days of follow-up received at least one COVID-19 vaccine dose (COMIRNATY, SPIKEVAX or VAXZEVRIA), and 986 patients (89 %) received 2 or 3 doses. The most common COVID-19 vaccines used, were COMIRNATY (67 %), and SPIKEVAX (30 %). Among the patients who received at least 2 vaccine doses, 859 (87 %) received 2 doses of the same type, 97 (10 %) received one SPIKEVAX and one COMIRNATY dose; and 30 (3 %) received VAXZEVRIA, with either COMIRNATY or SPIKEVAX dose. During the follow up period (281 days), 134 vaccinees (12.1 %) experienced a disease relapse on the basis on the primary outcome definition, which varied between 7.9 % vaccinees with FSGS, and 21.1 % of vaccinees with lupus nephritis.

Vaccinees who received at least one vaccine dose during the follow-up time, similar proportion of patients had a laboratory test performed within 30 days before vaccination, and within 30 days after vaccination (41.6 % versus 43.5 %; P=0.39), suggesting that testing frequency was not correlated with vaccination status. Authors noted an increased proteinuria at the time of relapse in all types of glomerular disease, whereas eGFR (Estimated Glomerular Filtration Rate) at the time of relapse was more variable, being most prominently reduced in patient with ANCA-GN and minimal change disease; of those who relapse, 24 vaccinees (18 %) had a COVID-19 vaccine exposure within 30 days before relapse.

In the overall cohort, to identify the relative risk (RR) of disease relapse after COVID-19 vaccination, exposure to any SARS-CoV-2 vaccine was not associated with an increased risk of disease relapse (hazard ratio [HR]=1.08; 95% confidence interval [CI], 0.65 to 1.8). An interaction analysis suggested that the relative risk of disease flare associated with any vaccine exposure was not significantly different on the basis of the type of glomerular disease (P value for interaction= 0.45). The risk of disease relapse was also estimated separately for exposure to the 1st dose and 2nd, or 3rd dose of COVID-19 vaccine compared with being unexposed. In the overall cohort, a 1st dose of COVID-19 vaccine was not associated with disease relapse (HR=0.67; 95% ci, 0.33 TO 1.36); however, there was a two-fold increase in the risk of disease relapse associated with a 2nd or 3rd dose of COVID-19 vaccine (HR=2.23; 95 % CI, 1.06 to 4.71). An interaction analysis suggested that the relative risk of disease relapse associated with either the 1st dose or with the 2nd or 3rd dose of COVID-19 vaccine was not significantly different on the basis of the type of glomerular disease (P value for interaction=0.5l). In a multivariable model that adjusted for patient characteristics at baseline, the risk of disease release associated with either the 1st dose (HR=0.65; 95 % CI, 0.32 to

1.32) or with the 2nd or 3rd dose of COVID-19 vaccine (HR=2.16; 95 % ci, 1.03 to 4.51) was similar to the unadjusted analysis.

In other hand the absolute risk of disease relapse after COVID-19 vaccination, after 210 days of follow-up with the 1st dose of COVID-19 vaccine was near zero for all types of glomerular disease. The absolute increase in risk associated with a 2nd or a 3rd dose of COVID-19 vaccine varied from 1%-2% in those with ANCA-GN, minimal change disease, membranous nephropathy or FSGS to as high as 3%-5% in those with IgA nephropathy or lupus nephritis, compared with the cumulative risk of a disease flare after 210 days of follow up in the absence of a COVID-19 vaccine and ranged from 6% (95% CI, 2% to 9%) in patient with membranous nephropathy to 19% (95% CI, 12% to 25%) in those with lupus nephritis.

There was no clear association between the type of COVID-19 vaccine and the risk of disease relapse (COMIRNATY: HR=0.99 [95% CI, 0.55 to 1.78]; SPIKEVAX: HR=1.3 [95% CI, 0.58 to 2.99]; VAXEVRIA: HR=1.64 [95% CI, 0.22 to 12.12]). The pattern of results was similar to the HR estimates from the extended Cox regression model, suggesting minimal unmeasured confounding in the primary analysis results. Nevertheless, the risk of glomerular disease relapse after the 1st dose of vaccination was negligible, the risk increased after the 2nd or 3rd dose.

AstraZeneca comment: In this article, the authors focused on determining relative and absolute risk of glomerular disease relapse after COVID-19 vaccination, and to evaluate the population level of incidence of glomerular disease relapse. Out of a total of 1016 adult patients with glomerular disease who received at least one COVID-19 vaccine dose, 134 patients developed a disease relapse suggesting that majority did not develop a relapse. The A self-controlled case series statistical analysis was used wherein, the occurrence of relapses is compared between "exposed" time (a 30-day exposure window after each vaccine dose they receive) and "unexposed" time (all other times). However, such comparison can be confounded by use of corrective treatment in unexposed time, but there was no information to confirm if effect of treatment was ruled out in comparisons. Other limitations are noted such as there were not a disease-specific definition of relapse; the narrative didn't provide vaccinees details about changes or modifications in their medications or treatments and, matching to disease activity at baseline. Considering the minority (3%) exposure to VAXZEVRIA, a comprehensive assessment was not possible.

Potential Mechanism of action

During the updated literature assessment, no relevant new safety information regarding Glomerulonephritis and Nephrotic Syndrome (Including Immunoglobulin A Nephropathy (IgAN)) and its association with VAXZEVRIA. In the updated review none of the articles provided relevant new hypothesised mechanism of action for Glomerulonephritis and Nephrotic Syndrome (Including IgAN) in association with mRNA or VAXZEVRIA.

Summary:

An analysis of the three relevant literature articles did not find any evidence of increased observed frequency of glomerulopathies in particular for adeno-vectored vaccines, compared to expected rates in general population. A further focus on literature cases for glomerulopathies and adeno-vectored vaccines did not find any significant safety concerns. There was insufficient evidence for a conclusive mechanism for glomerulopathies following VAXZEVRIA vaccination or adeno-vectored vaccines and that evidence from mRNA vaccine types cannot be comprehensively extrapolated to all other vaccines.

Conclusion

Based on the review of the currently available data, AstraZeneca considers that there is insufficient evidence to conclude a causal association between VAXZEVRIA and Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy). It is AstraZeneca's opinion that no updates to CDS or RMP are warranted at this time.

AstraZeneca will continue to monitor safety information for Glomerulonephritis AND Nephrotic syndrome (including IgA Nephropathy) as part of routine safety surveillance activities and take further actions as deemed necessary. AstraZeneca will no longer discuss this topic in future PBRERs, unless significant new safety information arises.

15.2.4 Venous Thromboembolism (VTE)

Background

In the updated assessment report received from the PRAC EMA (PRAC PAR (EMEA/H/C/PSUSA/00010912/202206) for the VAXZEVRIA PBRER (review period: 29 December 2021 to 28 June 2022), further information on the topic of Venous thromboembolism has been requested as follows:

The MAH is requested further investigate VTE by providing an updated literature review, with a focus on new relevant epidemiological studies.

AstraZeneca's responses to these requests are provided in the subsections below.

AstraZeneca performed a literature search for the period 29 June 2022 to 28 December 2022 in Embase and InsightMeme databases to identify any new articles discussing Venous Thromboembolism with COVID-19 vaccines, including VAXZEVRIA using the following search terms: venous thromboembolism, venous thrombosis, deep vein thrombosis, embolism, embolus, blood clot, infarction, occlusion, lung infarction, pulmonary thrombosis, cerebrovascular stroke, stroke, cerebral stroke, acute stroke, transient ischemic attack, ischemic strokes, brain vascular accident, brain infarction, intracranial venous thrombosis (ICVT).

The search yielded 129 articles (comprised of case reports, meta-analyses, and epidemiological studies). After review four full-text articles were considered relevant for discussion, (Burn Roel et al 2022 Ohaeri et al 2022). Two of the new studies by Burn Li et al

2022 (already discussed in the last PBRER) had previously been included as pre-publications in medRxiv and have now been published in a peer-reviewed journals, and the articles from medRxiv were hence replaced by the published studies. As these two studies (Burn Li et al 2022, Burn Roel et al 2022) following publication in peer-reviewed journals reported a longer follow-up period the effect estimates have been updated accordingly. Adding the new studies to the ones that had been included in the last PBRER resulted in a total of 14 studies (Table 49).

Cerebrovascular venous and sinus thrombosis (CVST), pulmonary embolism (PE) and Deep vein thrombosis (DVT)

Five studies out of the 14 assessed the association between VAXZEVRIA and CVST (Table 49 and Table 50), two of which reported a statistically significant association Burn Li et al 2022 and three did not find a significant association (Laporte et al 2021, Hviid et al 2022, Ohaeri et al 2022). Six studies out of 14 assessed the association between VAXZEVRIA and PE, three of which found no association (Burn Roel et al 2022, Hviid et al 2022, Li Burn et al 2022), one reported a decreased risk in those 70 or over, (Whiteley et al 2022), one found an increased risk after VAXZEVRIA vaccination (Botton et al 2022), and one found an increased risk after dose one and a decreased risk after dose 2 (Burn Li et al 2022). Five out of 14 studies assessed the association between VAXZEVRIA and DVT, whereof one found an increased risk after VAXZEVRIA vaccination (Hviid et al 2022), one found a decreased risk in those 70+ (Whiteley et al 2022), two found no association (Burn Li et al 2022, Burn Roel et al 2022) and one found an increased risk in one database but no association in the meta-analysis of all included databases Li Burn et al 2022 (Table 49 and Table 50).

Other venous thromboembolic events

Other venous thromboembolic events included in the studies included Portal vein thrombosis (PVT) (two studies, no association found in either (Laporte et al 2021, Whiteley et al 2022), intracranial venous thrombosis (ICVT) (one study that found an association in those <70 years old (Whiteley et al 2022), cerebral venous thrombosis (CVT) (one study that found an association in those below the age of 65 years (Andrews et al 2022), splanchnic venous thrombosis (SVT) (3 studies, where neither found an association (Burn Li et al 2022, Burn Roel et al 2022, Hviid et al 2022) and Mesenteric thrombosis (MEST) (one study that found no association (Laporte et al 2021) (Table 49 and Table 50).

Overall venous thromboembolic events (VTE)

Eleven studies out of 14 assessed the association between VAXZEVRIA and VTE, two reported no statistically significant association (Burn Roel et al 2022, Li Burn et al 2022, Li et al 2022) and one reported a decreased risk in those 70 or older (Whiteley et al 2022), one reported a decreased risk for those 70-79 and an increased risk for woman younger than 50 (Corrao et al 2022) six reported an increased risk after VAXZEVRIA vaccination (Hippisley-Cox et al 2021, Laporte et al 2021, Al Bakr and Alaithan 2022, Andrews et al 2022, Chen et

al 2022, Dag Berild et al 2022, Rahman and Seidler registered 02 July 2021) and one reported an increased risk after dose one and a decreased risk after dose two (Burn Li et al 2022) (Table 49 and Table 50).

The majority of the studies assessing the association between VAXZEVRIA and VTE reported an association between exposure to VAXZEVRIA and an increased risk of VTE. The associations were found in the SCCS studies that compared post vaccination time to control time in the cases, and cohort studies using non-vaccinated or historical controls. In the studies that presented results stratified by sex and age this increased risk was only reported in younger age groups and in women (Andrews et al 2022, Corrao et al 2022). Relative risks by sex and age group (for the studies where these estimates were available). The highest relative risk was reported by Laporte et al 2021, who found those vaccinated with VAXZEVRIA were 3.68 times more likely to experience VTE compared to historical controls. However, this study only adjusted the effect estimate for sex and age and did not exclude participants with history of study outcomes, making confounding likely. Other studies (Table 49) reported between a 10% (corresponding to 66 excess case per 1 million vaccinations, Hippisley-Cox et al 2021, and 2.43 times the risk (corresponding to 23,207 citizens vaccinated per one harmful event among women of less than 50 years of age, (Corrao et al 2022) and a risk difference of 8.35 cases (95% CI 0.21 to 16.49) of DVT per 100,000 vaccinations in frontline health care personnel consisting mainly of younger women (Hviid et al 2022).

Table 49 Design overview of large population-based studies (N=14) and AstraZeneca's comments

Reference, Country	Data source	Time period	Design	Comparator	AstraZeneca comments
England (Whiteley et al 2022)	Primary care (GPES), covid and vaccination (NIMS, GDPPR), secondary care (HES, SUS) pharmacy (NHS BSA), and death registrations.	08 December 2020 to 18 March 2021	Cohort study	Unvaccinated or pre-vaccination person time	Adjusted for several confounding factors. End date before diagnostic effort was expected to be concentrated in people receiving AZD1222. Unmeasured confounding and misclassification of confounding factors is probable.
England (Hippisley-Cox et al 2021)	COVID and vaccination (NIMS, GDPPR), secondary care (HES, SUS), and death registrations.	01 December 20 20 to 24 April 2021	Self-controlled case series (SCCS)	Exposed time periods (after vaccination or SARS-CoV-2 infection) compared with unexposed baseline periods in people with the outcome of interest (excluding the pre-risk interval)	SCCS method widely used in vaccine research. Robustness of the findings for most outcomes. Detailed data for risk periods after vaccine exposure. Less severe cases from primary care not included. Selection bias by including only those with outcome.
France (Botton et al 2022)	SNDS (France), hospital discharge diagnoses linked to vaccination files, 18 to 74 years old	06 February 202 1 to 20 July 2021 for AZD1222.	Self-controlled case series (SCCS)	Three weeks following the first dose, and if applicable the second and third doses. All other observation periods were considered reference periods.	Large study population representing the population of France with high vaccine exposure. SCCS design widely used in vaccine research Crude case definitions used for thrombosis. A case-only analysis risks selection bias by including only those individuals pre-disposed to experiencing thrombotic events.
England (Andrews et al 2022)	Vaccination (NIMS), secondary care (SUS), and death registrations.	30 November 20 20 to 18 April 2021	Cohort study	Unvaccinated period with an offset for population at risk (person days).	Less severe cases not included. Vaccinated cohort was compared to an unvaccinated cohort, but only for few confounders were adjusted for, not including health relevant comorbidities. This may have led to an overestimation of RIs.
Spain (Laporte et al 2021)	CMBD register (discharge diagnoses), Catalonia, Spain	01 January 2021 to 18 April 2021.	Cohort study with historical controls	General population in Catalonia on 01 January 2019 with	Differences in study periods when using historical controls can lead to confounding.

Table 49 Design overview of large population-based studies (N=14) and AstraZeneca's comments

Reference, Country	Data source	Time period	Design	Comparator	AstraZeneca comments
				follow up to 31 December 2019	Adjusted for age and sex only, thus risk of residual confounding.
Denmark, Norway and Finland (Dag Berild et al 2022)	The Norwegian Immunization Register SYSVAK, the Finnish National Vaccination Register, and the Danish Vaccination Register (exposure) and the national patient registers (outcome)	01 January 2020 to 16 May 2021.	Self-controlled case series	The risk period was 28 days postvaccination. The control period was 01 January 2020 to 14 days prior to vaccination, or COVID infection.	Nationwide registers including the whole populations used. However, less severe cases from primary care not included. Patient acted as their own control; therefore, time invariant confounding was controlled for. Selection effect by including only those with outcome Control period included 2020 to allow adjustment for seasonal variability, this may have introduced a bias, since access to health care may have been affected by the pandemic. A pre-risk period of 14-days was used to ensure events did not influence subsequent exposures.
Malaysia.(Ab Rahman et al 2022)	Malaysia Vaccine Administration System (MyVAS) database and the Malaysian Data Warehouse (MyHDW), a national health data repository that collects data from public and private hospitals in Malaysia	01 February 2021 to 30 September 2021	Self-controlled case series	The risk period was 21 days postvaccination. The control period was between 01 February 2021 and 30 September 2021, except a 14-day pre vaccination risk window and the vaccination day (day 0).	Nationwide registers including the whole populations used. About 8% were vaccinated with AZD1222. Less severe cases from primary care not included. Patient acted as their own control; therefore, time invariant confounding was controlled for. A pre-risk period of 14-days was used to ensure events did not influence subsequent exposures. Selection effect by including only those with outcome. Due to the vaccination roll out the sample have a large proportion of frontline health workers, elderly, and risk groups.

Table 49 Design overview of large population-based studies (N=14) and AstraZeneca's comments

Reference, Country	Data source	Time period	Design	Comparator	AstraZeneca comments
					Opt-in stream for the ChAdOx1-S vaccine was introduced in May 2021-due to high demand it was reintroduced to regular roll out.
Multicountry Chen et al 2022	Pubmed, Embase, Cochrane COVID-19 Study Register, Cochrane Library, Chinese National Knowledge Infrastructure, Wanfang Data Knowledge Service Platform (Wanfang) and SinoMed.	Published 01 January 2020 to 20 October 2021.	Systematic review and meta-analysis	Unvaccinated population or population that received placebo	Great heterogeneity among the studies, the I^2 of most AEs was above 90%. Grouped viral vector vaccines: Ad26.COV2.S, ChAdOx1 and Sputnik V Study population in some studies are comprised of patient groups such as transplant recipients or cancer patients, while some includes health care workers, health care workers with previous severe allergic diseases, and the general population. The adverse event rates of venous and arterial thrombosis would differ between these populations and to meta-analyse them makes interpretation difficult.
Lombardy, Italy (Corrao et al 2022)	The Regional Health Service (RHS) management, the registry of patients with a confirmed diagnosis of SARS-CoV-2 infection and the COVID-19 vaccination registry	27 December 20 20 to 03 May 2021	Cohort study	Unvaccinated or pre-vaccination person time, matched on sex and age 1:10	The outcomes were measured in a hospital setting, so they did not include milder cases treated in primary care. A large number of health conditions were considered as confounders and adjusted for. Residual confounding still probable. Population-based but only include one region.
Denmark (Hviid et al 2022)	The Danish vaccination register and the Danish National Patient Register	27 December 20 20 to 13 April 2021	Cohort study	Unvaccinated risk time from all individuals starting on 27 December 2020. Those who were still unvaccinated after 28 days then contributed with another 28-day	Only included frontline personnel: health care and social services workers. Adjusted for several confounding including comorbid conditions associated with risk for severe COVID-19 using inverse probability weights.

Table 49 Design overview of large population-based studies (N=14) and AstraZeneca's comments

Reference, Country	Data source	Time period	Design	Comparator	AstraZeneca comments
				observation period, and so forth until any vaccination, event, or censoring, whichever came first	Outcomes measured in a hospital setting- milder cases not included. The median age at study start was 44 years, and 82% of participants were female.
UK 2022 (Burn Li et al 2022)	Clinical Practice Research Datalink (CPRD) AURUM (primary care medical records)	08 December 20 20 and 02 May 2021. Follow up time was 28 days from their first vaccination.	Cohort study with historical controls	A general population background cohort included people in CPRD as of 1 January 2017. Follow-up for this cohort ran up to 31 December 2019.	Differences in study periods when using historical controls can lead to confounding. Primary care data, possible underestimation of outcomes diagnosed in hospital. Adjusted for age and sex only, thus risk of residual confounding.
Spain, (Burn Roel et al 2022)	SIDIAP, Catalonia, Spain	27 December 20 20 to 23 June 2021	Cohort study with historical controls	Historical controls present in the database 1 January 2017 followed until 31 December 2019	Differences in study periods when using historical controls can lead to confounding. Historical general population cohort were younger and healthier, compared to vaccinated cohorts, reflecting vaccination guidelines adjusted for age and sex only, thus risk of residual confounding.
(Li Burn et al 2022)	Clinical Practice Research Datalink Aurum (UK CPRD) Information System for Research in Primary Care with minimum basic set of hospital discharge data (CMBD-HA; Spain SIDIAP) Integrated Primary Care Information (Netherlands IPCI)	December 2020 to the latest data release available in each of the contributing databases (ie, mid-2021). Follow-up was to 28 days after vaccination	Retrospective Cohort Study	Active comparators, vaccinated with BioNTech, Pfizer vaccine	Only data from UK CPRD, Germany DA had sufficient cases to be reported separately, Netherlands IPCI and France LPD were included in the meta-analysis. The combined VTE variable also contained arterial TE, MI and ischemic stroke. Propensity score matched on age, sex, index year, and index month, Romano's adapted Charlson Comorbidity Index, CHA2DS2-VASc, congestive heart failure, hypertension, vascular disease, and

Table 49 Design overview of large population-based studies (N=14) and AstraZeneca's comments

Reference, Country	Data source	Time period	Design	Comparator	AstraZeneca comments
	IQVIA Longitudinal Patient Data France (France LPD) IQVIA Disease Analyser Germany (Germany DA)				total number of medicines, procedures, and measurement records. Primary care data, possible underestimation of outcomes diagnosed in hospital.
(Ohaeri et al 2022)	Secure Anonymized Information Linkage (SAIL) GP data from Wales, linked to NHS Wales.	01 January 2020 to 28 March 2021.	Retrospective Cohort Study	The pre-exposure period (the same participant could contribute both exposed and unexposed time under observation to the study)	Low vaccination exposure in the study period (34.0%) could affect generalisability. Adjusted for the confounders: age, sex, ethnicity, deprivation, comorbidity, and exposure to both SARS-CoV-2 virus and vaccination within 28 d of each other. Correlation between study participants as a person could contribute to both exposed and unexposed time were not considered in the statistical analysis.

BSA Business Services Authority; CMBD- Minimum Basic Data Set; CoV-2- Coronavirus -2; COVID-19- Coronavirus Disease Of 2019; CPRD- Clinical Practice Research Datalink; DA- Disease Analyser; GDPPR- General Practice Extraction Service Data for Pandemic Planning and Research; GPES- General Practice Extraction Service; HES- Hospital Episode Statistics; IPCI- Integrated Primary Care Information; LPD- Longitudinal Patient Data; MI- Myocardial Infarction; MyHDW - Malaysia Data Warehouse; MyVAS- Malaysia Vaccine Administration System; NHS- National Health Service; NIMS- National Immunisation Management System; RHS- Regional Health Service; SAIL- Secure Anonymized Information Linkage; SARS- Severe Acute Respiratory Syndrome; SCCS- Self-Controlled Case Series; SIDIAP- Spanish population primary care database; SNDS- French Administrative Health Care Database; SUS- Secondary Uses Service; TE- Thromboembolism; UK- United Kingdom; VTE- Venous Thromboembolism.

Table 50 Summary of large population-based studies on relative risk of studied events

Reference, Country	Design (time window)	Relative risk (95% Confidence interval)				
		VTE	CVST	PE	DVT	Other VTE
Whiteley et al 2022, England	Cohort study (fully adjusted rates 1-28 days)	<70 years: 0.97 (0.90–1.05), 70+years: **0.58 (0.53–0.63)**		<70 years: 0.95 (0.85–1.05), 70+years: **0.54 (0.48–0.61)**	<70 years: 0.99 (0.87–1.12), 70+years: **0.63 (0.54–0.74)**	PVT: <70 years: 1.00 (0.24–4.15), 70+years: 0.61 (0.10–3.71) ICVT: <70 years: **2.27 (1.33–3.88)**, 70+years: 0.67 (0.20–2.18)
Hippisley-Cox et al 2021 England	SCCS (8-14 days)	**1.10 (1.02 to 1.18)**	**4.01, (2.08 to 7.71)**			
Botton et al 2022, France	SCCS (8-14 days only the treatment studied)			**1.30 (1.04–1.62)**		
Andrews et al 2022 England	Cohort study (4-13 days fully adjusted rates)	15-39 years: **2.2 (1.7-3.0)**, 40-64 years: **1.3 (1.1-1.4)**, 65+ years: 0.9 (0.8-1.0)				CVT: 15-39 years: **16.3 (9.9-27)**, 40-64 years: **2.7 (1.6-4.6)**, 65+ years: 0.4 (0.1-1.7)
Laporte et al 2021 Spain	Cohort study, adjusted age/sex	**3.68 (2.27–6.01)**	0.42 (0.09 to 2.01)			MEST: 0.21 (0.04–1.74), PVT: 0.63 (0.12–2.39)
Dag Berild et al 2022 Denmark, Norway and Finland	Self-controlled case series (28-days)	**1.83 (1.56 to 2.15)**				
Ab Rahman et al 2022 Malaysia	Self-controlled case series (21-days)	**2.22 (1.17 to 4.21)**				

Table 50 Summary of large population-based studies on relative risk of studied events

Reference, Country	Design (time window)	Relative risk (95% Confidence interval)				
		VTE	CVST	PE	DVT	Other VTE
Chen et al 2022, multicountry.	Systematic review and meta-analysis (Differed between studies) **NOTE: viral vector vaccines**	**1.128 (1.023 to 1.1244)**				
Corrao et al 2022, Lombardy, Italy.	Cohort study (1-28 days)	Women: **<50: 2.43 (1.05 to 5.63)** 50–59: 1.53 (0.54 to 4.38) 60–69: 0.78 (0.28 to 2.18) **70–79: 0.39 (0.21 to 0.72)** 80+(no cases) Men <50: 0.29 (0.04–2.12) 50–59: 1.12 (0.34–3.69) 60–69: 0.81 (0.39–1.68) **70–79: 0.40 (0.24–0.69)** 80+: 1.18 (0.14–9.88)				

Table 50 Summary of large population-based studies on relative risk of studied events

Reference, Country	Design (time window)	Relative risk (95% Confidence interval)				
		VTE	CVST	PE	DVT	Other VTE
Hviid et al 2022, Denmark	Cohort study (0-28days) **NOTE: risk difference per 100 000 vaccinations**		1.68 (-0.64 to 4.00)	0.93 (-2.35 to 4.21)	**DVT: 8.35 (0.21 to 16.49)**	SVT: 0.84 (-0.80 to 2.48)
Burn Li et al 2022 UK 2022	Cohort study, rates age standardised	**First dose: 1.12 (1.05 to 1.20) Second dose: 0.84 (0.73 to 0.96)**	**First dose: 4.14 (2.54 to 6.76)**	**First dose: 1.26 (1.15 to 1.38) Second dose: 0.79 (0.65 to 0.97)**	First dose: 1.02 (0.93 to 1.11) Second dose: 0.86 (0.72 to 1.02)	SVT: First dose: 1.22 (0.76 to 1.97) Second dose: 1.34 (0.56 to 3.21)
Burn Roel et al 2022 Spain 2022	Cohort study, rates age standardised	0.92 (0.71–1.18)		0.78 (0.52–1.16)	0.89 (0.65–1.22)	SVT: 1.09 (0.54–2.18)
Lai et al 2016 (UK CPRD)	Cohort study with active comparators	First dose: 0.91 (0.78 to 1.06) Second dose: 0.87 (0.66 to 1.16)		First dose: 0.93 (0.77 to 1.12) Second dose: 0.86 (0.58 to 1.26)	First dose: 0.89 (0.71 to 1.11) Second dose: 0.93 (0.65 to 1.34)	
Lai et al 2016 (Germany DA)	Cohort study with active comparators	1.61 (0.92 to 2.83)		0.69 (0.26 to 1.83)	**2.62 (1.34 to 5.13)**	
Li et al 2022 (Meta analysis of UK CPRD, Germany DA Netherlands IPCI and France LPD)	Cohort study with active comparators	First dose:1.3 (0.75 to 2.26) Second dose (UK and Germany): 0.84 (0.65 to 1.09)		First dose: 0.96 (0.79 to 1.15) Second dose (UK and Germany): 0.83 (0.58 to 1.2)	First dose:1.58 (0.56 to 4.42) Second dose (UK and Germany): 0.93 (0.66 to 1.31)	

Table 50 Summary of large population-based studies on relative risk of studied events

Reference, Country	Design (time window)	Relative risk (95% Confidence interval)				
		VTE	CVST	PE	DVT	Other VTE
Ohaeri et al 2022	Cohort study comparing to the pre-exposure period		1.40 (0.95 to 2.05)			

CPRD- Clinical Practice Research Datalink; CVST: Cerebrovascular venous and sinus thrombosis; CVT- Cerebral venous thrombosis; DA- Disease Analyse; DVT-Deep vein thrombosis; IVCT- intracranial venous thrombosis; IPCI- Integrated Primary Care Information; LPD- Longitudinal Patient Data; , MEST: Mesenteric thrombosis; PE: Pulmonary embolism; PVT: Portal vein thrombosis; SCCS- Self-Controlled Case Series ; SVT: splanchnic venous thrombosis; UK United Kingdom; VTE: venous thromboembolism.

Table 51 Sex and age stratified results, exclusion of previous cases and definition of VTE

Study	Sex differences	Age differences	Previous cases excluded	Definition of VTE
Li et al 2022	Only in CPRD (UK) Men:0.88 (0.7 to 1.11) Women:0.92 (0.74 to 1.14)	Only in CPRD (UK) 30-39:1.38 (0.48 to 3.93) 40-49:0.75 (0.39 to 1.45) 50-59:0.68 (0.44 to 1.05) 60-69:0.81 (0.53 to 1.23) 70-79:1.01 (0.79 to 1.3) 80-89:1.11 (0.77 to 1.59)	No	SNOMED codes for: deep vein thrombosis or pulmonary embolism, cerebral venous sinus thrombosis, splanchnic and visceral vein thrombosis ischaemic stroke, myocardial infarction, arterial thromboembolism as a composite of ischaemic stroke, and other rare arterial thromboembolisms such as intestinal infarction (codes not included due to long list)
Ohaeri et al 2022	Men: 1.47 (0.95-2.28) Women:1.16 (0.66-2.06)	<50: 1.00 (1.00-1.00) 50+: 5.23 (4.43-6.17)	Yes 365 day washout period.	CVST hospitalization or GP contact identified using International Classification of Diseases-10 (ICD-10) codes in PEDW or Read codes in WLGP (codes not included due to long list)
Dag Berild et al 2022	Women, RR:2.46 (2.06-2.94) Men, RR:1. 47 (1.17-1.86)	1987 or later RR: 3.79 (2.29-6.29) Born 1972-1986 RR: 2.85 (1.96-4.13)	Yes, a washout period of 3 years (2017-2019).	ICD-10 codes Pulmonary embolism I26 Phlebitis and thrombophlebitis of femoral vein I80.1

Table 51 Sex and age stratified results, exclusion of previous cases and definition of VTE

Study	Sex differences	Age differences	Previous cases excluded	Definition of VTE
	NOTE: Stratified analysis is for coagulation disorders a measure that included venous thrombosis, arterial thrombosis, disseminated intravascular coagulation, purpura and other haemorrhagic conditions, thrombocytopenia and thrombotic microangiopathy.	Born 1971 or earlier: RR:1.80 (1.54-2.11)		Phlebitis and thrombophlebitis of other and unspecified deep vessels of lower extremities I80.2 Phlebitis and thrombophlebitis of lower extremities, unspecified I80.3 Phlebitis and thrombophlebitis of other sites I80.8 Phlebitis and thrombophlebitis of unspecified site I80.9 Portal vein thrombosis I81 Other venous embolism and thrombosis I82
Ab Rahman et al 2022	Men RR: 1.62 (0.75, 3.51) Women RR: 5.34 (1.45, 19.7)	Age <60 RR: 2.92 (1.23, 6.92) Age ≥60 RR: 1.38 (0.50, 3.85)	Yes, those who had records of hospital admissions for the same diagnosis in the two years before the study period were excluded.	ICD-10 codes: Include pulmonary embolism, lower limb venous thrombosis, splanchnic thrombosis, other venous thrombosis (I80, I80.1, I80.2, I80.29, I80.3, I82.2, I82.8, I82.9, I26, I26.9, I81, I82.0, I82.1, I82.3)
Corrao et al 2022	Women: <50: 2.43 (1.05 to 5.63) 50–59: 1.53 (0.54 to 4.38) 60–69: 0.78 (0.28 to 2.18) 70–79: 0.39 (0.21 to 0.72) 80+(no cases) Men <50: 0.29 (0.04–2.12) 50–59: 1.12 (0.34–3.69) 60–69: 0.81 (0.39–1.68) 70–79: 0.40 (0.24–0.69) 80+: 1.18 (0.14–9.88)		Unclear if excluded "Hospital admissions and drug prescriptions experienced within 2 years before the index date were used to investigate a list of 62 conditions possibly affecting the risks of severe/fatal clinical manifestations of SARS-CoV-2 infection, and/or venous thromboembolism"	ICD-9 codes: 415.1 Pulmonary embolism and infarction 437.6 Nonpyogenic thrombosis of intracranial venous system 451 Deep vein thrombosis 452 Portal vein obstruction 453.0 Budd-Chiari syndrome (hepatic vein thrombosis) 453.1 Thrombophlebitis migrans 453.2 Embolism of Vena Cava 453.3 Embolism and thrombosis in renal vein 557.1 Mesenteric vein thrombosis

Table 51 Sex and age stratified results, exclusion of previous cases and definition of VTE

Study	Sex differences	Age differences	Previous cases excluded	Definition of VTE
Hviid et al 2022	Not stratified, but sample contained 81.7% females.	Not stratified, participants median age at study start was 44 years (interquartile range [IQR], 32 to 54 years)	Yes, for each study outcome, persons who had that outcome between 1 January and 26 December 2020 were not included in the cohort for analysis of that specific outcome.	ICD-10 codes: Cerebral venous sinus thrombosis I636, I676 Splanchnic vein thrombosis I81, I820, I823 Pulmonary embolism I26 Deep venous thrombosis I801-I809, I821, I828, I829 (analysed separately, only CVT had a significant association)
Whiteley et al 2022	Men RR: 0.81 (0.75–0.87) Women RR: 0.90 (0.84–0.97)	<70 years: 0.97 (0.90–1.05), 70+years: 0.58 (0.53–0.63)	It was adjusted for: "We defined history of deep vein thrombosis (DVT) or pulmonary embolism (PE) as any record in primary care and/or hospital admission data before 8 December 2020".	Venous thromboembolic events: PE, lower limb DVT, intracranial venous thrombosis (ICVT), portal vein thrombosis, and venous thrombosis at other sites.
Hippisley-Cox et al 2021	Women 8-14 days RR: 1.17 (1.05, 1.29) Men 8-14 days RR: 1.04 (0.93, 1.16)	Age ≤ 50 8-14 days RR: 1.19 (0.96, 1.48) Age > 50 8-14 days RR: 1.09 (1.01, 1.18)	No, previous history of the outcomes are reported in Table 1.	ICD-10 I26 - Pulmonary embolism I260 - Pulmonary embolism with mention of acute cor pulmonale I269 - Pulmonary embolism without mention of acute cor pulmonale I81 - Portal vein thrombosis I81X - Portal vein thrombosis I82 - Other venous embolism and thrombosis I820 - Budd-Chiari syndrome I822 - Embolism and thrombosis of vena cava

Table 51 Sex and age stratified results, exclusion of previous cases and definition of VTE

Study	Sex differences	Age differences	Previous cases excluded	Definition of VTE
				I823 - Embolism and thrombosis of renal vein I828 - Embolism and thrombosis of other specified veins I829 - Embolism and thrombosis of unspecified vein
Andrews et al 2022	Not stratified	15-39 years: 2.2 (1.7-3.0), 40-64 years: 1.3 (1.1-1.4), 65+ years: 0.9 (0.8-1.0)	Yes, individuals with a prior admission with a thrombotic code in any of the first five diagnosis fields between 1st December 2019 and 29th November 2020 were excluded.	non-cerebral venous thrombosis included thrombophlebitis, deep venous or splanchnic vein thrombosis or pulmonary embolism- here termed "other venous thrombosis"
Laporte et al 2021	Not available	Not available	No	VTE was a composite variable of cerebral venous sinus thrombosis (CVST), mesenteric thrombosis (MesT), portal vein thrombosis (PVT)

CPRD- Clinical Practice Research Datalink; CVST: Cerebrovascular venous and sinus thrombosis; CVT- Cerebral venous thrombosis; DVT-Deep vein thrombosis; GP-General Practitioner; ICD-International Classification of Diseases; IVCT- intracranial venous thrombosis; IQR-Interquartile Range; PE: Pulmonary embolism; PEDW- Patient Episode Dataset For Wales; PVT: Portal vein thrombosis; RR- Relative Risk; SARS-Severe Acute Respiratory Syndrome; SNOMED-Systematized Nomenclature Of Medicine Clinical Terms; UK United Kingdom; VTE: venous thromboembolism; WLGP-Welsh Longitudinal General Practice Dataset.

Conclusion:

AstraZeneca performed a comprehensive literature review covering period 29 June 2022 to 28 December 2022 with focus on new relevant epidemiological studies. These new relevant studies were added to the cumulative review reported in the last PBRER. The studies included in this cumulative review showed varied results, with some finding an increased risk of VTE after VAXZEVRIA vaccination and some finding a protective effect. AstraZeneca acknowledges the authors' views and suggestions; however overall literature data did not suggest a causal

relationship between VAXZEVRIA and VTE. Given the heterogeneity of the published studies, AstraZeneca is of the opinion that conducting a meta-analysis of all available data would not add valuable information over the routine ongoing literature review. CVST is sufficiently characterised in the SmPC sections 4.4 and 4.8, and adequately managed through routine clinical practice with maintenance of a favourable benefit-risk balance.

15.2.5 Thrombosis

In the assessment report received from the PRAC (PAR (EMEA/H/C/PSUSA/00010912/202206) for the VAXZEVRIA PBRER (review period: 29 December 2021 to 28 June 2022), the PRAC requested AstraZeneca to provide a tabular summary of the fatal cases reporting a thrombotic event after dose 3 (or dose 4) of the vaccine.

AstraZeneca response:

A cumulative search (29-December-2020 to 28-December-2022), of the AstraZeneca Global Patient Safety Database was conducted using the following MedDRA (v25.1): SMQ of Embolic and thrombotic events (ETE). The search resulted in 25 cases with fatal outcome reported after dose 3 or dose 4 of Covid-19 vaccine. A tabular summary of the fatal cases is presented below. The primary dose information is unknown in most cases.

Table 52 Tabular Summary of Fatal Cases reporting Thrombotic event after dose 3 or 4 of vaccine

Sr. No	Case ID Country	Events (Preferred Term)	Age in years /Sex	Primary / Booster vaccine	Time to onset	WHO-UMC causality assessment	Comment
1	[redacted] Italy	Thrombosis; Platelet count decreased; Off label use	Unknown /M	Unknown/ Unidentified AstraZeneca Product	Unknown	Unassessable /Unclassifiable with Limited information	There is very limited information available for this case. Not clear if the vaccinee received VAXZEVRIA, as VAXZEVRIA is not used in Italy for booster dose. The patient died from the event of thrombosis during December 2021.No autopsy was performed. Report was based on a social media post
2.	[redacted] Unknown	Pulmonary embolism; Haemorrhagic stroke; Thrombocytopenia	38 /F	VAXZEVRIA booster	10	Possible with limited information	The vaccinee died due to pulmonary embolism, hemorrhagic stroke and thrombocytopenia. No autopsy was performed. This spontaneous case has limited information such as baseline health condition of the vaccinee before vaccination, relevant family and medical history, concurrent diseases and concomitant medications, clinical course of the events,

Table 52 Tabular Summary of Fatal Cases reporting Thrombotic event after dose 3 or 4 of vaccine

Sr. No	Case ID Country	Events (Preferred Term)	Age in years /Sex	Primary / Booster vaccine	Time to onset	WHO-UMC causality assessment	Comment
							treatment given, etiologic and diagnostic work up (physical and neurological evaluation), which precludes causality assessments
3.	[redacted] Unknown	Thrombosis with thrombocytopenia syndrome	37 /F	VAXZEVRIA booster	8	Possible with confounders	The vaccinee died from the event of thrombosis syndrome with thrombocytopenia. No autopsy was performed. The vaccinee was morbidly obese which could be a contributory factor to the fatal event.
4.	[redacted] Unknown	Loss of consciousness; Hypotension; Platelet disorder; Thrombosis	22/F	Pfizer/ AZD1222	10	Possible with limited information	The patient died from the event of loss of consciousness, hypotension, abnormal platelets and thrombosis. No autopsy was performed. This spontaneous case has limited information such as baseline health condition of the vaccinee before vaccination, relevant family and medical history, concurrent diseases and concomitant medications, clinical course of the events, treatment given, etiologic and diagnostic work up (physical and neurological evaluation), which precludes causality assessments.
5.	[redacted] Unknown	Thrombosis with thrombocytopenia syndrome	28/M	Unknown/ AZD1222	7	Possible with limited information	This is a spontaneous report. On 03-June-2022 patient took the 3rd dose of the AstraZeneca vaccine. Thrombosis at multiple sites was radiologically confirmed. Thrombocytopenia, Anti PF4 antibodies positive. D-dimer levels not reported, fibrinogen normal. Event had fatal outcome. No autopsy was performed.

Table 52 Tabular Summary of Fatal Cases reporting Thrombotic event after dose 3 or 4 of vaccine

Sr. No	Case ID Country	Events (Preferred Term)	Age in years /Sex	Primary / Booster vaccine	Time to onset	WHO-UMC causality assessment	Comment
6.	[redacted]/United Kingdom	Pulmonary embolism; Deep vein thrombosis; Vaccination error; Inflammatory marker increased; Decubitus ulcer; Peripheral swelling; Thrombocytopenia	86/F	AZD1222 / AZD1222	8	Possible with confounders	The vaccinee died due to pulmonary embolism. The vaccinee was elderly with a medical history of neoplasm malignant and vascular dementia, which would be considered as a confounder. No autopsy was performed.
7.	[redacted]/United Kingdom	Myocardial infarction; Eczema; Cardiac arrest; Cardiac death; Fatigue; Chest pain; Dyspnoea; Feeling cold; Asthenia	66/M	AZD1222 booster dose	10	Possible with confounder	The vaccinee died due to myocardial infraction. He felt cold and weak and had a cardiac arrest 10 days after booster dose. He died 2 weeks later. No autopsy was performed. The elderly age of the vaccinee and possible underlying hypercholesterolemia as suggested by the intake of concomitant statins could be considered as contributory factors to the fatal events Myocardial infarction.
8.	[redacted]/United Kingdom	Myocardial infarction	30/F	Unknown/ AZD1222	0	Possible with limited information	The vaccinee patient died from myocardial infarction the same day as vaccination. This spontaneous case has very limited information. No autopsy was performed.
9.	[redacted]/United	Ischaemic stroke	88/Unknown	Pfizer	91	Unlikely	The vaccinee died due to ischaemic stroke 91 days after the booster dose. He was

Table 52 Tabular Summary of Fatal Cases reporting Thrombotic event after dose 3 or 4 of vaccine

Sr. No	Case ID Country	Events (Preferred Term)	Age in years /Sex	Primary / Booster vaccine	Time to onset	WHO-UMC causality assessment	Comment
	Kingdom			/AZD1222			elderly with long term history of diabetes mellitus 2, which also be contributory factor to fatal event of ischaemic stroke. No autopsy was performed.
10.	[redacted] Mexico	Dyspnoea; Respiratory distress; Myocardial infarction	79/F	Unknown/ AZD1222	Unknown	Unassessable /Unclassifiable with Limited information	The vaccinee died from dyspnoea and respiratory distress on an unknown date. She was elderly with medical history of anteroseptal infarction. No autopsy was performed. This spontaneously reported case has very limited information.
11.	[redacted] Mexico	Guillain-Barre syndrome; Cerebral venous thrombosis; Headache; Myalgia	34/F	Unknown/ AZD1222	Unknown	Unassessable /Unclassifiable with Limited information	The vaccinee died from Guillain-Barre syndrome, Cerebral venous thrombosis, headache and myalgia on an unknown date. No autopsy was performed. There is limited information on the circumstances leading to the events, baseline health status, relevant medical and family history, concurrent diseases, concomitant medications, risk factors, etiological and complete diagnostic work-up (full diagnostic laboratory panel, physical examination, neurology examination, brain imaging), which preludes causality assessments.
12.	[redacted] United Kingdom	Cerebral infarction; Cerebral artery thrombosis; Cerebrovascular accident;	65/M	AZD1222 / Covid-19 Mrna Vaccine Biontech	Unknown	Unassessable /Unclassifiable with Limited information	The vaccinee died on an unknown date of atrial fibrillation, cerebral infarction and cerebral artery thrombosis. He had Covid-19 Mrna Vaccine Biontech booster dose. No autopsy was performed. This spontaneously reported case has

Table 52 Tabular Summary of Fatal Cases reporting Thrombotic event after dose 3 or 4 of vaccine

Sr. No	Case ID Country	Events (Preferred Term)	Age in years /Sex	Primary / Booster vaccine	Time to onset	WHO-UMC causality assessment	Comment
		Rhinorrhoea; Nasal congestion; Condition aggravated; Fatigue					very limited information which preludes causality assessment.
13.	[redacted]/United Kingdom	Myocardial infarction; Myelitis; Aphasia; Cardiac failure; Movement disorder; Amnesia	65/F	Unknown/ AZD1222	Unknown	Unassessable /Unclassifiable with Limited information	The vaccinee died from the event of heart attack on an unknown date. No autopsy was performed. This spontaneously reported case has very limited information which preludes causality assessment.
14.	[redacted]/Brazil	Pulmonary embolism	45/F	Pfizer/ AZD1222	Unknown	Unassessable /Unclassifiable with Limited information	The vaccinee died from pulmonary embolism on an unknown date. No autopsy was performed. There is very limited information on the fatal case such as risk factors, circumstances surrounding the event, concurrent conditions, concomitant medications, relevant medical history, detailed etiological and diagnostic work-up before death, which preludes causality assessment.
15.	[redacted]/United Kingdom	Myocardial infarction	64/F	Unknown/ AZD1222	0	Unassessable /Unclassifiable with Limited information	The vaccinee died from the event of myocardial infarction. She had a past medical history of malignant breast lump removal, radiotherapy which could be a contributory factor. An autopsy was performed, which concluded that the cause of death was heart attack, no other information was provided from the autopsy report.

Table 52 Tabular Summary of Fatal Cases reporting Thrombotic event after dose 3 or 4 of vaccine

Sr. No	Case ID Country	Events (Preferred Term)	Age in years /Sex	Primary / Booster vaccine	Time to onset	WHO-UMC causality assessment	Comment
16.	[redacted]/Philippines	Hemiparesis; Vomiting; Dysarthria	35/M	Unknown/ AZD1222	155	Unlikely	The vaccinee died due to left side body weakness, vomiting and slurred speech. No autopsy was performed. This spontaneously reported case has very limited information which preludes causality assessment.
17.	[redacted]/Brazil	Pulmonary thrombosis; Pulmonary embolism; Constipation; Syncope; Interchange of vaccine products; Malaise	73/M	Pfizer/ AZD1222 (4th Dose)	Unknown	Unassessable /Unclassifiable with Limited information	The vaccinee died from the event of pulmonary thrombosis and pulmonary thromboembolism. No autopsy was performed. He was elderly with a past medical history of smoking, this could be considered as a contributory factor to the fatal event of pulmonary thrombosis.
18.	[redacted]/Brazil	Pulmonary thrombosis; Loss of consciousness; Constipation; Syncope	72/M	Unknown/ AZD1222	Unknown	Unassessable /Unclassifiable with Limited information	The vaccinee died from the events of pulmonary thrombosis, sudden illness, constipation and fainting. No autopsy was performed. He was elderly with a past medical history of smoking, this could be considered as a contributory factory to the fatal outcome.
19.	[redacted]/United Kingdom	Cerebrovascular accident	92/F	Unknown/ AZD1222 / (3rd and 4th Dose)	Unknown	Unassessable /Unclassifiable with Limited information	The vaccinee had the fourth vaccine she suffered a major stroke and then died a few weeks later from stroke. No autopsy was performed. The vaccinee was elderly (92 year), which could be a confounder, there was limited information for this case which preludes causality assessment.

Table 52 Tabular Summary of Fatal Cases reporting Thrombotic event after dose 3 or 4 of vaccine

Sr. No	Case ID Country	Events (Preferred Term)	Age in years /Sex	Primary / Booster vaccine	Time to onset	WHO-UMC causality assessment	Comment
20.	[redacted] /Brazil	Embolism; Thrombocytopenia; COVID-19	57/M	Unknown/ AZD1222 (4th Dose)	19	Possible with limited information	The vaccinee died from the events of Embolism, Thrombocytopenia and COVID-19. No autopsy was performed. The vaccinee was tested positive for Covid-19 infection and also suffered pneumonia, which would be considered as contributory factor to the fatal event of embolism.
21.	[redacted] /Brazil	Haemorrhagic stroke; Headache	43/M	Unknown/ AZD1222	15	Possible with limited information	. The vaccinee died 15 days after taking the vaccine, from hemorrhagic stroke. No autopsy was performed. There is very limited information available for this case which preludes causality assessment. Report was based on a social media post
22.	[redacted] /Brazil	Thrombotic stroke	46/M	Unknown/ AZD1222 (4th Dose)	9	Possible with confounders	The vaccinee died 9 days after the 4th dose of AZD1222 vaccine. He had a past medical history of heart insufficiency and arterial hypertension which could be a contributory factor to the fatal thrombotic stroke. No autopsy was performed.
23.	[redacted] United States	Renal disorder; Deep vein thrombosis; Pulmonary embolism; Nephrotic syndrome; Dyspnoea; Dyspepsia;	Unknown/M	Pfizer/ AZD1222	Unknown	Unassessable /Unclassifiable with Limited information	On an unspecified date, the vaccinee died from the event of relapse of kidney disease, deep vein thrombosis and pulmonary embolism. No autopsy was performed. The reporter described off-label use of AZD1222 vaccine. There is limited information on baseline health condition before vaccination, demographic details, concurrent conditions and concomitant medications, relevant medical and family

Table 52 Tabular Summary of Fatal Cases reporting Thrombotic event after dose 3 or 4 of vaccine

Sr. No	Case ID Country	Events (Preferred Term)	Age in years /Sex	Primary / Booster vaccine	Time to onset	WHO-UMC causality assessment	Comment
		Cellulitis; Rash; Off label use; Interchange of vaccine products					history, onset dates of the events, details and circumstances surrounding the events, clinical course of the events, risk factors, and detailed diagnostic and etiologic workup, which preludes causality assessment.
24.	[redacted]/Brazil	Cerebrovascular accident	56/F	Unknown/ AZD1222	Unknown	Unassessable /Unclassifiable with Limited information	The vaccinee died from the event of cerebrovascular accident. No autopsy was performed. This spontaneously reported case has very limited information which preludes causality assessment.
25.	[redacted]/Philippines	Acute myocardial infarction	38/M	Unknown/ AZD1222	Unknown	Unassessable /Unclassifiable with Limited information	The vaccinee died from the event of acute myocardial infarction. No autopsy was performed. This spontaneously reported case has very limited information such as baseline health condition before vaccination, date of vaccine administration, relevant medical and family history, concurrent conditions and concomitant medications, risk factors, clinical course of the event, detailed diagnostic and etiologic workup (complete blood analysis including infectious workup, neurological examination, coagulation profile, cardiac profile, imaging studies of heart and brain),which preludes causality assessment

WHO Health Organization; UMC Uppsala Monitoring Centre

15.2.6 Use in immunocompromised patients

In the assessment report received from the PRAC (PAR (EMEA/H/C/PSUSA/00010912/202206) for the VAXZEVRIA PBRER (review period: 29 December 2021 to 28 June 2022), the PRAC requested AstraZeneca to is requested to verify the PTs reported in fatal cases, especially regarding TTS and Thrombocytopenia.

AstraZeneca Response:

AstraZeneca has verified all the PTs with fatal outcomes and including TTS and Thrombocytopenia for use of VAXZEVRIA in subjects with severe immunodeficiency, see section 16.3.5.2.

15.2.7 Severe cutaneous adverse reactions (SCAR)

Background

In the assessment report received from the PRAC (PRAC PAR (EMEA/H/C/PSUSA/00010912/202112) for the VAXZEVRIA PBRER (review period: 29 December 2021 to 28 June 2022), the PRAC requested *AstraZeneca to provide a cumulative review of cases of SCARs reported with VAXZEVRIA, as well as a review of the literature, and to discuss on the need to update the PI on this topic.*

AstraZeneca evaluation of this topic is presented below.

Pre-Clinical Data

There is no pre-clinical data on SCARs with VAXZEVRIA.

Clinical Study Data

A search was conducted in the AstraZeneca clinical database for AE reports of SCARs following the use of VAXZEVRIA reported from clinical studies (data cut-off of 07 December 2020 for the Oxford pooled studies [COV001, COV002, COV003, and COV005] and 11 March 2022 for United States Study [DCO4)]). The search utilized the following Medical Dictionary for Regulatory Activities (MedDRA version 23.1) SCARs SMQ narrow excluding PT Cutaneous vasculitis.

Preferred Term 'Cutaneous vasculitis' was excluded from the SCARs search strategy as this event is a listed ADR in section 4.8: Undesirable effects of VAXZEVRIA CDS (Version 21.0, dated: 08 November 2022).

The search resulted in no AEs of SCARs from the United States (US) study (DCO4) whereas 2 AEs of Exfoliative rash were received from the Oxford studies (one each from COV002 and COV003 respectively).

- A 53-year-old female participant ([redacted]) had mild Exfoliative rash (site: unknown) on day 1 after first dose of VAXZEVRIA which resolved on day 2. Investigator considered the event as possibly related to VAXZEVRIA. There was limited information on medical history, concomitant medications, etiological and diagnostic work-up.

- A 68-year-old female participant ([redacted]) had mild Exfoliative rash on day 19 after first dose of VAXZEVRIA which resolved on day 26. As per the investigator, the event was not related to VAXZEVRIA. There was limited information on medical history, concomitant medications, etiological and diagnostic work-up.

Summary:

On review of the clinical study data, no safety concerns were identified for SCARs with VAXZEVRIA. No AEs of SCARs were identified from the United States (US) study (DCO4). Two AEs of mild Exfoliative rash were "reported as non-serious" from the Oxford studies (one each from COV002 and COV003 respectively). As per the Investigator, one case was possible related whilst the other was not related to VAXZEVRIA. In both cases, there was limited information on medical history, concomitant medications, etiological and diagnostic work-up.

Global Patient Safety Database

A cumulative search through 28 December 2022 of the AstraZeneca Global Safety Database for SCARs with VAXZEVRIA was performed using MedDRA version 25.1. The search strategy considered SCARs SMQ narrow excluding PT Cutaneous vasculitis.

The search retrieved a total of 423 events of SCARs in 415 case reports. Out of the 415 case reports, there were 135 (32.5%) from the United Kingdom, 84 (20.2%) from Brazil, 34 (8.2%) from Italy, 27 (6.5%) from France, 20 (4.8%) from Australia, 14 (3.4%) from Spain, 13 (3.1%) from Germany, 11 (2.7%) from Poland, 9 (2.2%) from Netherlands, 7 (1.7%) from Mexico, 6 (1.4%) from Belgium, 5 (1.2%) cases each from India and Ireland, 4 (1.0%) from Sweden, 3 (0.7%) cases each from Austria, Canada, Finland, Philippines, Portugal and Thailand, 2 (0.5%) cases each from Argentina, Croatia, Greece, Iran and Tunisia and 1 (0.2%) case each from Czech Republic, Denmark, Estonia, Hungary, Japan, Kenya, Korea, Republic of, Latvia, Lithuania, Malaysia, Malta, Romania and Slovakia.

The distribution of the 423 events of SCARs by PT is presented in Table 53 as below in descending order of frequency.

Table 53 Distribution of MedDRA PTs (n = 423) pertaining to SCARs with VAXZEVRIA Cumulatively through 28 December 2022

MedDRA PT	Serious	Non-serious	Grand Total
Erythema multiforme	123	0	123
Dermatitis bullous	120	0	120
Stevens-Johnson syndrome	35	0	35
Exfoliative rash	15	16	31
Dermatitis exfoliative generalised	29	0	29
Drug reaction with eosinophilia and systemic symptoms	29	0	29
Skin necrosis	7	4	11
Toxic skin eruption	3	8	11
Acute generalised exanthematous pustulosis	10	0	10
Toxic epidermal necrolysis	6	0	6
Target skin lesion	3	2	5
Bullous haemorrhagic dermatosis	3	1	4
Dermatitis exfoliative	4	0	4
Generalised bullous fixed drug eruption	2	0	2
Epidermal necrosis	1	0	1
Erythrodermic atopic dermatitis	0	1	1
Severe cutaneous adverse reaction	1	0	1
Grand Total	**391**	**32**	**423**

MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term

The breakdown and overview of these 415 cases reporting 423 events of SCARs presented in Table 54 as below.

Table 54 Overview of SCARs Events/Cases Cumulatively through 28 December 2022

Parameter	Break-down	Numbers (%)
Case Count	Total	415
	Medically confirmed	241 (58.1%)
	Consumer Report	174 (41.9%)
Case Report Source	Non-interventional study	4 (1.0%)
	Spontaneous	101 (24.3%)
	Literature	19 (4.6%)
	Regulatory	291 (70.1%)
Sex [a]	Female N (%)	259 (65.1%)
	Male N (%)	139 (34.9%)

Table 54 Overview of SCARs Events/Cases Cumulatively through 28 December 2022

Parameter	Break-down	Numbers (%)
	Unknown	17
Age Group [a]	18-49	145 (38.5%)
	50-59	70 (18.6%)
	60-69	97 (25.7%)
	70-79	51 (13.5%)
	≥80	14 (3.7%)
	Unknown	38
	Median age (range)	56 years (18 to 94)
Case occurrence with dose [a] (total considered as 406 [100%] case reports with known dose details)	Dose 1 (%)	359 (88.4%)
	Dose 2 (%)	40 (9.9%)
	Dose 3 (%)	5 (1.2%)
	Dose 4 (%)	1 (0.2%)
	Multiple Doses (Dose 1 and Dose 2)	1 (0.2%)
	Unknown dose	9
Case level -TTO (days)[b]	0-14	251 (76.1%)
	15-21	20 (6.1%)
	22-28	10 (3.0%)
	29-42	15 (4.5%)
	≥43	34 (10.3%)
	Unknown	84
	Median TTO (range)	4 days (0 to 269)
Event Seriousness criteria	Medically important	288 (73.7%)
	Disability	17 (4.3%)
	Hospitalization	59 (15.1%)
	Life-threatening	24 (6.1%)
	Death	3 (0.8%)
AE Outcome	Recovered	84 (19.9%)
	Recovering	97 (22.9%)
	Recovered with sequelae	10 (2.4%)
	Not recovered	118 (27.9%)
	Fatal	3 (0.7%)
	Unknown	111 (26.2%)
Duration of recovered/recovered with sequelae events	Known duration (number of events)	52 (55.3%)
	Event recovered within 7 days (%)	23 (44.2%)
	Event recovered after 7 days (%)	29 (55.8%)

Table 54 Overview of SCARs Events/Cases Cumulatively through 28 December 2022

Parameter	Break-down	Numbers (%)
	Range (days)	0-122 days
	Mean (days)	24 days
	Unknown duration (number of events)	42 (44.7%)

[a] percentages, calculated based on known values

[b] TTO was reported for 330 case reports (total number of cases) used to calculate the percentage where multiple TTOs are present in a case, the most conservative TTO for the relevant event is chosen

AE Adverse Event; SCAR Severe Cutaneous Adverse Reactions, TTO, Time to Onset

SCARs Events with Fatal Outcome

Of the 423 total events reported, 3 (0.5%) events in 2 case reports were reported with a fatal outcome, of which 1 (50%) case was medically confirmed and 1 (50%) was a consumer report. The assessment of these 2 fatal case reports presented below.

Case ID [redacted]: This medically confirmed case concerns a 78-year-old elderly male patient who experienced dermatitis exfoliative generalized, Stevens-Johnson Syndrome (SJS), Disseminated Intravascular Coagulation (DIC), multiple organ dysfunction syndrome, Acute kidney injury, cholestasis, subdural haematoma and dehydration on day 7 after Dose 1 of VAXZEVRIA. On an unknown date after vaccination, the patient died, all events mentioned above were considered as fatal. It was not known whether an autopsy was performed. Concomitant medications included doxazosin, bisoprolol fumarate, hydrochlorothiazide/olmesartan medoxomil and acetylsalicylic acid. Chest X-ray and brain computerized tomography was done but results were unknown.

AstraZeneca Comment: Patient's elderly age, concomitant use of acetylsalicylic acid could be confounders for the event SJS. Event multiple organ dysfunction syndrome and disseminated intravascular coagulation could also have resulted in the fatal outcome. There is insufficient information on medical history, start date of concomitant medication, clinical course of the events, etiological and diagnostic workup, treatment details, and autopsy details. Hence this case is causally assessed as "Possible with limited information".

Case ID [redacted]: This consumer report concerns a 23-year-old male patient who experienced dermatitis bullous, pruritus, pyrexia and lip discolouration on day 1 after Dose 2 of VAXZEVRIA and died on the same day. The patient received Dose 1 of unspecified COVID-19 vaccine. As reported by patient's mother, next day after Dose 2, the patient was not hungry and around noon patient looked normal. However, at around 3.45 pm, his mother was shocked to see him with his lips turning green. An hour later dark spots appeared on his chest. Patient died about 24 hours after receiving his Dose 2 dose of vaccine. An autopsy was performed, cause of death was reported as dermatitis bullous, pruritus, pyrexia and lip discolouration.

AstraZeneca Comment: . This is a consumer report, and there is no information reported for medical history (ultraviolet light therapy, psoriasis, lichen planus, diabetes, rheumatoid arthritis), concurrent conditions (infections, skin injury, iron deficiency anaemia, cyanosis), risk factors, clinical course, detailed diagnostic and etiologic workup (complete physical exam with dermatological assessment, skin biopsy, indirect immunofluorescence, complete blood profile and blood chemistry panel, blood culture, relevant imaging studies and complete autopsy report) and treatment details. Hence this case is causally assessed as "Possible with limited information'.

Recurrence Case Reports

In 1 (0.2%) case out of 415 case reports of SCARs, event (PT: Erythema Multiforme) occurred with Dose 1 and a subsequently reappeared with Dose 2 of the vaccination. The summary of this recurrence case is presented in Table 56.

WHO-UMC Causality Assessment for SCARs Case Reports

Risk Window details

The risk window for the SCARs topic was considered 0-42 days except for Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Acute Generalised Exanthematous Pustulosis (AGEP). The risk window for DRESS (Hewitt et al 2012, Girijala et al 2019, Solak et al 2016, Criado et al 2012, O'Connor et al 2021, Griffin et al 2020) was considered as 0-28 days. For AGEP this was taken as 0-21 days (Daq et al 2022, Sidoroff et al 2007, Agaronov et al 2021, Mitri et al 2021, Vallejo-Yagüe et al 2022, Matsuo et al 2017, Stone et al 2019, Lospinoso et al 2021).

WHO-UMC causality assessment performed for SCARs case reports presented in Table 55 as below.

Table 55 Overview of WHO-UMC Causality Assessments for SCARs Case Reports with VAXZEVRIA Cumulatively through 28 December 2022

WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	Number of Cases (Percentage)
Certain	Certain	0
Probable/Likely	Probable-Likely	2 (0.5%)
Possible	Possible with risk factors/confounders[a]	79 (19.0%)
	Possible with limited information	215 (51.8%)
Unassessable/Unclassifiable	Unassessable/Unclassifiable with risk factors/confounders[a]	15 (3.6%)
	Unassessable/Unclassifiable with limited information	68 (16.4%)
Unlikely	Unlikely	34 (8.2%)
Conditional/Unclassified	Conditional/Unclassified	2 (0.5%)

Table 55 Overview of WHO-UMC Causality Assessments for SCARs Case Reports with VAXZEVRIA Cumulatively through 28 December 2022

WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	Number of Cases (Percentage)
Total		**415 (100%)**

[a] Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.

AZ, AstraZeneca, UMC Uppsala Monitoring Centre; WHO World Health Organization

Amongst 415 case reports of the SCARs topic, 2 (0.5%) cases were assessed with WHO-causality as "Probable".

The summary of 2 "Probable" case reports presented in Table 56 as below.

Table 56 Summary of Probable SCARs Case Reports as per WHO-UMC causality criteria Cumulatively through 28 December 2022

Case ID / Country / Medically confirmed (Y/N) / Source / Serious (Y/N)	Age (Years) / Gender (M/F)	Medical History / Concomitant medications	TTO (days) from AZ vaccine / Dose Information	Preferred Term / AE Outcome	AstraZeneca Comment
[redacted] / NO / Regulatory / Y	47 / F	Not reported / Not Reported	1 and Unk / Dose 1 and Dose 2	Erythema Multiforme / Recovering	TTO within risk window. However, medical history, concomitant medications and relevant investigations unknown. The case was assessed against the WHO-UMC criteria as "Probable", due to temporal relationship, and considering recurrence, and the fact that it is not likely that any other confounder was present during both occurrences and absent in between. There was limited information with regards to medical history, concomitant medications and relevant aetiological investigations (eg. FBC, serum electrolytes, HSV serology, rapid PCR, haematoxylin and eosin biopsy, immunofluorescence biopsy, HBV serology, LFTs, etc.)
[redacted] / YES / Literature / Y	25 / F	Not reported / Not Reported	3 / Dose 1	Erythema Multiforme / Recovered	TTO - 3 days; The patient denied history of any recent illness or intake of any medication. Hematological and biochemical investigations including serology (for HSV (Herpes Simplex Virus)) were normal. Histopathology revealed the presence of subepithelial bullae along with a predominantly perivascular lymphohistiocytic infiltrate in the upper dermis. The epidermis showed variable spongiosis as well as basal cell vacuolar damage.

F Female; FBC Full Blood Count; HBV Hepatitis B Virus, HSV Herpes Simplex Virus; LFT, Liver Function; M Male; PCR Polymerase Chain Reaction; S Serious, TTO, Time to Onset; Unk, Unknown; WHO, World Health Organization; Y Yes

Review of PT's representing SCARs

Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)

Out of 415 cases, 41 (9.9%) cases were related to events SJS (35) and TEN (6). All AEs were serious with reported seriousness criteria as follows: 18 (43.9%) medically important event, 14 (34.1%) hospitalization, 6 (14.6%) life threatening, 2 (4.9%) disability and 1 (2.4%) death.

Out of 41 cases, 23 (56.1%) were medically confirmed and 18 (43.9%) consumer reports. 30 (73.2%) cases were reported for females, 8 (19.5%) for male and 3 (7.3%) were reported with unknown gender.

Amongst 41 cases, Time to Onset (TTO) was reported for 27 (65.9%) cases and was unknown for 14 (34.1%). In 34 (82.9%) cases the event was reported after Dose 1, in 3 (7.3%) cases the event was reported after Dose 2, in 1 (2.4%) case event was reported after Dose 4 and for 3 (7.3%) cases Dose information was unknown/unspecified.

For the 41 cases the reported event outcomes were as follows: 7 (17.1%) recovered, 3 (7.3%) recovered with sequelae, 8 (19.5%) recovering, 5 (12.2%) not recovered, 1 (2.4%) event was reported as fatal and 17 (41.5%) with unknown outcome.

WHO-UMC causality assessment performed for SJS/TEN case reports presented in Table 57.

Table 57 Overview of WHO-UMC Causality Assessments for SJS/TEN Case Reports with VAXZEVRIA Cumulatively through 28 December 2022

WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	Number of Cases (Percentage)
Certain	Certain	0
Probable/Likely	Probable-Likely	0
Possible	Possible with risk factors/confounders[a]	13 (31.7%)
	Possible with limited information	11 (26.8%)
Unassessable/Unclassifiable	Unassessable/Unclassifiable with risk factors/confounders[a]	5 (12.2%)
	Unassessable/Unclassifiable with limited information	9 (22.0%)
Unlikely	Unlikely	3 (7.3%)
Conditional/Unclassified	Conditional/Unclassified	0
Total		**41**

[a] Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.

AZ AstraZeneca; UMC Uppsala Monitoring Centre; WHO World Health Organization

Amongst 41 cases for SJS/TEN, 20 (48.8%) were identified with relevant risk/confounding factors (Roujeau et al 1995, Sassolas et al 2010, Hsu et al 2016) presented in Table 58 as below. These are categorised as risk/confounding factors in descending order of frequency.

Table 58 Relevant Risk factors/Confounders identified for SJS/TEN Case Reports Cumulatively through 28 December 2022

Relevant Risk factors/ Confounders	Count
Concomitant medications (Such as NSAIDs, Anti-gout medication, Anticonvulsants, Antipsychotics, Proton-Pump inhibitors, Calcium channel blocker, ACE inhibitor, Antibiotics etc.)	17[a]
Chronic conditions (such as Diabetes mellitus, Thyroid adenoma, DiGeorge's syndrome)	3[a]
Previous history of SCARs events (such as Erythema multiforme, Stevens-Johnson Syndrome etc.)	3[a]
History of COVID-19	3[a]
History of viral Infections (Herpes virus infection, Urinary Tract Infection)	2[a]
Chronic Lymphocytic Leukaemia	1

[a] Cases may contain more than 1 risk factor

ACE angiotensin-converting enzyme; COVID-19 Coronavirus Disease 2019; NSAIDs Non-steroidal anti-inflammatory drugs

In the remaining 21 (51.2%) case reports, there was insufficient information with respect to either TTO, medical history/co-morbidities, concomitant medication details or clinical course for a comprehensive causal assessment.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Out of 415 cases, 29 (6.8%) cases were related to event DRESS. All AEs were serious with reported seriousness criteria as follows: 10 (34.5%) medically important event, 10 (34.5%) hospitalization, 5 (17.2%) disability and 4 (13.8%) life threatening.

Out of 29 cases, 13 (44.8%) were medically confirmed and 16 (55.2%) consumer reports. 19 (65.5%) cases were reported for females and 10 (34.5%) cases for male.

Amongst 29 cases, TTO was reported for 17 (58.6%) cases and was unknown for 12 (41.4%) . In 25 (86.2%) cases the event was reported after Dose 1, in 2 (6.9%) cases the event was reported after Dose 2 and for 2 (6.9%) cases Dose information was unknown.

For the 29 cases the reported event outcomes were as follows: 4 (13.8%) recovered, 11 (37.9%) recovering, 7 (24.1%) not recovered and 7 (24.1%) with unknown outcome.

WHO-UMC causality assessment performed for DRESS case reports presented in Table 59 as below.

Table 59 Overview of WHO-UMC Causality Assessments for DRESS Case Reports with VAXZEVRIA Cumulatively through 28 December 2022

WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	Number of Cases (Percentage)
Certain	Certain	0

Table 59 Overview of WHO-UMC Causality Assessments for DRESS Case Reports with VAXZEVRIA Cumulatively through 28 December 2022

WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	Number of Cases (Percentage)
Probable/Likely	Probable-Likely	0
Possible	Possible with risk factors/confounders[a]	1 (3.4%)
	Possible with limited information	10 (34.5%)
Unassessable/Unclassifiable	Unassessable/Unclassifiable with risk factors/confounders[a]	2 (6.9%)
	Unassessable/Unclassifiable with limited information	10 (34.5%)
Unlikely	Unlikely	6 (20.7%)
Conditional/Unclassified	Conditinal/Unclassified	0
Total		**29**

[a] Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.

AZ AstraZeneca; UMC Uppsala Monitoring Centre; WHO World Health Organization

Amongst 29 cases for DRESS, 4 (13.8%) were identified with relevant risk/confounding factors (Drug hypersensitivity syndrome 2004, Choudhary et al 2013) presented in below Table 60. These are categorised as risk/confounding factors in descending order of frequency.

Table 60 Relevant Risk factors/Confounders identified for DRESS Case Reports Cumulatively through 28 December 2022

Relevant Risk factors/ Confounders	Count
Concomitant medication (Amitriptyline and Rosuvastatin)	2[a]
Other conditions (such as Liver transplant, Immunodeficiency, Allergic rhinitis)	2[a]

[a] Cases may contain more than 1 risk factor

In the remaining 25 (86.2%) case reports, there was insufficient information with respect to either TTO, medical history/co-morbidities, concomitant medication details or clinical course for a comprehensive causal assessment.

Acute Generalised Exanthematous Pustulosis (AGEP)

Out of 415 cases, 10 (2.4%) cases were related to event AGEP. All AEs were serious with reported seriousness criteria as follows: 7 (70.0%) medically important event, 2 (20.0%) hospitalization and 1 (10.0%) life threatening.

Out of 10 cases, 9 (90.0%) were medically confirmed and 1 (10.0%) was consumer report. 5 (50.0%) cases were reported for females and 5 (50.0%) for male.

TTO was reported for all 10 cases. In 9 (90.0%) cases the event was reported after Dose 1 and in 1 (10.0%) case the event was reported after Dose 2.

For the 10 cases the reported event outcomes were as follows: 5 (50.0%) recovered, 4 (40.0%) recovering and 1 (10.0%) with unknown outcome.

WHO-UMC causality assessment performed for AGEP case reports presented in Table 61 as below.

Table 61 Overview of WHO-UMC Causality Assessments for AGEP Case Reports with VAXZEVRIA Cumulatively through 28 December 2022

WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	Number of Cases (Percentage)
Certain	Certain	0
Probable/Likely	Probable-Likely	0
Possible	Possible with risk factors/confounders[a]	2 (20.0%)
	Possible with limited information	7 (70.0%)
Unassessable/Unclassifiable	Unassessable/Unclassifiable with risk factors/confounders[a]	0
	Unassessable/Unclassifiable with limited information	0
Unlikely	Unlikely	1(10.0%)
Conditional/Unclassified	Conditional/Unclassified	0
Total		**10**

[a] Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.

AGEP Acute Generalised Exanthematous Pustulosis; AZ AstraZeneca; UMC Uppsala Monitoring Centre; WHO World Health Organization

Amongst 10 cases for AGEP, 2 (20.0%) were identified with relevant risk/confounding factors (Acute generalised exanthematous pustulosis 2008) presented in Table 62 as below. These are categorised as risk/confounding factors in descending order of frequency.

Table 62 Relevant Risk factors/Confounders identified for AGEP Case Reports Cumulatively through 28 December 2022

Relevant Risk factors/ Confounders	Count
History of Infections (HIV test positive, Vaginal infection, Cytomegalovirus colitis, Kaposi sarcoma), chronic conditions (such as Adrenal insufficiency, Psoriasis)	2[a]
Concomitant medications (Trimethoprim/Sulfamethoxazole, Darunavir)	1

[a] Cases may contain more than 1 risk factor

AGEP Acute Generalised Exanthematous Pustulosis; HIV human immunodeficiency virus

In the remaining 8 (80.0%) case reports, there was insufficient information with respect to either TTO, medical history/co-morbidities, concomitant medication details or clinical course for a comprehensive causal assessment.

Erythema Multiforme

Out of 415 cases, 123 (29.6%) cases were related to event Erythema Multiforme (123). All AEs were serious with reported seriousness criteria as follows: 102 (82.9%) medically important event, 14 (11.4%) hospitalization and 7 (5.7%) life threatening.

Out of 123 cases, 75 (61.0%) were medically confirmed and 48 (39.0%) were consumer reports. 73 (59.3%) cases were reported for females, 40 (32.5%) for male and 10 (8.1%) were reported with unknown gender.

Amongst 123 cases, TTO was reported for 95 (77.2%) cases and was unknown for 28 (22.8%). In 109 (88.6%) cases the event was reported after Dose 1, in 10 (8.1%) cases the event was reported after Dose 2, in 1 (0.8%) case event was reported after Dose 1 and Dose 2 and for 3 (2.4%) cases Dose information was unknown/unspecified.

For the 123 cases the reported event outcomes were as follows: 26 (21.1%) recovered, 4 (3.3%) recovered with sequelae, 26 (21.1%) recovering, 35 (28.5%) not recovered and 32 (26.0%) with unknown outcome.

WHO-UMC causality assessment performed for Erythema Multiforme case reports presented in Table 63.

Table 63 Overview of WHO-UMC Causality Assessments for Erythema Multiforme Case Reports with VAXZEVRIA reported Cumulatively through 28 December 2022

WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	Number of Cases (Percentage)
Certain	Certain	0
Probable/Likely	Probable-Likely	2 (1.6%)
Possible	Possible with risk factors/confounders[a]	29 (23.6%)
	Possible with limited information	56 (45.5%)
Unassessable/Unclassifiable	Unassessable/Unclassifiable with risk factors/confounders[a]	3 (2.4%)
	Unassessable/Unclassifiable with limited information	22 (17.9%)
Unlikely	Unlikely	9 (7.3%)
Conditional/Unclassified	Conditional/Unclassified	2 (1.6%)
Total		**123**

[a] Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.

AZ AstraZeneca; UMC Uppsala Monitoring Centre; WHO World Health Organization

The summary of 2 (1.6%) "Probable" Erythema Multiforme case reports presented in Table 56.

Amongst 123 cases for Erythema Multiforme, 32 (26.0%) were identified with relevant risk/confounding factors (Roujeau 2012, Huff et al 1983, Lerch et al 2018) presented in

Table 64 as below. These are categorised as risk/confounding factors in descending order of frequency.

Table 64 Relevant Risk factors/Confounders identified for Erythema Multiforme Case Reports Cumulatively through 28 December 2022

Relevant Risk factors/ Confounders	Count
Concomitant medications (Such as NSAIDs, Statins, Antidepressant, Antibacterial medications, Antibiotics, Proton-Pump inhibitors, Calcium channel blocker, ACE inhibitor etc.)	18[a]
Chronic conditions (such as Diabetes Mellitus, Immunodeficiency, Raynaud's phenomenon, Systemic Lupus Erythematosus, Dermatitis Herpetiformis etc.)	8[a]
History of viral Infections (Such as, Herpes Simplex, Varicella, Oral herpes, Chikungunya virus infection etc.)	4[a]
Previous history of Erythema Multiforme	4[a]
Neoplasms (Such as Metastatic non-small cell lung cancer, Colon cancer, Breast cancer)	3[a]

[a] Cases may contain more than 1 risk factor
ACE angiotensin-converting enzyme; NSAIDs Non-steroidal anti-inflammatory drugs

In the 89 (72.4%) case reports, there was insufficient information with respect to either TTO, medical history/co-morbidities, concomitant medication details or clinical course for a comprehensive causal assessment.

Bullous Lesions (Dermatitis Bullous, Bullous Haemorrhagic Dermatosis, Generalised Bullous Fixed Drug Eruption)

Out of 415 cases, 126 (30.4%) cases were related to events Dermatitis bullous (120), Bullous haemorrhagic dermatosis (4) and Generalised bullous fixed drug eruption (2). 125 (99.2%) AEs were serious, and 1 (0.8%) AE was non-serious. The seriousness criteria for the 125 AEs were reported as follows: 109 (87.2%) medically important event, 7 (5.6%) hospitalization, 4 (3.2%) disability, 4 (3.2%) life threatening and 1 (0.8%) death.

Out of 126 cases, 78 (61.9%) were medically confirmed and 48 (38.1%) were consumer reports. 86 (68.3%) cases were reported for females, 38 (30.2%) for male and 2 (1.6%) were reported with unknown gender.

Amongst 126 cases, TTO was reported for 112 (88.9%) cases and was unknown for 14 (11.1%). In 101 (80.2%) cases the event was reported after Dose 1, in 21 (16.7%) cases the event was reported after Dose 2 and in 4 (3.2%) cases event was reported after Dose 3.

For the 126 cases the reported event outcomes were as follows: 25 (19.8%) recovered, 1 (0.8%) recovered with sequelae, 25 (19.8%) recovering, 34 (27.0%) not recovered, 1 (0.8%) event was reported as fatal and 40 (31.7%) with unknown outcome.

WHO-UMC causality assessment performed for Bullous Lesions (Dermatitis Bullous, Bullous Haemorrhagic Dermatosis, Generalised Bullous Fixed Drug Eruption) case reports presented in Table 65 as below.

Table 65 Overview of WHO-UMC Causality Assessments for Bullous Lesions (Dermatitis Bullous, Bullous Haemorrhagic Dermatosis, Generalised Bullous Fixed Drug Eruption) Case Reports with VAXZEVRIA Cumulatively through 28 December 2022

WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	Number of Cases (Percentage)
Certain	Certain	0
Probable/Likely	Probable-Likely	0
Possible	Possible with risk factors/confounders[a]	19 (15.1%)
	Possible with limited information	84 (66.7%)
Unassessable/Unclassifiable	Unassessable/Unclassifiable with risk factors/confounders[a]	2 (1.6%)
	Unassessable/Unclassifiable with limited information	12 (9.5%)
Unlikely	Unlikely	9 (7.1%)
Conditional/Unclassified	Conditional/Unclassified	0
Total		**126**

[a] Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.

AZ, AstraZeneca; UMC Uppsala Monitoring Centre; WHO World Health Organization

Amongst 126 cases for Bullous Lesions (Dermatitis Bullous, Bullous Haemorrhagic Dermatosis, Generalised Bullous Fixed Drug Eruption), 22 (17.5%) were identified with relevant risk/confounding factors (Daulatabadkar et al 2017, Bullous Pemphigoid 1997, Bullous drug eruptions 2009) presented in Table 66 as below. These are categorised as risk/confounding factors in descending order of frequency.

Table 66 Relevant Risk factors/Confounders identified for Bullous Lesions (Dermatitis Bullous, Bullous Haemorrhagic Dermatosis, Generalised Bullous Fixed Drug Eruption) Case Reports Cumulatively thorough 28 December 2022

Relevant Risk factors/ Confounders	Count
Chronic conditions (such as Diabetes Mellitus, Metabolic syndrome, Coeliac disease, Autoimmune thyroiditis, End Stage Renal Disease etc.)	11[a]
Concomitant medications (Such as Statins, Antidepressants, Antipsychotics, Antiepileptics, Calcium channel blocker, ACE inhibitor etc.)	6[a]
Previous history of Allergy (Dermatitis bullous, Drug hypersensitivity, Hand dermatitis)	4[a]
Patient's age (Elderly age: ≥ 70 years)	2[a]
History of COVID-19	1

[a] Cases may contain more than 1 risk factor

ACE angiotensin-converting enzyme; COVID-19 Coronavirus Disease 2019

In the remaining 104 (82.5%) case reports, there was insufficient information with respect to either TTO, medical history/co-morbidities, concomitant medication details or clinical course for a comprehensive causal assessment.

Other SCARs PTs (Dermatitis Exfoliative, Dermatitis Exfoliative Generalised, Exfoliative Rash, Skin Necrosis, Target Skin Lesion, Toxic Skin Eruption, Epidermal Necrosis, Erythrodermic Atopic Dermatitis, Severe Cutaneous Adverse Reaction)

Out of 415 cases, 93 (22.5%) cases were related to 94 SCARs AEs including Exfoliative rash (31), Dermatitis exfoliative generalised (29), Skin necrosis (11), Toxic skin eruption (11), Target skin lesion (5), Dermatitis exfoliative (4), Epidermal necrosis (1), Erythrodermic atopic dermatitis (1), and Severe Cutaneous Adverse Reaction (1). 63 (67.0%) AEs were serious, and 31 (33.0%) AEs were non-serious. The seriousness criteria for the 63 AEs were reported as follows: 42 (66.7%) medically important event, 12 (19.0%) hospitalization, 6 (9.5%) disability, 2 (3.2%) life threatening and 1 (1.6%) death.

Out of 93 cases, 48 (51.6%) were medically confirmed and 45 (48.4%) were consumer reports. 51 (54.8%) cases were reported for females, 40 (43.0%) for male and 2 (2.2%) were reported with unknown gender.

Amongst 93 cases, TTO was reported for 74 (79.6%) cases and was unknown for 19 (20.4%). In 86 (92.5%) cases the event was reported after Dose 1, in 4 (4.3%) cases the event was reported after Dose 2, in 1 (1.1%) case event was reported after Dose 3 and for 2 (2.2%) cases Dose information was unknown/unspecified.

For the 93 cases the reported event outcomes for 94 AEs were as follows: 17 (18.1%) recovered, 2 (2.1%) recovered with sequelae, 23 (24.5%) recovering, 37 (39.4%) not recovered, 1 (1.1%) event was reported as fatal and 14 (14.9%) with unknown outcome.

WHO-UMC causality assessment performed for the other SCARs PTs (Dermatitis Exfoliative, Dermatitis Exfoliative Generalised, Exfoliative Rash, Skin Necrosis, Target Skin Lesion, Toxic Skin Eruption, Epidermal Necrosis, Erythrodermic Atopic Dermatitis, Severe Cutaneous Adverse Reaction) case reports presented in Table 67 below.

Table 67 Overview of WHO-UMC Causality Assessments for Other SCARs PTs (Dermatitis Exfoliative, Dermatitis Exfoliative Generalised, Exfoliative Rash, Skin Necrosis, Target Skin Lesion, Toxic Skin Eruption, Epidermal Necrosis, Erythrodermic Atopic Dermatitis, Severe Cutaneous Adverse Reaction) Case Reports with VAXZEVRIA Cumulatively through 28 December 2022

WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	Number of Cases (Percentage)
Certain	Certain	0
Probable/Likely	Probable-Likely	0

Table 67 Overview of WHO-UMC Causality Assessments for Other SCARs PTs (Dermatitis Exfoliative, Dermatitis Exfoliative Generalised, Exfoliative Rash, Skin Necrosis, Target Skin Lesion, Toxic Skin Eruption, Epidermal Necrosis, Erythrodermic Atopic Dermatitis, Severe Cutaneous Adverse Reaction) Case Reports with VAXZEVRIA Cumulatively through 28 December 2022

WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	Number of Cases (Percentage)
Possible	Possible with risk factors/confounders[a]	17 (18.3%)
	Possible with limited information	49 (52.7%)
Unassessable/Unclassifiable	Unassessable/Unclassifiable with risk factors/confounders[a]	4 (4.3%)
	Unassessable/Unclassifiable with limited information	15 (16.1%)
Unlikely	Unlikely	8 (8.6%)
Conditional/Unclassified	Conditional/Unclassified	0
Total		**93**

[a] Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.

AZ AstraZeneca; PT Preferred Term; UMC Uppsala Monitoring Centre; WHO World Health Organization

Amongst 93 cases for Other SCARs PTs (Dermatitis Exfoliative, Dermatitis Exfoliative Generalised, Exfoliative Rash, Skin Necrosis, Target Skin Lesion, Toxic Skin Eruption, Epidermal Necrosis, Erythrodermic Atopic Dermatitis, Severe Cutaneous Adverse Reaction), 22 (23.7%) cases were identified with relevant risk/confounding factors (Karakayli et al 1999, Harper-Kirksey 2018, Patterson 2021) presented in Table 68 as below. These are categorised as risk/confounding factors in descending order of frequency.

Table 68 Relevant Risk factors/Confounders identified for Other SCARs PTs (Dermatitis Exfoliative, Dermatitis Exfoliative Generalised, Exfoliative Rash, Skin Necrosis, Target Skin Lesion, Toxic Skin Eruption, Epidermal Necrosis, Erythrodermic Atopic Dermatitis, Severe Cutaneous Adverse Reaction) Case Reports Cumulatively through 28 December 2022

Relevant Risk factors/ Confounders	Count
Concomitant medications (Such as Statins, Anticonvulsants, Antibacterial sulfonamides, Proton-Pump inhibitors, Calcium channel blocker, ACE inhibitor etc.)	12[a]
Previous history of Allergy (Dermatitis exfoliative generalised, Eczema, Eczema infantile, Urticaria, Drug hypersensitivity)	6[a]
Neoplasms (Malignant melanoma, Breast neoplasm, Malignant melanoma)	3[a]
Chronic condition: Psoriasis	2[a]
Patient's age (Elderly age: ≥ 70 years)	2[a]
History of COVID-19	1

[a] Cases may contain more than 1 risk factor

ACE Angiotensin-converting enzyme; COVID-19 Coronavirus Disease 2019; PT Preferred Term

In the remaining 71 (76.3%) case reports, there was insufficient information with respect to either TTO, medical history/co-morbidities, concomitant medication details or clinical course for a comprehensive causal assessment.

Observed Versus Expected (O/E) Analyses

SJS-TEN Observed vs Expected Analysis

Observed versus expected analysis was performed for all cases cumulative through 28 December 2022, with 14-day and 42-day risk windows. The background rates were sourced from Frey et al 2017 a nationwide primary care database analysis. A sensitivity analysis was also done with multiple background rates as reported in Hsu et al 2016 a nationwide inpatient database analysis in adults) and Diphoorn et al 2016 (a local regional in-hospital registry analysis). Results of O/E are presented in Table 69.

Table 69 Observed versus Expected Cumulative Analyses through DLP 28 December 2022 for reports of SJS/TEN with Risk Windows of 14, 42 days including Cases with unknown TTO

AEs	Risk window	BG rates [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
SJS-TEN - All cases, RW 14 and RW 42							
SJS-TEN Overall, RW 14	14	0.576	466115644	21	102.91	0.2 (0.13 - 0.31)	Observed significantly < expected
SJS-TEN Overall, RW 14	14	0.14	466115644	21	25.01	0.84 (0.52 - 1.28)	Observed < expected
SJS-TEN Overall, RW 14	14	1.27	466115644	21	226.91	0.09 (0.06 - 0.14)	Observed significantly < expected
SJS-TEN Overall, RW 42	42	0.576	466115644	24	308.73	0.08 (0.05 - 0.12)	Observed significantly < expected
SJS-TEN Overall, RW 42	42	0.14	466115644	24	75.04	0.32 (0.2 - 0.48)	Observed significantly < expected
SJS-TEN Overall, RW 42	42	1.27	466115644	24	680.72	0.04 (0.02 - 0.05)	Observed significantly < expected
SJS-TEN - All cases, RW 14, RW 42, Unk							

Table 69 Observed versus Expected Cumulative Analyses through DLP 28 December 2022 for reports of SJS/TEN with Risk Windows of 14, 42 days including Cases with unknown TTO

AEs	Risk window	BG rates [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
SJS-TEN Overall, RW 14 + Unk	14	0.576	466115644	35	102.91	0.34 (0.24 - 0.47)	Observed significantly < expected
SJS-TEN Overall, RW 14 + Unk	14	0.14	466115644	35	25.01	1.4 (0.97 - 1.95)	Observed > expected
SJS-TEN Overall, RW 14 + Unk	14	1.27	466115644	35	226.91	0.15 (0.11 - 0.21)	Observed significantly < expected
SJS-TEN Overall, RW 42 + Unk	42	0.576	466115644	24	308.73	0.08 (0.05 - 0.12)	Observed significantly < expected
SJS-TEN Overall, RW 42 + Unk	42	0.14	466115644	24	75.04	0.32 (0.2 - 0.48)	Observed significantly < expected
SJS-TEN Overall, RW 42 + Unk	42	1.27	466115644	24	680.72	0.04 (0.02 - 0.05)	Observed significantly < expected
SJS-TEN - All cases, EU/UK only, RW 14, RW 42							
SJS-TEN Overall, EU/UK only	14	0.576	117724493	12	25.99	0.46 (0.24 - 0.81)	Observed significantly < expected
SJS-TEN Overall, EU/UK only	14	0.14	117724493	12	6.32	1.9 (0.98 - 3.32)	Observed > expected
SJS-TEN Overall, EU/UK only	14	1.27	117724493	12	57.31	0.21 (0.11 - 0.37)	Observed significantly < expected
SJS-TEN Overall, EU/UK only	42	0.576	117724493	14	77.98	0.18 (0.1 - 0.3)	Observed significantly < expected
SJS-TEN Overall, EU/UK only	42	0.14	117724493	14	18.95	0.74 (0.4 - 1.24)	Observed < expected
SJS-TEN Overall, EU/UK only	42	1.27	117724493	14	171.92	0.08 (0.04 - 0.14)	Observed significantly < expected

Table 69 Observed versus Expected Cumulative Analyses through DLP 28 December 2022 for reports of SJS/TEN with Risk Windows of 14, 42 days including Cases with unknown TTO

AEs	Risk window	BG rates [a]	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
SJS-TEN - All cases, EU/UK only, RW 14, RW 42, Unk							
SJS-TEN Overall, EU/UK only, RW 14 + Unk	14	0.576	117724493	14	25.99	0.54 (0.29 - 0.9)	Observed significantly < expected
SJS-TEN Overall, EU/UK only, RW 14 + Unk	14	0.14	117724493	14	6.32	2.22 (1.21 - 3.72)	Observed significantly > expected
SJS-TEN Overall, EU/UK only, RW 14 + Unk	14	1.27	117724493	14	57.31	0.24 (0.13 - 0.41)	Observed significantly < expected
SJS-TEN Overall, EU/UK only, RW 42 + Unk	42	0.576	117724493	16	77.98	0.21 (0.12 - 0.33)	Observed significantly < expected
SJS-TEN Overall, EU/UK only, RW 42 + Unk	42	0.14	117724493	16	18.95	0.84 (0.48 - 1.37)	Observed < expected
SJS-TEN Overall, EU/UK only, RW 42 + Unk	42	1.27	117724493	16	171.92	0.09 (0.05 - 0.15)	Observed significantly < expected

Sources: Frey et al 2017 IR-0.576 per 100,000 py. Hsu et al 2016 IR-1.27 per 100,000 py and Diphoorn et al 2016- IR 0.14 per 100,000 py.

CI Confidence Interval; O/E Observed versus Expected; SJS Stevens-Johnson Syndrome; TEN Toxic Epidermal Necrolysis; TTO Time to Onset; Unk Unknown

The observed versus expected analysis for all reported cases of SJS-TEN suggested that observed cases occurred less frequently than expected, except for background rate of 0.14 within risk window of 14 days including unknown TTO and same background rate of 0.14 within risk window of 14 days for region EU/UK including unknown TTO.

A similar trend was seen on sensitivity analysis with other background rates. A numerical increase in observed rates versus background rate (not statistically significant) with stratification of cases within risk window of 14 days including those with unknown TTO and background rate of 0.14 was identified. There is a possibility of reporting bias for increased reporting of cases with a shorter risk window for the passive event reporting of rare diseases, as majority of cases (54.5%) were reported where event onset occurred within 2 days of vaccination, a temporal plausibility of which is considered unlikely. Moreover, the background rate of 0.14 was based on a local regional in-hospital registry analysis (Diphoorn

et al 2016). This rate was at the more conservative end of the rates quoted in Frey et al 2017, and may not be appropriate. Observed cases were less than expected using the rate of 0.576 per 100,000 and at the higher rate of 1.27 per 100,000. It should be noted that the OE analyses does not account for confounding/risk factors which might be present in the cases, such concomitant medications, or illnesses, or for example, the effect of COVID-19 which may also contribute.

EM Observed vs Expected Analysis

Observed versus expected analysis was performed cumulatively to 28 December 2022, for cases globally, and also by regions, including UK by age and gender, and EU/UK/Brazil/Australia by age. Analysis was performed for 14-day and 42-day risk window. The background rate was sourced from a metanalysis from ACCESS. Observed versus expected analyses for EM is summarized below in Table 70.

Table 70 Observed versus Expected Cumulative Analyses through DLP 28 December 2022 for reports of EM with Risk Windows of 14, 42 days including Cases with Unknown TTO

AEs	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
EM - All, RW 14 and RW 42							
EM Overall, RW 14	14	7.03	466115644	65	1256.02	0.05 (0.04 - 0.07)	Observed significantly < expected
EM Overall, RW 42	42	7.03	466115644	86	3768.05	0.02 (0.02 - 0.03)	Observed significantly < expected
EM - All, RW 14, RW 42 and Unk							
EM Overall, RW 14 + Unk	14	7.03	466115644	93	1256.02	0.07 (0.06 - 0.09)	Observed significantly < expected
EM Overall, RW 42 + Unk	42	7.03	466115644	114	3768.05	0.03 (0.02 - 0.04)	Observed significantly < expected
EM - UK Females, RW 14							
EM, Female 18 to 29, UK, RW 14	14	8.1	1109488	1	3.44	0.29 (0.01 - 1.62)	Observed < expected
EM, Female 30 to 39, UK, RW 14	14	7.71	1892968	1	5.59	0.18 (0 - 1)	Observed significantly < expected
EM, Female 40 to 49, UK, RW 14	14	6.43	4412245	5	10.87	0.46 (0.15 - 1.07)	Observed < expected

Table 70 Observed versus Expected Cumulative Analyses through DLP 28 December 2022 for reports of EM with Risk Windows of 14, 42 days including Cases with Unknown TTO

AEs	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
EM, Female 50 to 59, UK, RW 14	14	7.75	5944683	1	17.66	0.06 (0 - 0.32)	Observed significantly < expected
EM, Female 60 to 69, UK, RW 14	14	5.98	4783416	2	10.96	0.18 (0.02 - 0.66)	Observed significantly < expected
EM, Female 70 to 79, UK, RW 14	14	5.86	3475875	2	7.81	0.26 (0.03 - 0.93)	Observed significantly < expected
EM, Female over 80, UK, RW 14	14	5.43	1630324	0	3.39	0 (0 - 1.09)	Observed < expected
EM - UK Females, RW 14 + Unk							
EM, Female 18 to 29, UK, RW 14 + Unk	14	8.1	1109488	1	3.44	0.29 (0.01 - 1.62)	Observed < expected
EM, Female 30 to 39, UK, RW 14 + Unk	14	7.71	1892968	2	5.59	0.36 (0.04 - 1.29)	Observed < expected
EM, Female 40 to 49, UK, RW 14 + Unk	14	6.43	4412245	7	10.87	0.64 (0.26 - 1.33)	Observed < expected
EM, Female 50 to 59, UK, RW 14 + Unk	14	7.75	5944683	2	17.66	0.11 (0.01 - 0.41)	Observed significantly < expected
EM, Female 60 to 69, UK, RW 14 + Unk	14	5.98	4783416	2	10.96	0.18 (0.02 - 0.66)	Observed significantly < expected
EM, Female 70 to 79, UK, RW 14 + Unk	14	5.86	3475875	2	7.81	0.26 (0.03 - 0.93)	Observed significantly < expected
EM, Female over 80, UK, RW 14 + Unk	14	5.43	1630324	0	3.39	0 (0 - 1.09)	Observed < expected
EM - UK Males, RW 14							
EM, Male 18 to 29, UK, RW 14	14	3.69	808938	0	1.14	0 (0 - 3.24)	Observed < expected
EM, Male 30 to 39, UK, RW 14	14	5.49	1415003	0	2.98	0 (0 - 1.24)	Observed < expected
EM, Male 40 to 49, UK, RW 14	14	3.76	4542157	6	6.55	0.92 (0.34 - 1.99)	Observed < expected

Table 70 Observed versus Expected Cumulative Analyses through DLP 28 December 2022 for reports of EM with Risk Windows of 14, 42 days including Cases with Unknown TTO

AEs	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
EM, Male 50 to 59, UK, RW 14	14	4.91	6510960	2	12.25	0.16 (0.02 - 0.59)	Observed significantly < expected
EM, Male 60 to 69, UK, RW 14	14	4.06	4934728	1	7.68	0.13 (0 - 0.73)	Observed significantly < expected
EM, Male 70 to 79, UK, RW 14	14	6.45	3137304	2	7.76	0.26 (0.03 - 0.93)	Observed significantly < expected
EM, Male over 80, UK, RW 14	14	7.88	1025046	0	3.1	0 (0 - 1.19)	Observed < expected
EM - UK Males, RW 14, Unk							
EM, Male 18 to 29, UK, RW 14 + Unk	14	3.69	808938	0	1.14	0 (0 - 3.24)	Observed < expected
EM, Male 30 to 39, UK, RW 14 + Unk	14	7.03	1415003	0	3.81	0 (0 - 0.97)	Observed significantly < expected
EM, Male 40 to 49, UK, RW 14 + Unk	14	3.76	4542157	8	6.55	1.22 (0.53 - 2.41)	Observed > expected
EM, Male 50 to 59, UK, RW 14 + Unk	14	4.91	6510960	2	12.25	0.16 (0.02 - 0.59)	Observed significantly < expected
EM, Male 60 to 69, UK, RW 14 + Unk	14	4.06	4934728	2	7.68	0.26 (0.03 - 0.94)	Observed significantly < expected
EM, Male 70 to 79, UK, RW 14 + Unk	14	6.45	3137304	2	7.76	0.26 (0.03 - 0.93)	Observed significantly < expected
EM, Male over 80, UK, RW 14 + Unk	14	7.88	1025046	0	3.1	0 (0 - 1.19)	Observed < expected
EM - UK Females, RW 42							
EM, Female 18 to 29, UK, RW 42	42	8.1	1109488	1	10.33	0.1 (0 - 0.54)	Observed significantly < expected
EM, Female 30 to 39, UK, RW 42	42	7.71	1892968	1	16.78	0.06 (0 - 0.33)	Observed significantly < expected

Table 70 Observed versus Expected Cumulative Analyses through DLP 28 December 2022 for reports of EM with Risk Windows of 14, 42 days including Cases with Unknown TTO

AEs	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
EM, Female 40 to 49, UK, RW 42	42	6.43	4412245	5	32.62	0.15 (0.05 - 0.36)	Observed significantly < expected
EM, Female 50 to 59, UK, RW 42	42	7.75	5944683	4	52.98	0.08 (0.02 - 0.19)	Observed significantly < expected
EM, Female 60 to 69, UK, RW 42	42	5.98	4783416	2	32.89	0.06 (0.01 - 0.22)	Observed significantly < expected
EM, Female 70 to 79, UK, RW 42	42	5.86	3475875	3	23.42	0.13 (0.03 - 0.37)	Observed significantly < expected
EM, Female over 80, UK, RW 42	42	5.43	1630324	0	10.18	0 (0 - 0.36)	Observed significantly < expected
EM - UK Females, RW 42 + Unk							
EM, Female 18 to 29 UK, RW 42 + Unk	42	8.1	1109488	1	10.33	0.1 (0 - 0.54)	Observed significantly < expected
EM, Female 30 to 39, UK, RW 42 + Unk	42	7.71	1892968	2	16.78	0.12 (0.01 - 0.43)	Observed significantly < expected
EM, Female 40 to 49, UK, RW 42 + Unk	42	6.43	4412245	7	32.62	0.21 (0.09 - 0.44)	Observed significantly < expected
EM, Female 50 to 59, UK, RW 42 + Unk	42	7.75	5944683	5	52.98	0.09 (0.03 - 0.22)	Observed significantly < expected
EM, Female 60 to 69, UK, RW 42 + Unk	42	5.98	4783416	2	32.89	0.06 (0.01 - 0.22)	Observed significantly < expected
EM, Female 70 to 79, UK, RW 42 + Unk	42	5.86	3475875	3	23.42	0.13 (0.03 - 0.37)	Observed significantly < expected
EM, Female over 80, UK, RW 42 + Unk	42	5.43	1630324	0	10.18	0 (0 - 0.36)	Observed significantly < expected
EM - UK Males, RW 42							
EM, Male 18 to 29, UK, RW 42	42	3.69	808938	0	3.43	0 (0 - 1.08)	Observed < expected

Table 70 Observed versus Expected Cumulative Analyses through DLP 28 December 2022 for reports of EM with Risk Windows of 14, 42 days including Cases with Unknown TTO

AEs	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
EM, Male 30 to 39, UK, RW 42	42	5.49	1415003	0	8.93	0 (0 - 0.41)	Observed significantly < expected
EM, Male 40 to 49, UK, RW 42	42	3.76	4542157	8	19.64	0.41 (0.18 - 0.8)	Observed significantly < expected
EM, Male 50 to 59, UK, RW 42	42	4.91	6510960	2	36.76	0.05 (0.01 - 0.2)	Observed significantly < expected
EM, Male 60 to 69, UK, RW 42	42	4.06	4934728	3	23.04	0.13 (0.03 - 0.38)	Observed significantly < expected
EM, Male 70 to 79, UK, RW 42	42	6.45	3137304	3	23.27	0.13 (0.03 - 0.38)	Observed significantly < expected
EM, Male over 80, UK, RW 42	42	7.88	1025046	0	9.29	0 (0 - 0.4)	Observed significantly < expected
EM - UK Males, RW 42 + Unk							
EM, Male 18 to 29, UK, RW 42 + Unk	42	3.69	808938	0	3.43	0 (0 - 1.08)	Observed < expected
EM, Male 30 to 39, UK, RW 42 + Unk	42	5.49	1415003	0	8.93	0 (0 - 0.41)	Observed significantly < expected
EM, Male 40 to 49, UK, RW 42 + Unk	42	3.76	4542157	10	19.64	0.51 (0.24 - 0.94)	Observed significantly < expected
EM, Male 50 to 59, UK, RW 42 + Unk	42	4.91	6510960	2	36.76	0.05 (0.01 - 0.2)	Observed significantly < expected
EM, Male 60 to 69, UK, RW 42 + Unk	42	4.06	4934728	4	23.04	0.17 (0.05 - 0.44)	Observed significantly < expected
EM, Male 70 to 79, UK, RW 42 + Unk	42	6.45	3137304	3	23.27	0.13 (0.03 - 0.38)	Observed significantly < expected
EM, Male over 80, UK, RW 42 + Unk	42	7.88	1025046	0	9.29	0 (0 - 0.4)	Observed significantly < expected
EM - EU / UK / Brazil / Australia, RW 14							

Table 70 Observed versus Expected Cumulative Analyses through DLP 28 December 2022 for reports of EM with Risk Windows of 14, 42 days including Cases with Unknown TTO

AEs	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
EM, Age 18 to 49, EU / UK / Brazil / Australia, RW 14	14	7.08	110094983	27	298.78	0.09 (0.06 - 0.13)	Observed significantly < expected
EM, Age, 50 to 59, EU / UK / Brazil / Australia, RW 14	14	6.7	58336094	10	149.82	0.07 (0.03 - 0.12)	Observed significantly < expected
EM, Age 60 to 69, EU / UK / Brazil / Australia, RW 14	14	5.07	57960860	14	112.64	0.12 (0.07 - 0.21)	Observed significantly < expected
EM, Age 70, EU / UK / Brazil / Australia, RW 14	14	7.01	32376365	9	86.99	0.1 (0.05 - 0.2)	Observed significantly < expected
EM - EU / UK / Brazil / Australia, RW 14 + Unk							
EM, Age 18 to 49, EU / UK / Brazil / Australia, RW 14 + Unk	14	7.08	110094983	38	298.78	0.13 (0.09 - 0.17)	Observed significantly < expected
EM, Age, 50 to 59, EU / UK / Brazil / Australia, RW 14 + Unk	14	6.7	58336094	12	149.82	0.08 (0.04 - 0.14)	Observed significantly < expected
EM, Age 60 to 69, EU / UK / Brazil / Australia, RW 14 + Unk	14	5.07	57960860	18	112.64	0.16 (0.09 - 0.25)	Observed significantly < expected
EM, Age 70, EU / UK / Brazil / Australia, RW 14 + Unk	14	7.01	32376365	12	86.99	0.14 (0.07 - 0.24)	Observed significantly < expected
EM - EU / UK / Brazil / Australia, RW 42							

Table 70 Observed versus Expected Cumulative Analyses through DLP 28 December 2022 for reports of EM with Risk Windows of 14, 42 days including Cases with Unknown TTO

AEs	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
EM, Age 18 to 49, EU / UK / Brazil / Australia, RW 42	42	7.08	110094983	33	896.33	0.04 (0.03 - 0.05)	Observed significantly < expected
EM, Age, 50 to 59, EU / UK / Brazil / Australia, RW 42	42	6.7	58336094	14	449.45	0.03 (0.02 - 0.05)	Observed significantly < expected
EM, Age 60 to 69, EU / UK / Brazil / Australia, RW 42	42	5.07	57960860	16	337.92	0.05 (0.03 - 0.08)	Observed significantly < expected
EM, Age 70, EU / UK / Brazil / Australia, RW 42	42	7.01	32376365	13	260.98	0.05 (0.03 - 0.09)	Observed significantly < expected
EM - EU / UK / Brazil / Australia, RW 42 + Unk							
EM, Age 18 to 49, EU / UK / Brazil / Australia, RW 42 + Unk	42	7.08	110094983	44	896.33	0.05 (0.04 - 0.07)	Observed significantly < expected
EM, Age, 50 to 59, EU / UK / Brazil / Australia, RW 42 + Unk	42	6.7	58336094	16	449.45	0.04 (0.02 - 0.06)	Observed significantly < expected
EM, Age 60 to 69, EU / UK / Brazil / Australia, RW 42 + Unk	42	5.07	57960860	20	337.92	0.06 (0.04 - 0.09)	Observed significantly < expected
EM, Age 70, EU / UK / Brazil / Australia, RW 42 + Unk	42	7.01	32376365	16	260.98	0.06 (0.04 - 0.1)	Observed significantly < expected

CI, Confidence Interval; O/E, Observed versus Expected; EM, Erythema Multiforme; TTO, Time to Onset; Unk, Unknown

For 42-day risk window, observed cases were significantly less than expected, globally and for all age/gender stratifications, including cases with unknown TTO.

For 14-day risk window, observed cases were significantly less than or less than expected, globally and for all age/gender stratifications except for males of 40-49 years of age, where Observed > Expected, only when cases with unknown TTO were also included. For this age stratification, observed numbers were small (8 cases), and the result was not significant.

It should be noted that the OE analyses does not account for confounding/risk factors which might be present in the cases, such as concomitant medications or illnesses, or for example the effect of COVID-19 which may also be a contributory factor. Also, when stratified by age/gender, there are small numbers of cases in each stratification, which should be considered when interpreting the significance of the results.

AGEP Observed vs Expected Analysis

Observed versus expected analyses for AGEP is summarized below in Table 71.

Table 71 Observed versus Expected Cumulative Analyses through DLP 28 December 2022 for reports of AGEP with Risk Windows of 21 days including Cases with Unknown TTO

AEs	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
AGEP, Overall global cases RW 21	21	0.097	466115644	9	26	0.35 (0.16 - 0.66)	Observed significantly < expected
AGEP, Overall global cases, RW 21 + Unk	21	0.097	466115644	9	26	0.35 (0.16 - 0.66)	Observed significantly < expected
AGEP, EU/UK only, RW 21	21	0.097	117724493	6	6.57	0.91 (0.34 - 1.99)	Observed < expected
AGEP, EU/UK only, RW 21 + Unk	21	0.097	117724493	6	6.57	0.91 (0.34 - 1.99)	Observed < expected

CI, Confidence Interval; O/E, Observed versus Expected; AGEP, Acute Generalised Exanthematous Pustulosis; TTO, Time to Onset; Unk, Unknown

For 21-day risk window, observed cases were significantly less than expected, globally and for EU/UK region, including cases with unknown TTO.

DRESS Observed vs Expected Analysis

Observed versus expected analyses for DRESS is summarized below in Table 72.

Table 72 Observed versus Expected Cumulative Analyses through DLP 28 December 2022 for reports of DRESS with Risk Windows of 28 days including Cases with Unknown TTO

AEs	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
DRESS, Overall global cases, RW 28	28	2.18	466115644	11	778.98	0.01 (0.01 - 0.03)	Observed significantly < expected
DRESS, Overall global cases, RW 28 + Unk	28	2.18	466115644	23	778.98	0.03 (0.02 - 0.04)	Observed significantly < expected
DRESS, EU/UK only, RW 28	28	2.18	117724493	10	196.74	0.05 (0.02 - 0.09)	Observed significantly < expected
DRESS, EU/UK only, RW 28 + Unk	28	2.18	117724493	20	196.74	0.1 (0.06 - 0.16)	Observed significantly < expected

CI, Confidence Interval; O/E, Observed versus Expected; DRESS, Drug Reaction with Eosinophilia and Systemic Symptoms; TTO, Time to Onset; Unk, Unknown

For 28-day risk window, observed cases were significantly less than expected, globally and for EU/UK region, including cases with unknown TTO.

Other SCARs Observed vs Expected Analysis

Observed versus expected analyses for some of the more common SCARs are summarized below in Table 73.

Table 73 Observed versus Expected Cumulative Analyses through DLP 28 December 2022 for reports of Other SCARs with Risk Windows of 21 days including Cases with Unknown TTO

AEs	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Generalized exfoliative dermatitis including Dermatitis exfoliative, Overall cases, RW 42	42	1	466115644	44	536	0.08 (0.06 - 0.11)	Observed significantly < expected
Generalized exfoliative dermatitis including Dermatitis exfoliative, Overall cases, RW 42 + Unk	42	1	466115644	59	536	0.11 (0.08 - 0.14)	Observed significantly < expected

Table 73 Observed versus Expected Cumulative Analyses through DLP 28 December 2022 for reports of Other SCARs with Risk Windows of 21 days including Cases with Unknown TTO

AEs	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Generalized exfoliative dermatitis including Dermatitis exfoliative, EU/UK only, RW 42	42	1	117724493	40	135.37	0.3 (0.21 - 0.4)	Observed significantly < expected
Generalized exfoliative dermatitis including Dermatitis exfoliative, EU/UK only, RW 42 + Unk	42	1	117724493	47	135.37	0.35 (0.26 - 0.46)	Observed significantly < expected

CI, Confidence Interval; O/E, Observed versus Expected; TTO, Time to Onset; Unk, Unknown

For 42-day risk window, observed cases were significantly less than expected, globally and for EU/UK region, including cases with unknown TTO.

Literature

A cumulative literature search through 28 December 2022 of the databases in Embase, InsightMeme and PubMed was conducted using the SCARs Narrow SMQ PTs. The following search terms were used: Acute generalised exanthematous pustulosis; Bullous haemorrhagic dermatosis; Dermatitis bullous; Dermatitis exfoliative; Dermatitis exfoliative generalised; Drug reaction with eosinophilia and systemic symptoms; Epidermal necrosis; Erythema multiforme; Erythrodermic atopic dermatitis; Exfoliative rash; Generalised bullous fixed drug eruption; Oculomucocutaneous syndrome; Severe cutaneous adverse reaction; SJS-TEN overlap; Skin necrosis; Stevens-Johnson syndrome; Target skin lesion; Toxic epidermal necrolysis; Toxic skin eruption.

The searches yielded 234 articles, of these:

- 19 articles were case reports for VAXZEVRIA concerning SCARs PTs (Case IDs: [redacted])
- 4 articles illustrated proposed mechanism of action between COVID-19 vaccines and SCARs
- Remaining 211 articles did not have adequate relevant information to require further review

Mechanism of Action articles Review and Summary Cumulatively through 28 December 2022

The proposed mechanisms between COVID-19 vaccines and SCARs from published literature are provided below:

- **(For cutaneous adverse reactions)** Immediate reactions to COVID-19 vaccines may be IgE-dependent or independent of IgE. For Comirnaty vaccine, polyethylene glycol (PEG), also known as macrogol, is a possible adjuvant responsible for immediate reactions. The CoronaVac vaccine contains SARS-CoV-2 (strain CZ02) inactivated with β-propiolactone and aluminum hydroxide as an adjuvant; thus, immediate reactions may be due to the inactivated vaccine component or the adjuvant. (Cebeci Kahraman et al 2022). **(For PTs associated with autoimmune bullous dermatoses)** Many components of vaccines can act like hapten and trigger a Th2-polarized inflammatory reaction, resulting in urticarial reactions, and exacerbation of atopic dermatitis, contact dermatitis, and autoimmune bullous dermatoses (Cebeci Kahraman et al 2022).
- **(For TEN)** The Com-COV trial (Com-Cov vaccine trial is studying the use of different combinations of approved COVID-19 vaccines for the first and second immunisation doses: VAXZEVRIA and Comirnaty) data suggest greater systemic reactogenicity and increased risks of mild-to-moderate symptoms. Given that mixing vaccination mechanism of action is associated with a heightened T-cell response, this could be considered a potential driver for TEN: a T-cell-driven, type IV hypersensitivity reaction (Jmor et al 2022).
- **(For TEN)** The pathogenic mechanisms behind these vaccine reactions are poorly clarified. Some authors suggest the role of vaccine virotopes, which are expressed on the keratinocyte surface, which could lead to the activation of cytotoxic T lymphocytes and the death of epidermal cell (Seck et al 2022, Dash et al 2021).
- **(For cutaneous adverse reactions associated with oral lesions)** The main pathogenic mechanisms potentially implied in the onset of oral lesions following the COVID-19 vaccination comprise hypersensitivity reactions, molecular mimicry, immune cross-reactivity and autoimmunity, allergy to vaccine excipients, and reactivation of latent viral infections Di Spirito et al 2022.
- Literature overview

On review of cumulative literature search through 28 December 2022, 234 articles were further assessed. 211 articles did not have adequate relevant information to require further review. No epidemiological articles with relevant new safety information were identified. 19 articles describing VAXZEVRIA in association with SCARs were discussed in the previous review of ICSRs retrieved from the AstraZeneca Global Patient Safety Database. No new safety concerns regarding SCARs and association with VAXZEVRIA was identified. Upon review of relevant articles related to SCARs subsequent to COVID-19 vaccination, mechanism of actions postulated are: May be due to the inactivated vaccine component or the adjuvant (1); Triggering a Th2-polarized inflammatory reaction (1); A T-cell-driven, Type IV hypersensitivity reaction (1); Activation of cytotoxic T lymphocytes and the death of epidermal cell (2); and Hypersensitivity reactions, molecular mimicry, immune cross-reactivity and autoimmunity, allergy to vaccine excipients, and reactivation of latent viral infections (1).

Summary

In the assessment report received from the PRAC (PRAC PAR (EMEA/H/C/PSUSA/00010912/202112) for the VAXZEVRIA PBRER (review period: 29 June 2022 to 28 December 2022), the PRAC requested a review of SCARs in this PBRER. Cumulatively, a total of 415 SCARs cases concerning 423 events were reported in AstraZeneca's global Safety database. Cases were assessed by age, sex, type of event and outcome. A female (65.1%) prevalence versus male (34.9%) was expressed. The median age was 56 years. The majority (88.4%) of events were reported after Dose 1. In 1 case, the event (PT: Erythema Multiforme) occurred after Dose 1 and subsequently reappeared after Dose 2 of the vaccination. The recurrence case was assessed against the WHO-UMC causality criteria as 'Probable', due to temporal relationship, and considering recurrence, and the fact that it is not likely that any other confounder was present during both occurrences and absent in between. Amongst 423 SCARs events, 391 (94.2%) were serious of which 3 (0.8%) resulted in death, 94 (22.2%) events had favourable outcome (either 'recovered' or 'recovered with sequelae). Event duration was reported for 52 (55.3%) cases of which majority 29 (55.8%) were resolved after 7 days. The risk window for the SCARs topic was considered as 0-42 days except for DRESS and AGEP. The risk window for DRESS was considered as 0-28 days whereas for AGEP this was taken as 0-21 days. The time to onset (TTO) was available in 330 (78.0%) case reports and ranged from 0 days to 269 days (median: 4 days) of which 271 (82.1%) case reports were within TTO range of 0-21 days, and 281 (85.2%) case reports were within range of 0-28 days. Amongst 415 cases, 2 (0.5%) cases met WHO-UMC causality criteria for 'Probable/Likely' (PT: Erythema Multiforme) and 293 (70.6%) were considered as 'Possible', of which 78 (26.6%) were identified with relevant risk/confounding factors. Of 415 cases, 2 fatal cases were assessed against the WHO-UMC causality criteria as 'Possible and limited information' respectively. None of the fatal cases reported detailed autopsy results. The O/E analysis results for SCARs showed observed cases to be significantly less than expected for all age, global and EU/UK reports.

A review of the literature suggests various hypothesized mechanisms for development of SCARs in association with COVID-19 vaccines.

Conclusion

Based on the review of cumulative information from clinical, post-marketing and literature articles, AstraZeneca considers that there is insufficient evidence to suggest a causal association between SCARs and VAXZEVRIA. No changes to the CDS or RMP are recommended for SCARs. SCARs will continue to be monitored as part of AstraZeneca's routine safety surveillance activities for VAXZEVRIA. AstraZeneca will no longer discuss this topic in future PBRERs, unless significant new safety information arises.

The event of cutaneous vasculitis is included as an ADR in section 4.8 of the VAXZEVRIA CDS.

15.2.8 Hearing loss (HL)

In the assessment report received from the PRAC EMA (PRAC PAR EMEA/H/C/PSUSA/00010912/202206) for the VAXZEVRIA PBRER (review period: 29 December 2021 to 28 June 2022), further information on the topic of Hearing Loss (HL) has been requested as follows:

"The MAH is requested to provide and discuss an updated review of hearing loss cases with a recovered with sequelae or not recovered outcome."

Global Patient Safety Database

A cumulative search till 28 December 2022 of the AstraZeneca Global Safety Database for HL with VAXZEVRIA was performed using MedDRA version 25.1. The search strategy included HLT 'Hearing losses' only including cases with a recovered with sequelae or not recovered outcome.

The search retrieved a total of 1793 case reports, out of which 1034 reports (1073 events) with the outcome of recovered with sequelae (75 events) or not recovered (998 events) have been reviewed. These 1034 cases were reported most frequently from United Kingdom (n = 559, 54.1%); Germany (n = 123, 11.9%); Australia (n = 75, 7.3%); France (n = 43, 4.2%) and Italy (n = 33, 3.2%). The majority of the cases with the outcome recovered with sequelae are from the regulatory with limited scope of follow up. However, none of the cases has reported any information about what the sequalae was in the events reported with that outcome. During the assessment of case date reported and case date birth, there was no trend identified across seasonal sickness.

The distribution of the 1073 events of interest [HL] by event outcome are presented in Table 74 below in descending order of no of events:

Table 74 Distribution of MedDRA PTs (n = 1073) pertaining to HL with VAXZEVRIA received cumulatively through DLP

MedDRA PT	Not recovered		Recovered with sequelae		Grand Total
	Serious	Non-serious	Serious	Non-serious	
Hypoacusis	374	0	13	0	387
Deafness neurosensory	162	144	17	9	332
Deafness unilateral	122	33	20	3	178
Sudden hearing loss	64	21	4	0	89
Deafness	34	7	6	1	48
Deafness bilateral	24	0	1	0	25
Neurosensory hypoacusis	5	1	0	0	6
Deafness transitory	0	1	1	0	2

Table 74 Distribution of MedDRA PTs (n = 1073) pertaining to HL with VAXZEVRIA received cumulatively through DLP

MedDRA PT	Not recovered		Recovered with sequelae		Grand Total
	Serious	Non-serious	Serious	Non-serious	
Hypoacusis	374	0	13	0	387
Deafness neurosensory	162	144	17	9	332
Deafness unilateral	122	33	20	3	178
Sudden hearing loss	64	21	4	0	89
Mixed deafness	1	1	0	0	2
Conductive deafness	0	1	0	0	1
Vibration syndrome	1	0	0	0	1
Deafness traumatic	0	1	0	0	1
Presbyacusis	0	1	0	0	1
Grand total	**787**	**211**	**62**	**13**	**1073**

MedDRA Medical Dictionary for Regulatory Activities; PT Preferred Term

Of the 1973 cases reports of HL received cumulatively through DLP, 1513 case reports were initial ICSRs while follow-up information has been received for the for the remaining 280 case reports. Out of these 280 cases, 120 reported an event with the outcome of 'Not recovered' and 8 reported event with the outcome of 'Recovered with sequelae'. However, further review of these 128 cases did not yield any detailed or significant information on clinical course, treatment details, any additional work up nor any trend of a singular etiopathogenesis of a systemic insult showing either a unilateral or bilateral presentation.

The breakdown and overview of these 1034 cases reporting 1073 events of topic is presented in the below Table 75 .

Table 75 Overview of Events/Cases cumulatively through DLP

Parameter	Break-down	Values (%)[b]
Event Count	Total	1073 (100%)
	Serious	849 (79.1%)
	Non serious	224 (20.9%)
Case Count	Medically confirmed	127 (12.3%)
Case Report Source	Interventional Clinical study	0 (0%)
	Non-interventional study	12 (1.2%)
	Spontaneous	59 (5.7%)
	Literature	1 (0.1%)
	Regulatory	962 (93%)

Table 75 Overview of Events/Cases cumulatively through DLP

Parameter	Break-down	Values (%)[b]
Sex	Female	618 (61.4%)
	Male	388 (38.6%)
	Unknown/not reported	28
Age Group	18-49	348 (37.2%)
	50-59	223 (23.8%)
	60-69	254 (27.1%)
	70-79	91 (9.7%)
	80+	19 (2%)
	Unknown	98
	Median age (range)	55 years (18 to 93)
Event occurrence with dose	Dose 1	486 (69.5%)
	Dose 2	208 (29.8%)
	Dose 3	5 (0.7%)
	Dose 4	0 (0%)
	Multiple Doses	5 (8.8%)
	Unknown dose	335
Case level -TTO (days)[a]	0-14	597 (72.4%)
	15-28	98 (11.9%)
	29-42	50 (6.1%)
	43 and above	80 (9.7%)
	Unknown	209
	Median TTO (range)	5 days (0 to 455)
Event Seriousness criteria	Medically important	655 (61%)
	Disability	282 (26.3%)
	Hospitalisation	85 (7.9%)
	Congenital anomaly	0 (0%)
	Life Threatening	10 (0.9%)
	Death	0 (0%)
AE Outcome[c]	Recovered with sequelae	75 (7%)[c]
	Not recovered	998 (92.9%)
Duration of recovered with sequelae events	Range (days)	0 - 365
	Mean (days)	122.75
	Unknown duration (number of events)	63

[a] TTO was reported for 825 case reports (total number of cases) used to calculate the percentage. Additionally, where multiple TTOs are present in a case, the most conservative TTO within the risk window of 0 to 42 days for the relevant event is chosen

[b] Percentages for all, calculated based on known values

[c] The majority of the cases with the outcome recovered with sequelae are from the regulatory with limited scope of follow up. However, none of the cases has reported any information about what the sequalae was in the events reported with that outcome

DLP Data Lock Point; TTO Time To Onset

The events most commonly co-reported with HL cumulatively are presented in Table 76 and Table 77 below.

Table 76 Distribution of most frequently co-reported events (≥ 5%) in case reports for HL with outcome of 'Not recovered' or 'Recovered with sequelae', cumulatively through DLP

Adverse events (PT)	Number of events	Percentage (%)
Tinnitus	380	36.8
Headache	211	20.4
Fatigue	145	14
Dizziness	144	13.9
Pyrexia	92	8.9
Nausea	90	8.7
Chills	83	8
Vertigo	69	6.7
Myalgia	66	6.4
Ear pain	61	5.9
Arthralgia	58	5.6
Hypoaesthesia	53	5.1

DLP Data lock point, PT preferred term

Table 77 Distribution of most frequently co-reported events (≥ 5%) in case reports for HL, cumulatively through DLP

Adverse events (PT)	Number of events	Percentage (%)
Tinnitus	620	34.6
Headache	450	25.1
Dizziness	295	16.5
Fatigue	290	16.2
Pyrexia	262	14.6
Chills	191	10.7
Nausea	190	10.6
Myalgia	148	8.3
Arthralgia	142	7.9
Vertigo	117	6.5
Ear pain	102	5.7

DLP Data Lock Point; HL Hearing Loss; PT Preferred Term

Recurrence and worsening case reports

Cumulatively, in 5 (8.8%) out of 1034 case reports, the event of HL occurred after 1st and 2nd dose. Of the 5 case reports, 1 (20%) case report was medically confirmed.

Out of 5 case reports, 4 of them were reported as worsening scenario, and in 1 case [redacted]) the vaccinee reported improvement of the symptoms (unspecified treatment), however, HL was once more experienced after dose 2. Due to limited information on latencies, following both doses of vaccination the causality assessment was considered Unassessable/Unclassifiable with limited information. Alternative causal factors were noted in 2 (40%) case reports (Deafness; Tinnitus; Otitis externa; Ear pain), and a comprehensive causal attribution of other disease and drugs was not possible for 2 (40%), due to insufficient information on start dates for HL, relevant medical history, and concomitant medications.

Alternative causal factors were noted in 2 (40%) case reports (Deafness; Tinnitus; Otitis externa; Ear pain), and a comprehensive causal attribution of other disease and drugs was not possible for 2 (40%), due to insufficient information on start dates for HL, relevant medical history, and concomitant medications.

Table 78 Summary of recurrence case reports for HL (N = 5) cumulatively through DLP of the PBRER

Case ID/Age (Years)/Sex/Medically confirmed (Y/N)/Serious(Y/N)/Source /Country	Recurrence or worsening event	TTO First occurrence/ subsequent occurrence (days)	Corrective treatment first episode/ second episode	Outcome(s)	Relevant Medical History (Risk factors)/ Concomitant medications	Level of certainty (LOC) classification/WHO UMC Causality Assessment	Comment for LOC/WHO
[redacted] / 47 / M / N / YES / Regulatory / [redacted]	Worsening event	Dose 1: 36 Dose 2: 5	Treatment with ear drops and antibiotics / Steroids on unspecified time	Not recovered	Deafness; Tinnitus / Unknown relevant concomitant medication	BCC 3 / Possible with risk factors/confounders	Medical history included hearing loss and tinnitus. However, it is noted the lack of information regarding complete diagnosis and etiology workup for local symptoms as HL was unilateral.
[redacted] / 32 / F / N / YES / Spontaneous / [redacted]	Worsening event	Dose 1: ~1 month Dose 2: ~1 month	Not reported	Not recovered	Hearing impaired since childhood / Unknown relevant concomitant medication	BCC 4/ Possible with risk factors/confounders	Medical history included hearing impaired since childhood. Limited information regarding evaluation, etiology workup.

Table 78 Summary of recurrence case reports for HL (N = 5) cumulatively through DLP of the PBRER

Case ID/Age (Years)/Sex/Medically confirmed (Y/N)/Serious(Y/N)/Source /Country	Recurrence or worsening event	TTO First occurrence/ subsequent occurrence (days)	Corrective treatment first episode/ second episode	Outcome(s)	Relevant Medical History (Risk factors)/ Concomitant medications	Level of certainty (LOC) classification/WHO UMC Causality Assessment	Comment for LOC/WHO
[redacted] / 70 / M / N / YES / Regulatory / [redacted]	Worsening event	Dose 1: 1 month Dose 2: Unknown	Not reported / Not reported	Not recovered	Unknown relevant medical history and concomitant medication	BCC 4 / Possible with limited information	Limited information regarding medical history and concomitant medications. No information regarding diagnostic and etiology workup
[redacted] / Unknown / Unknown / Y / YES / Regulatory / [redacted]	Worsening event	Dose 1: ~1 month Dose 2: Unknown	Not reported / Not reported	Not recovered	Otitis externa; Ear pain / Unknown relevant concomitant medication	BCC 4 / Possible with risk factors/confounders	Medical history included otitis externa and ear pain, however no details on dates or outcome of this previous events. No etiology or diagnostic workup

Table 78 Summary of recurrence case reports for HL (N = 5) cumulatively through DLP of the PBRER

Case ID/Age (Years)/Sex/Medically confirmed (Y/N)/Serious(Y/N)/Source /Country	Recurrence or worsening event	TTO First occurrence/ subsequent occurrence (days)	Corrective treatment first episode/ second episode	Outcome(s)	Relevant Medical History (Risk factors)/ Concomitant medications	Level of certainty (LOC) classification/WHO UMC Causality Assessment	Comment for LOC/WHO
[redacted] / 50 / M / N / YES / Spontaneous / [redacted]	Recurrence	Dose 1: Unknown Dose 2: Unknown	Not reported / Ear lavage	Not recovered	Not Reported / Unknown relevant concomitant medication	BCC 4 / Unassessable/Unclassifiable with limited information	HL event after 1st dose reported as improved,(treatment unspecified), however event was described again after 2nd dose with no improvement of symptoms after ear lavage.

TTO Time to onset; UMC Uppsala Monitoring Centre; WHO World Health Organization

Events after third dose

Of the 5 cases reported after the third dose, 1 (20%) case report were medically confirmed and 4 (80%) were non-medically confirmed. These case reports for HL were reported in the following countries: United Kingdom (4) and Brazil (1). Vaccinee age was reported in all the case reports and ranged 37 to 62 years (mean: 51.6 years; median: 51 years). Of these case reports, 80% (4) concerned male patients and 20% (1) concerned female patients. Of the 5 case reports, TTO identified from VAXZEVRIA administration to the event of interest was reported in 4 case reports and ranged from 0 to 202 days (mean: 51.5 days; median: 2 days).

Of the 5 case reports, homologues booster was seen in 2 (of the case reports. In the remaining 3 (reports the vaccination series cannot be verified. No trend was seen for HL on correlation with primary vaccination series (homologous/heterologous).

On review of the 5 cases, the causality were assessed as 'Possible with limited information' (3), 'Unassessable/Unclassifiable with limited information' (1) and as 'Unlikely' (1). Of the 3 cases considered to be 'Possible with limited information' as per WHO-UMC causality criteria, none of the case reports fit any of the BCC levels defined by Carol Liu et al 2020.

WHO -UMC causality and Brighton Collaboration Classification Assessment

WHO-UMC criteria has been used to assess causality of all cases of HL based on information available. The Brighton Collaboration Classification (BCC) for diagnostic certainty (Carol Liu et al 2020) was used for review of information available in these case reports of HL.

According to Carol Liu et al 2020, Sensorineural Hearing Loss (SNHL) is hearing loss of more than 30 dB in three sequential frequencies in the standard pure tone audiogram. Thus, a case report of SNHL can be ascertained in 3 categories: Level 1 - Definite case of SNHL; Level 2 - Probable case of SNHL; Level 3 - Possible case of SNHL. Of the 1034 case reports with recovered with sequelae and not recovered outcome, 12 cases meet the BCC level 1-3. In total 1014 cases were classified as Level 4 since it could not be determined whether the HL was sensory neural in nature or due to conductive/functional causes, due to insufficient information on audiometry or Tuning fork. In the remaining 8 cases the occurrence of SNHL was excluded. These cases were wrongly coded as HL, thus assessed as assessed as Level 5.

Out of 12 cases classified as BCC level 1-3, 6 of them (2 cases with outcome of recovered with sequelae and 4 with outcome of not recovered) reported treatment which included steroids (intratympanic, oral and IV), antibiotics (not specified), ear drops (not specified), oral antivirals, and vitamins. Remaining 6 other case reports did not provide any information on treatment.

On review remaining 1022 cases fulfilling BCC Level 4 and 5, 98 cases were medically confirmed serious, of which 43 cases had additional confounding factors and unlikely related to VAXZEVRIA. In the remaining 55 of the 98 cases, just 4 of them reported HL treatment,

such as steroids (3) and corticoids (1), no trend cannot be concluded due to insufficient information.

Causality assessment of all cases was performed using WHO-UMC causality assessment criteria with a risk window of 0 to 42 days.

Table 79 Overview of BCC 1-3 and WHO-UMC Causality Assessments for case reports of HL with VAXZEVRIA reported cumulatively through DLP

WHO-UMC/BCC Level	Level 1	Level 2	Level 3	Grand Total
Certain	0	0	0	**0**
Probable-Likely	0	0	0	**0**
Possible with risk factors/confounders[a]	0	0	1	**1**
Possible with Limited information	4	1	4	**9**
Unlikely	0	0	1	**1**
Conditional / Unclassified	0	0	0	**0**
Unassessable/Unclassifiable with risk factors/confounders[a]	0	0	0	**0**
Unassessable/Unclassifiable with limited information	1	0	0	**1**
Total	**5**	**1**	**6**	**12**

[a] Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, or where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported

BCC Brighton Collaboration Criteria; DLP Data Lock Point; HL Hearing Loss; WHO World Health Organization; UMC Uppsala Monitoring Centre

Cumulatively through DLP, none of the case reports of HL were classified with Certain causality or Probable-Likely.

Amongst 1034 cases for HL, 151 (14.6%) were identified either with relevant risk / confounding factors as presented in Table 80 in descending order of frequency.

Table 80 Relevant Risk factors / Confounders identified for case reports cumulatively through DLP

Relevant Risk factors/ Confounders[a]	Number of reports
Age above 65	67
COVID-19 positive	15
Hypertension	15
Deafness	13
Diabetes	7
Ibuprofen	7
Atorvastatin	6
Meniere's disease	3
Medical history of COVID-19	2

Table 80 Relevant Risk factors / Confounders identified for case reports cumulatively through DLP

Relevant Risk factors/ Confounders[a]	Number of reports
Influenza	2
Myocardial infarction (Carol Liu et al 2020)	2
Ear infection	2
Hypoacusis	2
Otitis	2
Labyrinthitis	1
Tinnitus	1
Hearing impaired since childhood	1
Otitis externa	1
Ear pain	1
Tacrolimus	1

Some cases have more than 1 relevant risk/confounding factors.
Coronavirus Disease 2019; DLP Data Lock Point

Summary

Cumulatively till 28 December 2022, a total of 1034 reports of HL with a outcome of 'Recovered with sequelae' or 'Not recovered' with the use of VAXZEVRIA have been received, of which 1021 (98.7%) of the 1034 cases were reported from spontaneous sources.

486 (69.5%) of the reported events occurred after first dose, 208 (29.8%) after second dose and 5 (0.7%) after booster. The review of HL cases post COVID-19 booster dosing did not show any significant safety concern.

Of the 1034 cases reports, 39 cases were initial ICSRs whereas 995 cases received follow-up information. 127 (12.3%) of the 1034 cases were medically confirmed, and 79.1% of the reported events were serious. In 85 (7.9%) events, HL was reported to cause hospitalization and in 655 (61%) events HL was considered a medically important event. The majority of these cases are from the regulatory authority source with limited scope of follow up. In addition, the cases have insufficient information about the sequalae that was reported as outcome.

Cumulatively through DLP, distribution of most frequently co-reported events in case reports for HL with outcome of 'Not recovered' or 'Recovered with sequelae' and distribution of most frequently co-reported events in case reports for HL concludes that the most frequently co-reported PTs for HL are Tinnitus, Headache, Dizziness and Fatigue. This is as expected as these PTs often are symptoms related to HL.

Out of 1073 events, 178 events were pertaining to unilateral hearing loss while 25 events were pertaining to bilateral hearing loss. This distribution precludes any trend of a singular etiopathogenesis of a systemic insult (such as parenteral vaccination) which is expected to show either a unilateral or bilateral presentation. This is also supported by the case onset

window – majority of the events had onset within 0 to 28 days, however, the TTO ranged widely from 0-455 days, with the median of 5 days.

Five (8.8%) events were identified to have reoccurrence or worsened after the 2nd dose. In the recurrence case, the latency of recurrence was not reported. However, for the worsened event scenario, the latency varied widely (5 days after dose 2 and 1 month after dose 2), which do not suggest any particular trend. Diagnosis details such as audiometry or Tuning fork examination was not available in any of the cases. None of the cases reported any etiological workup. Hence reoccurrence cannot be comprehensively confirmed.

Median age was 55 years (range: 18 to 93 years). Gender was reported in 1006 cases, of which there is a female preponderance (eg, female = 61.4% and male = 38.6%).

Out of the 1034 cases, 5 (0.5%) fulfilled BCC level 1, 1 (0.1%) fulfilled BCC level 2 and 6 (0.6%) fulfilled BCC level 3. Of the 5 cases fulfilling BCC level 1: 4 cases were assessed as possible with limited information and 1 case were assessed as unassessable/unclassifiable with limited information. The one case fulfilling BCC level 2 were assessed as possible with limited information. Of the 6 cases fulfilling BCC level 3: 1 case were assessed as possible with risk factors/confounders and 4 cases were assessed as possible with limited information. Treatment was reported in 6 cases report out of 12 cases with BCC 1-3, treatment included steroids (intratympanic, oral and IV), antibiotics (not specified), ear drops (not specified), oral antivirals, and vitamins. Remaining 6 other case reports did not provide any detail for treatment in their narratives.

On review remaining 1022 cases fulfilling BCC Level 4 and 5, 98 cases were medically confirmed serious, of which 43 cases had additional confounding factors and unlikely related to VAXZEVRIA. In the remaining 55 of the 98 cases, just 4 of them reported HL treatment, such as steroids (3) and corticoids (1), no trend cannot be concluded due to insufficient information. On review of 127 (12.3%) medically confirmed cases, 4 (3.1%) cases met BCC level 1, 1 (0.8%) case met BCC level 2 and 3 (2.4%) of the cases met BCC level 3. The WHO-UMC causality was assessed as follows: Possible with risk factors/confounders in 33 (26%) cases; Possible with Limited information in 62 (48.8%) cases; Unlikely in 13 (10.2%) cases; Unassessable/Unclassifiable with risk factors/confounders in 9 (7.1%) cases; Unassessable/Unclassifiable with limited information in 10 (7.9%) cases.

In summary, on review of available data from AZ safety database of HL did not identify an index case or other evidence of a new or emerging signal.

The annual reporting rate of all cases of HLT 'Hearing loss' (1793 cumulatively) is 0.2/100 000 which is lower than the reported annual incidence of SNHL from an observational study (OBS) done by Nieminen et al 2022, although this is not a direct comparison. The exposure for VAXZEVRIA is 466115644 doses administered (cumulatively through DLP 28 December 2022). In the same study the authors also compared the incidence rate of SNHL following COVID-19 vaccination to the background rates and concluded that there is no evidence of an increased risk of SNHL following COVID-19 vaccination. Other large

observational studies also reported similar findings (Yanir et al 2022 article and Formeister et al 2022).

Conclusion

This updated cumulative review found insufficient evidence for a new or emerging signal regarding HL and VAXZEVRIA. No changes to the CDS or RMP are recommended for HL, and the Company therefore proposes discontinuation of presentation of this topic in future PBRERs, and monitoring through routine pharmacovigilance and ongoing surveillance activities.

15.2.9 New daily persistent headache

In the updated assessment report received from the PRAC EMA (PRAC PAR (EMEA/H/C/PSUSA/00010912/202206) for the VAXZEVRIA PBRER (review period: 29 December 2021 to 28 June 2022):

"The MAH is requested to provide a cumulative review of cases of new daily persistent headache (NDPH) in association with VAXZEVRIA, including spontaneous reports and data from the literature and clinical trials. The analysis should include an overall discussion of the cases, as well as an individual causality assessment of each cases."

AstraZeneca evaluation of this topic is presented below.

Disease Background

New Daily Persistent Headache (NDPH) is a clinical diagnosis characterised by persistent headaches of acute onset (Peng and wang et al 2022; ICHD-3 2018). The headaches can be tension type, migrainous or thunderclap in nature with or without associating symptoms like nausea, photophobia (ICHD-3 2018; Rozen 2019).

No specific biomarkers exist for NDPH (Peng and wang et al 2022).

Rozen 2016), in a retrospective analysis of headache speciality clinics from 2009-2013 (n = 97), reported that 53% of the patients had no specific triggers. In the remaining patients the triggers identified were infection or flu-like illness (22%), a stressful life event (9%), a procedure (surgical, intubation) in 9%, and other triggers in 7%.

Infectious triggers (Epstein Barr virus, Dengue, Salmonella, Escherichia coli, COVID-19) have been seen, however no specific pathogen have beeen idenitified (Bordini and Valença 2017; Caronna et al 2020; Diaz Mitoma et al 1987; Santoni and Santoni-Williams 1993; Sampaio and Voss 2020).

There is limited evidence of disease burden of NDPH. A retrospective analysis of a registry of patients presenting to a multidisciplinary headache centre found comparable levels of migraine-related functional disability in approx. 986 patients with chronic migraine (CM) and 115 patients with NDPH. There were no clinically meaningful differences in headache

features and associated disability, suggesting the disease burden of NDPH may be as high as CM in adolescent patients (Reidy et al 2020).

According to the International Classification of Headache Disorders, 3rd edition (ICHD-3) ICHD-3, the description and diagnostic criteria of New daily persistent headache are presented below:

Description: Persistent headache, daily from its onset, which is clearly remembered. The pain lacks characteristic features and may be migraine-like or tension-type-like or have elements of both.

Table 81 Diagnostic criteria of New daily persistent headache

Type of Headache	Certain new daily persistent headache	Probable new daily persistent headache
Diagnostic criteria	A. Persistent headache fulfilling criteria B and C B. Distinct and clearly remembered onset, with pain becoming continuous and unremitting within 24 hours C. Present for >3 months D. Not better accounted for by another ICHD-3 diagnosis.	A. Persistent headache fulfilling criteria B and C B. Distinct and clearly remembered onset, with pain becoming continuous and unremitting within 24 hours C. Present for ≤ 3 months D. Not fulfilling ICHD-3 criteria for any other headache disorder E. Not better accounted for by another ICHD-3 diagnosis.

ICHD; International Classification of Headache Disorders

Clinical Study Data

A search was conducted in the AstraZeneca clinical database for adverse event (AE) reports of New daily persistent headache following the use of AZD1222 reported from clinical studies (data cut-off of 07 December 2020 for the Oxford pooled studies [COV001, COV002, COV003, and COV005] and 11 March 2022 for the United States (US) study [D8110C00001]). The search utilized Medical Dictionary for Regulatory Activities (MedDRA version 23.1) with the following Preferred Terms (PT): New daily persistent headache.

There were no AEs of NDPH in the clinical database.

Global Patient Safety Database

A cumulative search till 28 December 2022 of the AstraZeneca Global Safety Database for NDPH with VAXZEVRIA was performed using MedDRA version 25.1. The search strategy included the following PT: New daily persistent headache.

The search retrieved a total of 53 events pertaining to the PT of NDPH in 53 case reports. These cases were reported most frequently in the following countries: United Kingdom (49.1%), Ireland (20.8%), Norway (9.4%), France (5.7%), Germany (5.7%), and Spain (5.7%).

The breakdown and overview of these 53 cases reporting the event of NDPH presented in the below Table 82.

Table 82 Overview of NDPH events/case reports

Parameter	Break-down	Numbers[b]
Event Count	Total	53
	Serious	26 (49.1%)
	Non serious	27 (50.9%)
Case Count	Medically confirmed	12 (22.6%)
Case Report Source	Interventional Clinical study	-0
	Non-interventional study	-0
	Spontaneous	1 (1.9%)
	Literature	-0
	Regulatory	52 (98.1%)
Sex	Female N (%)	37 (74%)
	Male N (%)	13 (26%)
	Unknown/not reported N (%)	3
Age Group	18-49	25 (52.1%)
	50-59	11 (22.9%)
	60-69	9 (18.9%)
	70-79	3(6.3%)
	80+	0
	Unk	5
	Median age (range)	49 years (23 to 75)
Event occurrence with dose	Dose 1 (%)	10 (83.3%)
	Dose 2 (%)	2 (16.7%)
	Dose 3 (%)	-
	Dose 4 (%)	-
	Multiple Doses	-
	Dose unspecified	41
Case level -TTO (days)[a]	0-2	25 (56.8%)
	3-7	9 (20.5%)

Table 82 Overview of NDPH events/case reports

Parameter	Break-down	Numbers[b]
	8-14	5 (11.4%)
	15-30	5 (11.4%)
	Unknown	9
	Median TTO (range)	2 (0 to 30)
Event Seriousness criteria (29 out of 53 AEs)	Medically important	22 (75.9%)
	Disability	3 (10.3%)
	Hospitalization	4 (13.8%)
	Congenital anomaly	0
	Life-threatening	0
	Death	0
AE Outcome	Recovered	8 (16.3%)
	Recovering	2 (4.1%)
	Recovered with sequelae	2 (4.1%)
	Not recovered	37 (75.5%)
	Fatal	0
	Unknown	4
Duration of all events	Known duration (number of cases)	10
	Unknown duration (number of events)	43

[a] TTO was reported for 42 case reports (*total number of cases*) used to calculate the percentage. Where multiple TTOs are present in a case, the most conservative TTO for the relevant event is chosen

[b] percentages for all, calculated based on known values

AE Adverse Event; NDPH New Daily Persistent Headache; TTO Time To Onset

The events most commonly co-reported with NDPH cumulatively are presented in Table 83.

Table 83 Distribution of most frequently co-reported events (2% or more) in case reports for New daily persistent headache, cumulatively

Adverse events (PT)	Number of events	Percentage (%)
Headache[a]	21	9.8%
Fatigue	10	4.7 %
Pyrexia	10	4.7%
Dizziness	5	2.3%
Nausea	5	2.3%

[a] In 21 cases received from Regulatory Authorities the PT of "Headache" was co-reported with New Daily Persistent Headache and the verbatim used was "Headache" with limited description of clinical presentation.

PT Preferred Term

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WHO -UMC causality and International Classification of Headache Disorders, 3rd edition (ICHD-3) Assessment

The International Classification of Headache Disorders, 3rd edition (ICHD-3) for diagnostic certainty was used for review of information available in the case reports of New daily persistent headache.

Forty-four (44) cases were assessed as probable NDPH as per the ICHD-3 diagnostic certainty criteria and nine (9) cases were unassessable due to insufficient information on clinical features and duration of headache. There were no cases assessed as certain NDPH according to the ICHD-3 diagnostic certainty criteria.

WHO-UMC assessment was used for the causality assessment of NDPH.

The ICHD-3 and WHO-UMC assessment performed for these cases is provided in the following Table 84.

Table 84 Overview of WHO-UMC Causality Assessments for case reports of New daily persistent headache with VAXZEVRIA reported cumulatively

WHO-UMC causality/ICHD-3 diagnostic certainty criteria	Certain (New daily persistent headache)	Probable (Probable new daily persistent headache)	Unassessable	Grand total
Certain	0	0	0	
Probable/Likely	0	0	0	
Possible with risk factors/confounders	0	15	0	15
Possible with limited information	0	29	0	29
Unassessable/Unclassifiable with limited information	0	0	6	6
Unassessable/Unclassifiable with risk factors/confounders	0	0	3	3
Unlikely	0	0	0	
Conditional /Unclassified	0	0	0	
Total	0	**44**	**9**	**53**

Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, or where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.
ICHD International Classification of Headache Disorders; UMC Uppsala Monitoring Centre; WHO World Health Organization

Cases with diagnostic certainty of Probable new daily persistent headache

Summary of cases fulfilling the ICHD-3 certainty criteria as "Probable" (Probable new daily persistent headache. Of the forty-four (44) cases assessed as "Probable" twenty-nine (29) concerned females and thirteen (13) concerned males. For two (2) case reports the gender was unknown. The age range was (24-76) years.

In these forty-four (44) cases the TTO range was between same day onset to thirty (30) days. The median TTO was 2days. Twenty-nine (29) cases were assessed (using WHO-UMC causality assessment criteria) as "Possible with limited information", and fifteen (15) were assessed as "Possible with confounders".

Review of all reports as per WHO-UMC causality/ICHD-3 diagnostic certainty criteria are presented in the table in Appendix 13.

Amongst fifty-three (53) cases for New daily persistent headache, eighteen (18) (34%) were identified either with relevant risk / confounding factors as presented in Table 85. These are presented into the following categories for risk / confounding factors in descending order of frequency.

Table 85 Relevant Risk factors / Confounders identified for case reports cumulatively

Relevant Risk factors/ Confounders[a]	Number of reports
Chronic conditions (Rheumatoid arthritis, Immunodeficiency, Hypercholesterolemia, Fibromyalgia, Gastroesophageal reflux, Ovarian Cancer, Asthma, Chronic fatigue, Autoimmune disorder, Nervous system disorder, Diabetes mellitus, Hypertension)	10
Covid-19, Suspected Covid-19	3
Headache, Migraine	3
Hay fever	1
Pyrexia	1

[a] Some cases have more than 1 relevant risk/confounding factors.
COVID-19 Coronavirus Disease 2019

Two (2) case reports had medical history of Covid-19 and one (1) case had medical history of Suspected Covid-19. Two (2) of these case reports concerned females and one (1) case report was reported in a male vaccinee. The age range for the females was (23-42) and the age of the male was unknown. The median TTO was 4,5 days. All three (3) cases were assessed as Possible with confounding factor Covid-19.

In only three (3) case reports treatment was given for New daily persistent headache. The treatment included paracetamol (2), ibuprofen (1) and co-adamol (1).

Literature

A cumulative literature search of the databases in Embase, InsightMeme and PubMed was conducted for relevant articles on New daily persistent headache in association with VAXZEVRIA.

The search did not yield any articles that were considered relevant for further evaluation and presentation.

Summary

Cumulatively, a total of fifty-three (53) reports of New daily persistent headache with the use of VAXZEVRIA have been received, of which twenty-six (26) (49.1%) of the reported events were serious. Twenty-two (22) (41.5%) had a seriousness criteria of Medically Important, three (3) (5.7%) of Disability and four (4) (7.5%) of Hospitalisation. Median age was 49 years. 37 (74%) were females and 13 (26%) were males.

10 events (83.3%) events occurred after first dose, 2 (16.7%) after 2nd dose, and for 41 events the dose was unknown. There were no recurrence cases reported.

Of the total number of case reports cumulatively, twelve (12) (22.6%) were medically confirmed.

Forty-four (44) cases were assessed as probable as per the ICHD-3 diagnostic certainty criteria and nine (9) cases were unassessable. There were no cases assessed as certain according to the ICHD-3 diagnostic certainty criteria. Of these forty-four (44) cases, twenty-nine (29) were assessed as "Possible with limited information", and fifteen (15) were assessed as "Possible with confounders" based on WHO-UMC causality.

There were no fatal cases reported.

Conclusion

This cumulative review of available information on this topic found insufficient evidence for a new or emerging signal regarding NDPH and VAXZEVRIA. No changes to the CDS or RMP are recommended for this topic. The topic will not be discussed in the next future PBRERs, unless significant new safety information arises.

15.2.10 Myositis

Introduction

ASTRAZENECA received the following requests from PRAC in the Assessment Report (AR) for PBRER (Procedure no.: EMEA/H/C/PSUSA/00010912/202206 (European Pharmacovigilance Issues Tracking Tool (EPITT) no: 19882) and in the assessment report

EMA/PRAC/4898/2023 and requested evaluation of Myositis in the next PSUR (DLP 28 December 2022).

The MAH is requested to present:

- a cumulative review of cases of idiopathic inflammatory myopathies (IIM)/myositis from all sources inc*luding, but not limited to available data from clinical trials, scientific literature and post-marketing exposure. The search strategy should be conducted at the level of HLT "Muscle infections and inflammations" and PT's included Anti-melanoma differentiation-associated protein 5 antibody positive; Anti- Signal Recognition Particle (SRP) antibody positive; Necrotising myositis; Overlap syndrome*
- *a causality assessment of the cases*
- *an observed vs expected (O/E) analysis for all cases identified in EU and UK of myositis and related conditions with a risk window of 0 to 28 days and also including events with unknown TTO. For the calculations of the O/E analysis, the relevant and justifiable background incidence rate(s) should be used as well as exposure in EU/UK*
- *a discussion on the plausibility and biological mechanism(s) for a possible causal association between myositis and related conditions and vaccination with VAXZEVRIA*
- *a discussion on the need for updating product information and/or risk management plan, (RMP) and submit proposal as required*
- *The MAH should ensure that all identified literature cases have been submitted to EudraVigilance and efforts should be made to follow up on other spontaneous cases which are currently subject to limited information.*

AstraZeneca evaluation of this topic is presented below.

Disease Background

Autoimmune myositis is characterized by inflammatory and degenerative changes in the muscles (Polymyositis, necrotizing immune-mediated myopathy) or in the skin and muscles (Dermatomyositis). Manifestations include symmetric weakness, occasionally tenderness, and fibrous replacement of muscle, sometimes with atrophy, principally of the proximal limb girdle muscles. Treatment is with corticosteroids combined with immunosuppressants and/or IV immune globulin**.** Autoimmune myositis is more common in females than males by a 2:1 ratio. The incidence is 3 to 4 times higher in African American population than in Caucasians. These disorders may appear at any age but occur most commonly from age 40 to 60 or, in children, from age 5 to 15 (Nevares 2022).

Etiology of Autoimmune Myositis

The cause of autoimmune myositis seems to be an autoimmune reaction to muscle tissue in genetically susceptible individuals. Familial clustering occurs, and human leukocyte antigen (HLA) subtypes are associated with myositis. Possible inciting events include viral myositis and underlying cancer. The association of cancer with Dermatomyositis (less so with Polymyositis) suggests that a tumour may incite myositis as the result of an autoimmune reaction against a common antigen in muscle and tumour (Nevares 2022).

Drug induced muscle injury

Some of the drugs suspected to be myotoxic are Hydroxymethylglutaryl-Coenzyme A (HMG-CoA) reductase inhibitors (statins), fibrates, immunosuppressants (glucocorticoids, leflunomide, Tumor Necrosis Factor (TNF) inhibitors), antimalarials (Chloroquine, hydroxychloroquine, quinacrine etc.,), antiemetics (emetine, ipecac), antinucleotide analogues (Zidovudine, Clevudine) and colchicine. Myopathies induced by drugs result in necrosis, vacuolar changes, or mitochondrial dysfunction or disruption of myofilaments or myofibrillar proteins (Valiyil and Christopher-Stine 2010).

COVID-19 infection induced Myositis

COVID-19 infection has been reported to be associated with various skeletal muscle complications, ranging from asymptomatic increase of creatine kinase (CK) level in blood to myalgia, myositis, and rhabdomyolysis (Paliwal et al 2020) Several mechanisms have been hypothesized, which include direct viral invasion of the myocytes or hyperinflammation syndrome (Tan et al 2022 and Galluzzo et al 2022) however, evidence favours indirect muscle injury, based on an autopsy case-control study most patients who died of COVID-19 had myositis with little evidence of direct muscle infection (Ashman et al 2021) COVID-19 myositis could, therefore, be due to deposition of virus-antibody complexes on myocytes or expression of muscle antigen on cell membrane induced by the virus and damage by cytokine damage by cytokine storm (Saud et al 2021 and Tan et al 2022) speculated that, post-vaccination inflammatory myositis could possibly develop due to the same mechanisms. It is suggested that SARS-CoV-2 may be the first virus capable of infecting muscle fibres directly (Saud et al 2021).

Pathophysiology of Autoimmune Myositis

Pathologic changes include cellular damage and atrophy, with variable degrees of inflammation. Muscles in the hands, feet, and face are affected less than other skeletal muscles. Involvement of muscles in the pharynx and upper esophagus and occasionally the cardiac muscles can impair the functions of those organs. Inflammation may occur in joints and lungs, especially in patients with antisynthetase antibodies. Dermatomyositis is characterized by immune complex deposition in the vessels and is considered a complement-mediated vasculopathy. In contrast, Polymyositis (PM) is characterized by direct T cell–

mediated muscle injury and necrotizing immune-mediated myopathies are characterized by macrophage-predominant infiltrates and myophagocytosis (Nevares 2022) Yin et al 2016 were able to prove the importance of the NLRP3 inflammasome in the pathophysiology of Dermatomyositis. NLRP3 inflammasome activation has also been detected in myocarditis after mRNA vaccination. It is assumed by Holzer et al 2022 that similarly to SARS-CoV-2 infection, spike protein might trigger NLRP3 inflammasome activity, or the lipid nanoparticles used might stimulate the NLRP3 inflammasome. This might present another additional pathomechanism in the development of autoimmune diseases like dermatomyositis following mRNA vaccination.

Classification of Autoimmune Myositis

Autoimmune myositis can be classified into 4 groups, mainly based on histopathology and clinical presentation: Polymyositis, Dermatomyositis, necrotizing immune-mediated myopathies and inclusion body myositis (Nevares 2022)

Diagnosis of Autoimmune Myositis

Establishing the diagnosis of autoimmune myositis requires as many as possible of the following 5 criteria: proximal muscle weakness, characteristic rash, elevated serum muscle enzymes (if creatine kinase is not elevated, aminotransferases or aldolase, which are far less specific than CK), characteristic electromyographic or MRI muscle abnormalities, muscle biopsy changes (the definitive test) (Nevares 2022).

Treatment

The first line treatment is with high doses of glucocorticoids (prednisolone and methylprednisolone) and in addition immunosuppressants (eg., methotrexate, azathioprine, mycophenolate mofetil, rituximab (RTX), tacrolimus) and IV immune globulin (IVIG). The 'second-line' treatments, such as CYC, rituximab (RTX), IVIG and abatacept, for patients with persistent active disease despite glucocorticoid and conventional synthetic disease modifying antirheumatic drugs (csDMARD) therapy. Management of IIM should include a safe and appropriate exercise programme led and monitored by a specialist physiotherapist and/or a specialist occupational therapist to improve quality of life and function (Oldroyd et al 2022).

Prognosis for Autoimmune Myositis

Long remissions (even apparent recovery) occur in up to 50% of treated patients within 5 years, more often in children. Relapse, however, may still occur at any time. Overall, 5-year survival rate is 75% and is higher in children.

Death in adults is preceded by severe and progressive muscle weakness, dysphagia, undernutrition, aspiration pneumonia, or respiratory failure with superimposed pulmonary infection. The mortality rate in IIM cohort as determined in a retrospective evaluation of (1997-2011) Norwegian registry was 27% (Dobloug et al 2015). The cumulative 2-year survival rate across the IIM was 87% (86% in DM, 87% in PM and 87% in sporadic inclusion body myositis) compared to 96% for age- and gender-matched unexposed individuals.

Dermatomyositis and polymyositis have been linked to an increased cancer risk. Cancer, if present, generally determines the overall prognosis.

Pre-Clinical Data

There is no pre-clinical data on Myositis with VAXZEVRIA.

Clinical Study Data

A search was conducted in the ASTRAZENECA clinical database for AE reports of Myositis following the use of VAXZEVRIA reported from clinical studies (data cut-off of 31 December 2021 for the Oxford pooled studies [**COV001, COV002, COV003**, and **COV005**] and 11 March 2022 for United States (US) Study [**D8110C00001**]). The search utilized the following Medical Dictionary for Regulatory Activities (MedDRA version 23.1) following Preferred Terms (PTs): Dermatomyositis, Antisynthetase syndrome, Autoimmune myositis, Bacterial myositis, Eosinophilia myalgia syndrome, Focal myositis, Fungal myositis, Myositis, Idiopathic inflammatory myopathy, Immune-mediated myositis Inclusion body myositis, Infective myositis, Juvenile polymyositis, Lupus myositis Muscle abscess, Muscular sarcoidosis, Myositis-like syndrome, Orbital myositis Polymyositis, Psoas abscess, Pyomyositis, Sarcocystis infection, Trichiniasis Viral myositis, Anti-SRP antibody positive, Anti-melanoma differentiation-associated protein 5 antibody positive, Necrotising myositis and Overlap syndrome.

The search resulted in two AEs (PTs: Dermatomyositis and Psoas abscess).

- The first AE was reported for a participant in the Control arm of **COV003** (**participant ID** [redacted] and was not exposed to AZD1222 The report concerned a 28-year-old female patient of mixed race. No relevant medical history and concomitant medications were reported. The patient experienced a new onset of Dermatomyositis 327 days post Dose 1 and 292 post Dose 2 of the vaccine (during the treatment period of the study). The event was non-serious and of moderate severity. The event resolved after 9 days. The investigator considered the event unlikely related to the vaccine.
- The second AE (was reported for a participant in the AZD1222 arm of **D8110C00001** (**participant ID:** [redacted]. The report (**Case ID**: [redacted]) concerned a 49-year-old male participant of Caucasian ethnic origin. Relevant medical history included intestinal cramps (13 December 2020 to 15 December 2020), obesity (since

1999), tobacco smoking (since 1990), and concurrent colostomy. Concomitant medications included valsartan (for hypertension), Relpax (for migraine), ibuprofen (for intermittent headache and intestinal cramps) and flonase (for seasonal allergies). The patient experienced a new onset of psoas abscess 77 days post Dose 1 and 48 days post Dose 2 of the vaccine (during the treatment period of the study). The event was serious due to hospitalization and of severe intensity. The treatment for the event included surgical drainage. The event resolved on day 81 (duration 5 days). The investigator considered the event unlikely related to the vaccine.

AZ Comment: In the first AE with a TTO of 327 days the subject was not exposed to AZD1222. AZ concurs with investigator assessment of unlikely causal relationship with trial vaccine. Lack of information on medical history, concomitant medications, status prior to the diagnosis of dermatomyositis and details of diagnostic work-up preclude full medical assessment. In the second AE, there is limited information on diagnostic work, whether culture and sensitivity were performed on the pus and whether infectious origin was ruled out. The patient could be prone to infection from concurrent colostomy.

Global Patient Safety Database

A cumulative search through 28 December 2022 of the ASTRAZENECA Global Safety Database for Myositis with VAXZEVRIA was performed using MedDRA version 25.1. The search strategy considered 'Muscle infections and inflammations' HLT including following MedDRA PTs: Antisynthetase syndrome; Autoimmune myositis; Anti-melanoma differentiation-associated protein 5 antibody positive; Anti-SRP antibody positive Bacterial myositis; Dermatomyositis; Eosinophilia myalgia syndrome; Focal myositis; Fungal myositis; Idiopathic inflammatory myopathy; Immune-mediated myositis; Inclusion body myositis; Infective myositis; Juvenile polymyositis; Lupus myositis; Muscle abscess; Muscular sarcoidosis; Myositis; Myositis-like syndrome; Necrotising myositis; Orbital myositis; Overlap syndrome; Polymyositis; Psoas abscess; Pyomyositis; Sarcocystis infection; Trichiniasis; and Viral myositis.

The search retrieved a total of 274 events of Myositis in 267 case reports. Two cases (**Case IDs:** [redacted]) were excluded from the search results, the reasons highlighted as below:

- Case ID: [redacted] had similar information and were considered as potential duplicates.
- Case ID: [redacted] (PT: Overlap syndrome) had no information regarding Myositis associated events, the information was related to Lichen Planus and Discoid Lupus Erythematosus overlap Garg et al 2022 (B).

A total of 272 events for Myositis in 265 case reports were further considered for evaluation (Refer Appendix 14. Out of the 265 case reports, there were 85 (32.1%) from the United Kingdom, 42 (15.8%) from Germany, 27 (10.2%) from Brazil, 15 (5.7%) from Australia, 14

(5.3%) from Italy, 12 (4.5%) from France, 8 (3.0%) cases each from India and Sweden, 6 (2.3%) from Spain, 5 (1.9%) cases each from Austria and Netherlands, 4 (1.5%) cases each from Canada, Norway and Poland, 3 (1.1%) cases each from Belgium and Ireland, 2 (0.8%) cases each from Hungary, Mexico, Portugal, Romania and United States and 1 (0.4%) case each from Chile, Croatia, Denmark, Finland, Iceland, Luxembourg, Philippines, Slovakia, Slovenia and Taiwan.

The distribution of the 272 events of Myositis by PT is presented in Table 86 as below in descending order of frequency.

Table 86 Distribution of MedDRA PTs (n = 272) pertaining to Myositis with VAXZEVRIA Cumulatively through 28 December 2022

AE Preferred Term	Serious	Non-serious	Grand Total
Myositis	108	84	192
Dermatomyositis	27	3	30
Polymyositis	17	7	24
Autoimmune myositis	6	0	6
Muscle abscess	3	3	6
Antisynthetase syndrome	4	0	4
Immune-mediated myositis	4	0	4
Eosinophilia myalgia syndrome	0	1	1
Focal myositis	0	1	1
Infective myositis	1	0	1
Orbital myositis	1	0	1
Viral myositis	1	0	1
Necrotising myositis	1	0	1
Grand Total	**173**	**99**	**272**

MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term

The breakdown and overview of the 265 cases reporting 272 events of Myositis are presented in Table 87 as below.

Table 87 Overview of Myositis Events/Cases Cumulatively through 28 December 2022

Parameter	Break-down	Values (%)
Case count	Total	265
	Medically confirmed	108 (40.8%)
	Consumer report	157 (59.2%)

Table 87 Overview of Myositis Events/Cases Cumulatively through 28 December 2022

Parameter	Break-down				Values (%)
Case report source	Non-interventional / Post-market study				6 (2.3%)
	Spontaneous				46 (17.4%)
	Literature				25 (9.4%)
	Regulatory				188 (70.9%)
Sex[a]	Female N (%)				172 (66.4%)
	Male N (%)				87 (33.6%)
	Unknown				6
Age group [a]/Gender	Age Group	M	F	Unk	Total (%)
	18-49	24	75	1	100 (40.0%)
	50-59	13	42	1	56 (22.0%)
	60-69	28	33	1	62 (24.8%)
	70-79	14	12	0	26 (10.4%)
	≥80	1	4	1	6 (2.4 %)
	Unknown	7	6	2	15
	Median age (range)				53 years (19 to 86)
Event occurrence with dose[a]	Dose 1 (%)				201 (78.5%)
	Dose 2 (%)				54 (21.1%)
	Dose 3 (%)				1 (0.4%)
	Multiple Doses				0
	Dose unspecified				9
Case level- TTO (days)[b]	0 to 7				114 (54.8%)
	8 to 14				29 (13.9%)
	15-21				17 (8.2%)
	22-28				10 (4.8%)
	29-42				12 (5.8%)
	≥43				26 (12.5%)
	Unknown				57
	Median TTO (range)				6 days (0 to 335)
Event seriousness criteria (for serious cases)	Medically important				60 (34.7%)
	Disability				25 (14.5%)
	Hospitalization				65 (37.6%)
	Life-threatening				18 (10.4%)
	Death				5 (2.9%)

Table 87 Overview of Myositis Events/Cases Cumulatively through 28 December 2022

Parameter	Break-down	Values (%)
AE outcome	Recovered	34 (12.5%)
	Recovering	61 (22.4%)
	Recovered with sequelae	11 (4.0%)
	Not recovered	100 (36.8%)
	Fatal	5 (1.8%)
	Unknown	61 (22.4%)
Duration of recovered/recovered with sequelae events	Known duration (number of events)	20 (44.4%)
	Event recovered within 7 days (%)	6 (30.0%)
	Event recovered after 7 days (%)	14 (70.0%)
	Range (days)	1-180 days
	Mean (days)	51
	Unknown duration (number of events)	25 (55.6%)
Myositis events (New onset/Flare-up)[c]	New Onset	253 (95.5%)
	Flare-up	12 (4.5%)

[a] percentages, calculated based on known values

[b] TTO was reported for 208 case reports (total number of cases) used to calculate the percentage where multiple TTOs are present in a case, the most conservative TTO for the relevant event is chosen

Flare up was defined based on a reported medical history of myositis event; the remaining cases with no reported or missing medical history were considered new onset

AE Adverse Event; TTO, Time to Onset

Co-reported events with Myositis

Among the 265 cases, 256 (97%) cases were reported with other co-reported events. Most related events included myalgia (n=67), headache (n=45), fatigue (n=43), pyrexia (n=39), arthralgia (n=38), pain in extremity (n=29), pain (n=20), muscular weakness (n=18), asthenia and malaise (n=16, each), arthritis (n=11), muscle spasms (n=9), neck pain and hypoaesthesia (n=8), rhabdomyolysis, paraesthesia and musculoskeletal stiffness (n=7, each), tendonitis (n=5), muscle disorder (n=3) and movement disorder, mobility decreased and musculoskeletal pain (n=2, each). Of the 7 cases reporting rhabdomyolysis, one case was confounded by underlying medical condition of osteoarthritis, tendon disorder and type 2 Diabetes Mellitus and the remaining cases had limited information precluding medical assessment. The other respective related events were signs and symptoms.

Myositis Events with Fatal Outcome

Of the 265 case reports, 5 (1.9%) case reports were reported with a fatal outcome, of which 3 (60.0%) were medically confirmed and 2 (40.0%) were a consumer report. In 4 (80.0%) cases Myositis was reported after Dose 1 and in 1 (20.0%) case the event was reported after Dose 2. Out of 5 fatal case reports, the time to onset of myositis event in 2 cases (40.0%) were within the risk window of 0-28 days and in 3 cases (60.0%) were outside the risk window. Overall, the TTO of fatal events ranged from 12 to 63 days after receiving VAXZEVRIA. WHO-UMC causality criteria was assessed as 'Possible with confounders' for 2 (40.0%) case reports and 'Unlikely' for 3 (60.0%) case reports. Amongst the 5 case reports, 3 (60.0%) cases had risk factors for Myositis. The remaining 2 (40.0%) cases lacked sufficient case details such as medical history, concomitant medications, etiological and diagnostic work-up, autopsy details etc.

The summary of the fatal case reports is presented below in Table 88.

Table 88 Summary of Case Reports with Fatal Outcome for Myositis (N = 5) Cumulatively through 28 December 2022

Sr No.	Case ID / Country / Medically confirmed (Y/N) / Source	Age (Years) / Gender (M/F)	Medical History / Concomitant medications	TTO (days) from VAXZEVRIA[a] / Dose Information	Adverse Event PT's	Cause of Death PTs / Autopsy Performed (Yes / No / Unk) / Time to death from VAXZEVRIA [a]	WHO-UMC Causality Assessment
1	[redacted] / Brazil / NO / Spontaneous	44 / F	Nicotine dependence, Tobacco user / Not Reported	54 / Dose 1	Dermatomyositis	Dermatomyositis; Cardiac arrest / Unk / 127 days	Unlikely
AZ Comment: Patient was initially diagnosed with motor deficit syndrome about 54 days from first dose of vaccine which suggests unlikely causal association, subsequently Dermatomyositis was suspected. Patient was a smoker. Details of muscle biopsy or myositis specific antibodies were not provided. Patient had a cardiac arrest about 5 months from initial symptoms (loss of muscle strength, joint pain, and immobility) and died. Limited information on baseline health status, concomitant mediations and autopsy report among others preclude complete medical assessment of this case.							
2	[redacted] / Australia / YES / Literature (Nguyen et al 2022 [B])	76 / M	Hypertension, Diabetes Mellitus / Not Reported	12 / Dose 1	Autoimmune Hepatitis; Myositis; Renal failure; Hepatic failure	Autoimmune Hepatitis; Myositis; Renal failure; Hepatic failure / UNK / 35 days	Possible with Confounders
AZ Comment: Underlying diabetes mellitus and positive ANA (anti-nuclear antibody) can be considered as confounding factors to autoimmune hepatitis, which can further contribute to hepatic failure and myositis. Underlying hypertension and diabetes mellitus along with advanced age of patient may be considered as risk factors for renal failure. Limited information on baseline laboratory data including LFTs, baseline health status before vaccination, clinical course and treatment given, etiological and diagnostic workup prior to fatal outcome and autopsy report preclude complete medical assessment of this case.							

Table 88 Summary of Case Reports with Fatal Outcome for Myositis (N = 5) Cumulatively through 28 December 2022

Sr No.	Case ID / Country / Medically confirmed (Y/N) / Source	Age (Years) / Gender (M/F)	Medical History / Concomitant medications	TTO (days) from VAXZEVRIA[a] / Dose Information	Adverse Event PT's	Cause of Death PTs / Autopsy Performed (Yes / No / Unk) / Time to death from VAXZEVRIA [a]	WHO-UMC Causality Assessment
3	[redacted] / France / YES / Regulatory	64 / M	Hypertriglyceridemia, Thyroid cancer, Glaucoma, Cholecystectomy, Thyroidectomy / Levothyroxine, Fenofibrate, Bimatoprost / Timolol, Sotalol, Citicoline	14 / Dose 1	Myositis; Spontaneous haematoma	Myositis and Sepsis / No / 87 days	Possible with Confounders
AZ Comment: The onset of event after vaccination was reported as 14 days (diagnostic evidence was not provided). the patient died on day 87 after vaccination. Cause of death was reported as sepsis (no further details) and Myositis. Autopsy was not performed. This case is confounded by concomitant fenofibrate (no details on dates and duration) and history of thyroid cancer. Limited information on baseline labs, diagnostic work-up, details of sepsis and autopsy report preclude complete medical assessment.							

Table 88 Summary of Case Reports with Fatal Outcome for Myositis (N = 5) Cumulatively through 28 December 2022

Sr No.	Case ID / Country / Medically confirmed (Y/N) / Source	Age (Years) / Gender (M/F)	Medical History / Concomitant medications	TTO (days) from VAXZEVRIA[a] / Dose Information	Adverse Event PT's	Cause of Death PTs / Autopsy Performed (Yes / No / Unk) / Time to death from VAXZEVRIA [a]	WHO-UMC Causality Assessment
4	[redacted] / Brazil / NO / Spontaneous	65 / F	Not Reported / Not Reported	63 / Dose 1	Cardiac arrest; Dermatomyositis; Arthralgia; Muscular weakness; Immobile; Post-vaccination syndrome; Myositis; Incorrect route of product administration; Incorrect dose administered; Motor dysfunction; Dysphagia; Myalgia; Myopathy; Rash erythematous; Dyspnoea exertional; Asthenia; Eye swelling	Dermatomyositis and Cardiac arrest / Yes (result not reported) / 127 days	Unlikely
AZ Comment: This case information seems to be potential duplicate of case [redacted] However, considering the age and batch number difference both the cases were processed separately (unable to receive follow-up). Patient presented initial symptoms including muscular weakness and total immobility about 54 days from first dose of vaccine which suggests unlikely causal association. Dermatomyositis was suspected 63 days from first dose. Subsequently on an unknown date the patient experienced a cardiac arrest and died about 5 months from the initial symptoms. It was reported that autopsy was performed with a cause of death of cardiac arrest. It was unclear from the reported details if Dermatomyositis was a confirmed cause of death at autopsy. This case is poorly documented, missing important details for full medical assessment including concomitant medications, medical history, diagnostic details and full details of the autopsy report.							

Table 88 Summary of Case Reports with Fatal Outcome for Myositis (N = 5) Cumulatively through 28 December 2022

Sr No.	Case ID / Country / Medically confirmed (Y/N) / Source	Age (Years) / Gender (M/F)	Medical History / Concomitant medications	TTO (days) from VAXZEVRIA[a] / Dose Information	Adverse Event PT's	Cause of Death PTs / Autopsy Performed (Yes / No / Unk) / Time to death from VAXZEVRIA [a]	WHO-UMC Causality Assessment
5	[redacted] / United Kingdom /YES/Literature De Marco et al 2022	67 / M	Not Reported / Atorvastatin	42 days / Dose 2	Myositis	Myositis / No / Unk	Unlikely
AZ Comment: There is limited information on the clinical course, chronology of events, medical history and autopsy report in this patient which limits complete medical assessment. The time to onset of Myositis was reported as 6 weeks which suggests unlikely causal association. The case is further confounded by concomitant atorvastatin (no details on indication and duration). The additional reported symptoms of anuria (renal failure haemodialysis-dependant), respiratory arrest (dependent on intensive care support), suspected myocarditis and multiple supra-infections could be contributory to the fatal outcome.							

[a] shortest

Unk, Unknown; TTO, Time to onset; F, Female; M, Male; PT's, Preferred Term; LFTs, Liver function tests; AZ, ASTRAZENECA

Recurrence Case Reports

There were no case reports identified for Myositis recurrence/worsening after multiple doses of vaccination.

WHO-UMC Causality Assessment for Myositis Case Reports

The risk window for the Myositis topic was considered as 0-28 days (Stübgen 2014, Shinjo et al 2012) the WHO-UMC causality assessment performed for Myositis case reports is presented in Table 89 as below.

Table 89 Overview of WHO-UMC Causality Assessments for Myositis Case Reports with VAXZEVRIA Cumulatively through 28 December 2022

WHO-UMC Causality category	WHO-UMC Causality assessment scale (AZ adapted)	Number of Cases (Percentage)
Certain	Certain	0
Probable/Likely	Probable-Likely	0
Possible	Possible with risk factors/confounders[a]	32 (12.1%)
	Possible with limited information	138 (52.1%)
Unassessable/Unclassifiable	Unassessable/Unclassifiable with risk factors/confounders[a]	19 (7.2%)
	Unassessable/Unclassifiable with limited information	38 (14.3%)
Unlikely	Unlikely	38 (14.3%)
Conditional/Unclassified	Conditional/Unclassified	0
Total		**265**

[a] Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.

AZ, ASTRAZENECA; UMC Uppsala Monitoring Centre; WHO World Health Organization

Amongst 265 cases for Myositis, 67 (25.3%) were identified with relevant risk/confounding factors (Lundverg et al 2021, Miller et al 2018) resented in Table 90 as below. These are categorised as risk/confounding factors in descending order of frequency.

Table 90 Relevant Risk factors/Confounders identified for Myositis Case Reports Cumulatively through 28 December 2022

Relevant Risk factors/ Confounders	Count [a]
Chronic conditions (such as acute ulcerative colitis; post viral fatigue syndrome; pericarditis, interstitial lung disease; hyperthyroidism; influenza like illness; multiple sclerosis; thyroid disorder; immunodeficiency, myasthenia gravis; diabetes mellitus; carpal tunnel syndrome; myalgia; osteoarthritis; rheumatoid arthritis; chronic fatigue syndrome; HIV infection-since 2008; myelodysplastic syndrome; autoimmune thyroiditis; hepatitis B core antigen positive; systemic lupus erythematosus etc.)	39
Concomitant medications such as statins (atorvastatin, rosuvastatin, simvastatin) and fenofibrate	12

Table 90 Relevant Risk factors/Confounders identified for Myositis Case Reports Cumulatively through 28 December 2022

Relevant Risk factors/ Confounders	Count [a]
Previous history of myositis events (such as myositis, dermatomyositis, polymyositis)	10
Neoplasm (metastatic lung cancer, neoplasm malignant, chronic myeloid leukaemia, prostate cancer etc.)	7
Concurrent COVID-19 infection	5
Concurrent events (such as supraspinatus syndrome, influenza like illness, multiple sclerosis)	3

[a] Cases may contain more than 1 risk factor
COVID-19, Coronavirus Disease 2019

In the remaining 198 (74.7%) case reports, there was insufficient information with respect to either TTO, medical history/co-morbidities, concomitant medication details or clinical course for a comprehensive causal assessment.

Observed Versus Expected (O/E) Analyses

The observed versus expected (O/E) analyses were carried out using the background incidence rates (IR) from Svensson et al 2017. A subgroup analysis based on stratifications of age group, region (EU/EEA, UK and worldwide) and risk windows (7 days, 14 days, 28 days, and 30 days) was performed. As a conservative approach, all cases with time to onset within 0 to 7 days, 0-14 days, 0-28 days 0-30 days and all cases with unknown time to onset were included in the O/E analysis. The vaccine exposure by doses administered for O/E analysis within the above mentioned RW were considered from EU, UK where the relevant exposure data were available.

Table 91 Observed versus Expected Cumulative Analyses through DLP 28 December 2022 for reports of Myositis with Risk Windows of 7, 14, 28, 30 days including Cases with unknown TTO

Myositis- Age group / Region / RW	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Myositis - Overall global cases, (RW 7, RW 14, RW 28, RW 30)							
Overall global cases, RW 7	7	13	466115644	115	1161.32	0.1 (0.08 - 0.12)	Observed significantly < expected
Overall global cases, RW 14	14	13	466115644	142	2322.65	0.06 (0.05 - 0.07)	Observed significantly < expected
Overall global cases, RW 28	28	13	466115644	170	4645.3	0.04 (0.03 - 0.04)	Observed significantly < expected

Table 91 Observed versus Expected Cumulative Analyses through DLP 28 December 2022 for reports of Myositis with Risk Windows of 7, 14, 28, 30 days including Cases with unknown TTO

Myositis- Age group / Region / RW	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Overall global cases, RW 30	30	13	466115644	172	4977.11	0.03 (0.03 - 0.04)	Observed significantly < expected
Myositis - Overall global cases, (RW 7, RW 14, RW 28, RW 30 + Unk)							
Overall global cases, RW 7 + Unk	7	13	466115644	172	1161.32	0.15 (0.13 - 0.17)	Observed significantly < expected
Overall global cases, RW 14 + Unk	14	13	466115644	199	2322.65	0.09 (0.07 - 0.1)	Observed significantly < expected
Overall global cases, RW 28 + Unk	28	13	466115644	227	4645.3	0.05 (0.04 - 0.06)	Observed significantly < expected
Overall global cases, RW 30 + Unk	30	13	466115644	229	4977.11	0.05 (0.04 - 0.05)	Observed significantly < expected
Myositis - EU / UK / Brazil / Australia cases, (RW 7)							
18 to 49, EU/UK/BR/AU, RW 7	7	3.6	110094983	54	75.96	0.71 (0.53 - 0.93)	Observed significantly < expected
50 to 59, EU/UK/BR/AU, RW 7	7	15	58336094	20	167.7	0.12 (0.07 - 0.18)	Observed significantly < expected
60 to 69, EU/UK/BR/AU, RW 7	7	24	57960860	19	266.6	0.07 (0.04 - 0.11)	Observed significantly < expected
Over 70 years, EU/UK/BR/AU, RW 7	7	35	32376365	11	217.18	0.05 (0.03 - 0.09)	Observed significantly < expected
Myositis - EU / UK / Brazil / Australia cases, (RW 7 + Unk)							
18 to 49, EU/UK/BR/AU, RW 7 + Unk	7	3.6	110094983	70	75.96	0.92 (0.72 - 1.16)	Observed < expected
50 to 59, EU/UK/BR/AU, RW 7 + Unk	7	15	58336094	32	167.7	0.19 (0.13 - 0.27)	Observed significantly < expected
60 to 69, EU/UK/BR/AU, RW 7 + Unk	7	24	57960860	30	266.6	0.11 (0.08 - 0.16)	Observed significantly < expected

Table 91 Observed versus Expected Cumulative Analyses through DLP 28 December 2022 for reports of Myositis with Risk Windows of 7, 14, 28, 30 days including Cases with unknown TTO

Myositis- Age group / Region / RW	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Over 70 years, RW 7 + Unk	7	35	32376365	15	217.18	0.07 (0.04 - 0.11)	Observed significantly < expected
Myositis - EU / UK / Brazil / Australia cases, (RW 14)							
18 to 49, EU/UK/BR/AU, RW 14	14	3.6	110094983	57	151.92	0.38 (0.28 - 0.49)	Observed significantly < expected
50 to 59, EU/UK/BR/AU, RW 14	14	15	58336094	25	335.41	0.07 (0.05 - 0.11)	Observed significantly < expected
60 to 69, EU/UK/BR/AU, RW 14	14	24	57960860	29	533.2	0.05 (0.04 - 0.08)	Observed significantly < expected
Over 70 years, EU/UK/BR/AU, RW 14	14	35	32376365	18	434.35	0.04 (0.02 - 0.07)	Observed significantly < expected
Myositis - EU / UK / Brazil / Australia cases, (RW 14 + Unk)							
18 to 49, EU/UK/BR/AU, RW 14 + Unk	14	3.6	110094983	73	151.92	0.48 (0.38 - 0.6)	Observed significantly < expected
50 to 59, EU/UK/BR/AU, RW 14 + Unk	14	15	58336094	37	335.41	0.11 (0.08 - 0.15)	Observed significantly < expected
60 to 69, EU/UK/BR/AU, RW 14 + Unk	14	24	57960860	40	533.2	0.08 (0.05 - 0.1)	Observed significantly < expected
Over 70 years, RW 14 + Unk	14	35	32376365	22	434.35	0.05 (0.03 - 0.08)	Observed significantly < expected
Myositis - EU / UK / Brazil / Australia cases, (RW 28)							
18 to 49, EU/UK/BR/AU, RW 28	28	3.6	110094983	70	303.84	0.23 (0.18 - 0.29)	Observed significantly < expected
50 to 59, EU/UK/BR/AU, RW 28	28	15	58336094	32	670.82	0.05 (0.03 - 0.07)	Observed significantly < expected
60 to 69, EU/UK/BR/AU, RW 28	28	24	57960860	36	1066.41	0.03 (0.02 - 0.05)	Observed significantly < expected

Table 91 Observed versus Expected Cumulative Analyses through DLP 28 December 2022 for reports of Myositis with Risk Windows of 7, 14, 28, 30 days including Cases with unknown TTO

Myositis- Age group / Region / RW	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Over 70 years, EU/UK/BR/AU, RW 28	28	35	32376365	18	868.71	0.02 (0.01 - 0.03)	Observed significantly < expected
Myositis - EU / UK / Brazil / Australia cases, (RW 28 + Unk)							
18 to 49, EU/UK/BR/AU, RW 28 + Unk	28	3.6	110094983	86	303.84	0.28 (0.23 - 0.35)	Observed significantly < expected
50 to 59, EU/UK/BR/AU, RW 28 + Unk	28	15	58336094	44	670.82	0.07 (0.05 - 0.09)	Observed significantly < expected
60 to 69, EU/UK/BR/AU, RW 28 + Unk	28	24	57960860	47	1066.41	0.04 (0.03 - 0.06)	Observed significantly < expected
Over 70 years, EU/UK/BR/AU, RW 28 + Unk	28	35	32376365	22	868.71	0.03 (0.02 - 0.04)	Observed significantly < expected
Myositis - EU / UK / Brazil / Australia cases, (RW 30)							
18 to 49, EU/UK/BR/AU, RW 30	30	3.6	110094983	70	325.54	0.22 (0.17 - 0.27)	Observed significantly < expected
50 to 59, EU/UK/BR/AU, RW 30	30	15	58336094	32	718.73	0.04 (0.03 - 0.06)	Observed significantly < expected
60 to 69, EU/UK/BR/AU, RW 30	30	24	57960860	37	1142.58	0.03 (0.02 - 0.04)	Observed significantly < expected
Over 70 years, EU/UK/BR/AU, RW 30	30	35	32376365	18	930.76	0.02 (0.01 - 0.03)	Observed significantly < expected
Myositis - EU / UK / Brazil / Australia cases, (RW 30 + Unk)							
18 to 49, EU/UK/BR/AU, RW 30 + Unk	30	3.6	110094983	86	325.54	0.26 (0.21 - 0.33)	Observed significantly < expected
50 to 59, EU/UK/BR/AU, RW 30 + Unk	30	15	58336094	44	718.73	0.06 (0.04 - 0.08)	Observed significantly < expected
60 to 69, EU/UK/BR/AU, RW 30 + Unk	30	24	57960860	48	1142.58	0.04 (0.03 - 0.06)	Observed significantly < expected

Table 91 Observed versus Expected Cumulative Analyses through DLP 28 December 2022 for reports of Myositis with Risk Windows of 7, 14, 28, 30 days including Cases with unknown TTO

Myositis- Age group / Region / RW	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Over 70 years, EU/UK/BR/AU, RW 30 + Unk	30	35	32376365	22	930.76	0.02 (0.01 - 0.04)	Observed significantly < expected
Myositis - UK cases, (RW 7)							
18 to 29 UK, RW 7	7	3.6	1918869	2	1.32	1.52 (0.18 - 5.47)	Observed > expected
30 to 39 UK, RW 7	7	5.9	3308256	4	3.74	1.07 (0.29 - 2.74)	Observed > expected
40 to 49 UK, RW 7	7	7.8	8954709	7	13.39	0.52 (0.21 - 1.08)	Observed < expected
50 to 59, UK, RW 7	7	15	12455887	9	35.81	0.25 (0.11 - 0.48)	Observed significantly < expected
60 to 69, UK, RW 7	7	24	9718273	3	44.7	0.07 (0.01 - 0.2)	Observed significantly < expected
70 to 79 UK, RW 7	7	35	6613249	4	44.36	0.09 (0.02 - 0.23)	Observed significantly < expected
Over 80 UK, RW 7	7	13	2655389	2	6.62	0.3 (0.04 - 1.09)	Observed < expected
Myositis - UK cases, (RW 7 + Unk)							
18 to 29 UK, RW 7 + Unk	7	3.6	1918869	3	1.32	2.27 (0.47 - 6.64)	Observed > expected
30 to 39 UK, RW 7 + Unk	7	5.9	3308256	7	3.74	1.87 (0.75 - 3.86)	Observed > expected
40 to 49 UK, RW 7 + Unk	7	7.8	8954709	9	13.39	0.67 (0.31 - 1.28)	Observed < expected
50 to 59, UK, RW 7 + Unk	7	15	12455887	14	35.81	0.39 (0.21 - 0.66)	Observed significantly < expected
60 to 69, UK, RW 7 + Unk	7	24	9718273	7	44.7	0.16 (0.06 - 0.32)	Observed significantly < expected

Table 91 Observed versus Expected Cumulative Analyses through DLP 28 December 2022 for reports of Myositis with Risk Windows of 7, 14, 28, 30 days including Cases with unknown TTO

Myositis- Age group / Region / RW	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
70 to 79 UK, RW 7 + Unk	7	35	6613249	6	44.36	0.14 (0.05 - 0.29)	Observed significantly < expected
Over 80 UK, RW 7 , + Unk	7	13	2655389	2	6.62	0.3 (0.04 - 1.09)	Observed < expected
Myositis - UK cases, (RW 14)							
18 to 29 UK, RW 14	14	3.6	1918869	2	2.65	0.75 (0.09 - 2.73)	Observed < expected
30 to 39 UK, RW 14	14	5.9	3308256	4	7.48	0.53 (0.15 - 1.37)	Observed < expected
40 to 49 UK, RW 14	14	7.8	8954709	8	26.77	0.3 (0.13 - 0.59)	Observed significantly < expected
50 to 59, UK, RW 14	14	15	12455887	10	71.62	0.14 (0.07 - 0.26)	Observed significantly < expected
60 to 69, UK, RW 14	14	24	9718273	7	89.4	0.08 (0.03 - 0.16)	Observed significantly < expected
70 to 79 UK, RW 14	14	35	6613249	7	88.72	0.08 (0.03 - 0.16)	Observed significantly < expected
Over 80 UK, RW 14	14	13	2655389	2	13.23	0.15 (0.02 - 0.55)	Observed significantly < expected
Myositis - UK cases, (RW 14 + Unk)							
18 to 29 UK, RW 14 + Unk	14	3.6	1918869	3	2.65	1.13 (0.23 - 3.31)	Observed > expected
30 to 39 UK, RW 14 + Unk	14	5.9	3308256	7	7.48	0.94 (0.38 - 1.93)	Observed < expected
40 to 49 UK, RW 14 + Unk	14	7.8	8954709	10	26.77	0.37 (0.18 - 0.69)	Observed significantly < expected
50 to 59, UK, RW 14 + Unk	14	15	12455887	15	71.62	0.21 (0.12 - 0.35)	Observed significantly < expected

Table 91 Observed versus Expected Cumulative Analyses through DLP 28 December 2022 for reports of Myositis with Risk Windows of 7, 14, 28, 30 days including Cases with unknown TTO

Myositis- Age group / Region / RW	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
60 to 69, UK, RW 14 + Unk	14	24	9718273	11	89.4	0.12 (0.06 - 0.22)	Observed significantly < expected
70 to 79 UK, RW 14 + Unk	14	35	6613249	9	88.72	0.1 (0.05 - 0.19)	Observed significantly < expected
Over 80 UK, RW 14 + Unk	14	13	2655389	2	13.23	0.15 (0.02 - 0.55)	Observed significantly < expected
Myositis - UK cases, (RW28)							
18 to 29 UK, RW 28	28	3.6	1918869	2	5.3	0.38 (0.05 - 1.36)	Observed < expected
30 to 39 UK, RW 28	28	5.9	3308256	6	14.96	0.4 (0.15 - 0.87)	Observed significantly < expected
40 to 49 UK, RW 28	28	7.8	8954709	8	53.55	0.15 (0.06 - 0.29)	Observed significantly < expected
50 to 59, UK, RW 28	28	15	12455887	13	143.23	0.09 (0.05 - 0.16)	Observed significantly < expected
60 to 69, UK, RW 28	28	24	9718273	8	178.8	0.04 (0.02 - 0.09)	Observed significantly < expected
70 to 79 UK, RW 28	28	35	6613249	7	177.44	0.04 (0.02 - 0.08)	Observed significantly < expected
Over 80 UK, RW 28	28	13	2655389	2	26.46	0.08 (0.01 - 0.27)	Observed significantly < expected
Myositis - UK cases, (RW 28 + Unk)							
18 to 29 UK, RW 28 + Unk	28	3.6	1918869	3	5.3	0.57 (0.12 - 1.65)	Observed < expected
30 to 39 UK, RW 28 + Unk	28	5.9	3308256	9	14.96	0.6 (0.28 - 1.14)	Observed < expected
40 to 49 UK, RW 28 + Unk	28	7.8	8954709	10	53.55	0.19 (0.09 - 0.34)	Observed significantly < expected

Table 91 Observed versus Expected Cumulative Analyses through DLP 28 December 2022 for reports of Myositis with Risk Windows of 7, 14, 28, 30 days including Cases with unknown TTO

Myositis- Age group / Region / RW	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
50 to 59, UK, RW 28 + Unk	28	15	12455887	18	143.23	0.13 (0.07 - 0.2)	Observed significantly < expected
60 to 69, UK, RW 28 + Unk	28	24	9718273	12	178.8	0.07 (0.03 - 0.12)	Observed significantly < expected
70 to 79 UK, RW 28 + Unk	28	35	6613249	9	177.44	0.05 (0.02 - 0.1)	Observed significantly < expected
Over 80 UK, RW 28 + Unk	28	13	2655389	2	26.46	0.08 (0.01 - 0.27)	Observed significantly < expected
Myositis - UK cases, (RW 30)							
18 to 29 UK, RW 30	30	3.6	1918869	2	5.67	0.35 (0.04 - 1.27)	Observed < expected
30 to 39 UK, RW 30	30	5.9	3308256	6	16.03	0.37 (0.14 - 0.81)	Observed significantly < expected
40 to 49 UK, RW 30	30	7.8	8954709	8	57.37	0.14 (0.06 - 0.27)	Observed significantly < expected
50 to 59, UK, RW 30	30	15	12455887	13	153.46	0.08 (0.05 - 0.14)	Observed significantly < expected
60 to 69, UK, RW 30	30	24	9718273	8	191.58	0.04 (0.02 - 0.08)	Observed significantly < expected
70 to 79 UK, RW 30	30	35	6613249	7	190.12	0.04 (0.01 - 0.08)	Observed significantly < expected
Over 80 UK, RW 30	30	13	2655389	2	28.35	0.07 (0.01 - 0.25)	Observed significantly < expected
Myositis - UK cases, (RW 30 + Unk)							
18 to 29 UK, RW 30 + Unk	30	3.6	1918869	3	5.67	0.53 (0.11 - 1.55)	Observed < expected
30 to 39 UK, RW 30 + Unk	30	5.9	3308256	9	16.03	0.56 (0.26 - 1.07)	Observed < expected

Table 91 Observed versus Expected Cumulative Analyses through DLP 28 December 2022 for reports of Myositis with Risk Windows of 7, 14, 28, 30 days including Cases with unknown TTO

Myositis- Age group / Region / RW	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
40 to 49 UK, RW 30 + Unk	30	7.8	8954709	10	57.37	0.17 (0.08 - 0.32)	Observed significantly < expected
50 to 59, UK, RW 30 + Unk	30	15	12455887	18	153.46	0.12 (0.07 - 0.19)	Observed significantly < expected
60 to 69, UK, RW 30 + Unk	30	24	9718273	12	191.58	0.06 (0.03 - 0.11)	Observed significantly < expected
70 to 79 UK, RW 30 + Unk	30	35	6613249	9	190.12	0.05 (0.02 - 0.09)	Observed significantly < expected
Over 80 UK, RW 30 + Unk	30	13	2655389	2	28.35	0.07 (0.01 - 0.25)	Observed significantly < expected
Myositis - EU-EEA cases, (RW 7)							
18 to 79, EU-EEA, RW 7	7	13	46978064	52	117.05	0.44 (0.33 - 0.58)	Observed significantly < expected
Over 80, EU-EEA, RW 7	7	13	1165347	0	2.9	0 (0 - 1.27)	Observed < expected
Myositis - EU-EEA cases, (RW 7 + Unk)							
18 to 79, EU-EEA, RW 7 + Unk	7	13	46978064	65	117.05	0.56 (0.43 - 0.71)	Observed significantly < expected
Over 80, EU-EEA, RW 7 + Unk	7	13	1165347	0	2.9	0 (0 - 1.27)	Observed < expected
Myositis - EU-EEA cases, (RW 14)							
18 to 79, EU-EEA, RW 14	14	13	46978064	66	234.09	0.28 (0.22 - 0.36)	Observed significantly < expected
Over 80, EU-EEA, RW 14	14	13	1165347	0	5.81	0 (0 - 0.63)	Observed significantly < expected
Myositis - EU-EEA cases, (RW 14 + Unk)							
18 to 79, EU-EEA, RW 14 + Unk	14	13	46978064	79	234.09	0.34 (0.27 - 0.42)	Observed significantly < expected
Over 80, EU-EEA, RW 14 + Unk	14	13	1165347	0	5.81	0 (0 - 0.63)	Observed significantly < expected

Table 91 Observed versus Expected Cumulative Analyses through DLP 28 December 2022 for reports of Myositis with Risk Windows of 7, 14, 28, 30 days including Cases with unknown TTO

Myositis- Age group / Region / RW	Risk window	BG rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Myositis - EU-EEA cases, (RW 28)							
18 to 79, EU-EEA, RW 28	28	13	46978064	87	468.18	0.19 (0.15 - 0.23)	Observed significantly < expected
Over 80, EU-EEA, RW 28	28	13	1165347	0	11.61	0 (0 - 0.32)	Observed significantly < expected
Myositis - EU-EEA cases, (RW 28 + Unk)							
18 to 79, EU-EEA, RW 28 + Unk	28	13	46978064	100	468.18	0.21 (0.17 - 0.26)	Observed significantly < expected
Over 80, EU-EEA, RW 28 + Unk	28	13	1165347	0	11.61	0 (0 - 0.32)	Observed significantly < expected
Myositis - EU-EEA cases, (RW 30)							
18 to 79, EU-EEA, RW 30	30	13	46978064	88	501.62	0.18 (0.14 - 0.22)	Observed significantly < expected
Over 80, EU-EEA, RW 30	30	13	1165347	0	12.44	0 (0 - 0.3)	Observed significantly < expected
Myositis - EU-EEA cases, (RW 30 + Unk)							
18 to 79, EU-EEA, RW 30 + Unk	30	13	46978064	101	501.62	0.2 (0.16 - 0.24)	Observed significantly < expected
Over 80, EU-EEA, RW 30 + Unk	30	13	1165347	0	12.44	0 (0 - 0.3)	Observed significantly < expected

CI, Confidence Interval; O/E, Observed versus Expected; TTO, Time to Onset; Unk, Unknown; RW, Risk Window; EU, European Union; EEA, European Economic Area; European Economic Area; UK, United Kingdom; BR, Brazil; AU, Australia

Results

Overall, the observed cases were significantly less than expected. The subgroup-analysis of the stratifications also provided a similar O/E trend to the overall result, and no statistically significant increase in observed cases to expected cases was seen. Observed cases were significantly less than the expected in the stratified risk windows of 7 days, 14 days, 28 days and including unknown TTO. In the sub-group analysis stratified by country of UK, a numerical increase was observed in the age group 18-29 (7 days including unknown TTO),

30-39 (7 days including unknown TTO) and 18-29 (14 days + Unknown TTO) for UK region. Six cases were reported with the Myositis onset within 0 to 2 days of VAXZEVRIA vaccination. A latency of Myositis within 0 to 2 days of immunization is considered too short (Liozon et al 2021) and cases less than 2 days from vaccination would be questionable in any causative association and may be possibly indicative of pre-existing conditions. In the article used for expected rates, Svensson et al 2017 excluded the cases that dispensed immunosuppressive medications >6 or >12 months prior to the index date or were identified through contributory diagnoses. Moreover, the background incidence rate of IIM as provided by Meyer et al 2014 based on a systematic literature review and meta-analysis in UK is higher by 9.9 per 1,000,000 per year. If the 6 cases reports are excluded, the observed cases are less than expected. Also, there is a possibility of reporting bias for increased reporting of cases with a shorter risk window for the passive event reporting of rare diseases.

The O/E analyses provided is based on the most recent and available data, but there is a level of assumption made and any change in the data would impact the results. The following are some of the limitations/assumptions of the data used:

- The background incidence rate used for the calculation is the same as the population vaccinated: The identification of incidence rates can vary depending on the source of the data.
  - Most of the observed events are spontaneously reported: Spontaneously reported events may only represent a fraction of the events that have actually occurred. Both under-reporting for certain events, and conversely, over-reporting for certain events could have played a role.
  - The risk period reflects the period of time an event would occur post-vaccination: Over-estimating the risk window would increase the "Person-Years at Risk" period and include events that are outside the actual period of time a true event would occur. Under-estimating the risk window will result in reduced sensitivity making it difficult to reach statistical significance.
  - The O/E analyses does not account for confounding/risk factors which might be present in the cases. Also, when stratified by age/gender, there are small numbers of cases in each stratification, which should be considered when interpreting the significance of the results.

Quantitative Data Review

ASTRAZENECA retrieved the data from EVDAS on 16 January 2023 (DLP: 31 December 2022). The ROR is calculated based on the lower bound of the 95% confidence interval of the ROR for the concerned drug event combination (DEC), using all other DECs available in the database as reference. EudraVigilance criteria for signals of disproportionality are ROR (-) > 1 and the number of cases ≥ 3 (if on additional monitoring list), otherwise n ≥ 5 and event is an important medical event.

On review of the data, no signal of disproportionate reporting in EudraVigilance was observed for PT of 'Myositis' [ROR (-) All 0.43, 159 Cases] or any other related term Table 92.

Table 92 EVDAS scores for VAXZEVRIA

Preferred Term	EVDAS Tot EVPM	EVDAS ROR (-) All
Myositis	159	0.43
Autoimmune myositis	7	0.38
Polymyositis	23	0.26
Dermatomyositis	31	0.25
Antisynthetase syndrome	4	0.23
Muscle abscess	4	0.08
Immune-mediated myositis	4	0.03

EVDAS, EudraVigilance Data Analysis System; EVPM, EudraVigilance Post-Authorization Module: ROR, Reporting Odds Ratio.

There was no disproportionate reporting of cases with myositis.

Literature

A search of medical databases (including Embase and Insight Meme database) up to 28 December 2022 was conducted to obtain information on literature articles for Myositis reported in patients receiving VAXZEVRIA and other COVID-19 vaccines.

Search strategy: Using the key terms VAXZEVRIA and HLT "Muscle infections and inflammations" with additional PTs "anti-SRP antibody positive, anti-melanoma differentiation-associated protein 5 antibody positive, necrotising myositis and overlap syndrome".

The search retrieved 120 articles related to Myositis in relation to COVID-19 vaccines. Of the 120 articles, 111 articles were excluded due to the following reasons:

- 33 of the articles did not describe Myositis in connection with COVID-19 vaccines
- 2 of the articles were not related to Myositis
- 74 articles described Myositis-related events with other COVID-19 vaccines
- 2 were duplicate articles.

The remaining 9 articles pertaining to the VAXZEVRIA vaccine covering 25 case reports have already been described as case reports within the Global Safety Database Section (Case IDs: [redacted]

[redacted]

[redacted]

Mechanisms

Out of the above 120 articles, different mechanisms were hypothesised in 16 articles and enumerated as below:

Note: *More than one mechanism of action may be proposed by the author in the same article.*

Molecular mimicry

Vaccine-induced autoimmunity may be due to molecular mimicry between host cell and antigen or to a direct response to vaccine adjuvants (Gonzalez et al 2022, Chaima et al 2022, Jack et al 2022, Ding and Ge 2022 and Chen Y et al 2022).

Bystander activation with epitope spreading

COVID-19 vaccines have been shown to have a high capability to elicit critical immune regulators like cytotoxic CD4+, CD8+ T cells and memory cell (Chan et al 2022 and Barisic et al 2021) severe myositis is associated with haplotypes HLA-B∗35 and DRB1∗15. Based on Punzi et al 2022 hypothesis, the binding sites HLA-B∗35 and DRB1∗15 is linked to high-affinity interactions to S-protein T-cell epitope that triggers immunogenic responses to the S protein of SARS-CoV-2.

Cross reactivity

Bose et al 2022 and Wang et al 2022 [B] suspected that autoimmunity with vaccines can be attributed to the cross-reactivity between antigens or to the effect of adjuvants and may be related to specific HLA phenotypes, that development autoantibodies, which evolve into a rheumatological disorder.

Genetic susceptibility

Wang et al 2022 [B] suspected the viral RNA helicase encoded by the melanoma differentiation–associated gene 5 triggers the innate immune system Gonzalez et al 2022 and Barisic et al 2021, hypothesizes, upregulation of immunological pathways leading to immune-mediated diseases in genetically predisposed individual who have impaired clearance of nucleic acids and also abnormalities in Toll-like receptors (eg, TLR3 and TLR4).

Direct viral invasion of the myocytes or hyperinflammation syndrome Saud et al 2021 and Jacobs et al 2022 suggested T-cell clonal expansion and production of proinflammatory cytokines leading to muscle damage after vaccination. SARS-CoV-2 may bind and activate TLR4 to increase ACE2 expression facilitating entry and causing hyperinflammation.

Deposition of virus-antibody complexes on myocytes

Tan et al 2022 and Bose et al 2022, suspected the occurrence of COVID-19 myositis due to deposition of virus-antibody complexes on myocytes or expression of muscle antigen on cell membrane induced by the virus and damaged by cytokine storm.

Direct myocyte injury following internalisation using ACE-2 receptor

Direct entry of vaccine through ACE-2 receptor on the muscle cells can lead to COVID-19-induced myositis by triggering autoinflammation or innate or adaptive immunity (Saud et al 2021, Chan et al 2022 and Gonzalez et al 2022)

Damage by cytokine storm

Cytokine storm is seen in COVID-19 infection and the increased levels of cutaneous T cell attracting Chemokine (CTACK), Interferons (IFN)-gamma, IL-8, monocyte chemoattractant protein-3 (MCP-3), and stem cell growth factor beta (SCGF-beta) were observed in MDA5-DM RP-ILD (Saud et al 2021, Tan et al 2022)

The immunological mechanism proposed by authors for COVID-19 vaccination is similar to COVID-19 induced myositis.

Statin-induced Necrotizing Autoimmune Myopathy (SNAM)

Statin-induced Necrotizing Autoimmune Myopathy (SNAM) is a rare manifestation of autoimmune myositis. In the anti-HMG-CoA reductase subtype, the immune system is sensitized to HMG-CoA reductase resulting in immune-mediate cellular injury. The duration of exposure to statins prior to development of SNAM varies from 2 months to 10 years, with an average of 3 years. In the article, Verma et al 2022 the patient was on statin therapy for 15 years without issue and subsequently developed SNAM after receiving a COVID-19 booster.

Literature overview

On review of the cumulative literature search through 28 December 2022, no new safety concerns regarding Myositis and association with VAXZEVRIA was identified. Upon review of relevant articles with possible mechanisms/pathogenesis no co-relation between vaccine and Myositis can be concluded. Most of the articles highlighted the mechanism similar to COVID-19 induced myositis and hence, further evaluation by large epidemiological studies considering pre- and post-COVID-19 vaccination data is needed. The case studies reporting use of VAXZEVRIA are databased and are submitted to EudraVigilance by AstraZeneca as per the reporting guidelines.

Summary

In the assessment report received from the PRAC for the VAXZEVRIA PBRER, the PRAC requested a cumulative review of all cases of idiopathic inflammatory myopathies (IIM)/myositis from all sources. Cumulatively, a total of 265 Myositis cases concerning 272 events were reported globally and included in ASTRAZENECA's Global Safety

Database. Cases were assessed by age, sex, type of event and outcome. A female (66.4%) prevalence versus male (33.6%) was expressed. The median age was 53 years. The majority (78.5%) of events were reported after Dose 1. There were no case reports of recurrence/worsening of Myositis after a subsequent dose of vaccination. Amongst 272 Myositis events, 173 (65.3%) were serious, 5 (1.8%) resulted in death and 45 (15.5%) events had a favourable outcome (either 'recovered' or 'recovered with sequelae). Event duration was reported for 20 (44.4%) cases of which majority 14 (70.0%) were resolved after 7 days. Of 265 case reports, 253 (95.5%) cases had a new onset of Myositis as compared to 12 (4.5%) cases which had Myositis flare-up. The risk window for the Myositis topic was considered as 0-28 days. The time to onset (TTO) was available in 208 (78.5%) case reports and ranged from 0 days to 335 days (median: 6 days) of which 170 (81.7%) case reports were within TTO range of 0-28 days. Amongst 265 cases, no cases met the WHO-UMC causality criteria for 'Certain' or 'Probable (Likely)'. The majority 170 (64.2%) of cases were assessed as WHO-UMC causality criteria of 'Possible' of which 32 (18.8%) cases were identified with relevant risk/confounding factors and 138 (81.2%) cases had limited information on medical history, concomitant medications, etiological and diagnostic work-up. Amongst 5 fatal cases, 2 cases were within the risk window (0-28 days) for which WHO-UMC causality criteria was assessed as 'Possible with confounders' and 3 cases were outside the risk window (range: 42 days to 63 days) with WHO-UMC causality assessed as 'Unlikely'. None of the fatal cases reported autopsy results. The O/E analysis results for Myositis showed observed cases to be significantly less than expected for all age, global and EU/UK reports.

A review of the literature suggests various hypothesized mechanisms for development of Myositis in association with COVID-19 vaccines.

Conclusion

Based on the review of the cumulative data, AstraZeneca considers that there is insufficient evidence to suggest a causal association between myositis and VAXZEVRIA . No changes to the CDS or RMP are recommended for Myositis and the topic will continue to be monitored as part of ASTRAZENECA's ongoing safety surveillance activities for VAXZEVRIA.

15.2.11 Corneal graft rejections

Background

Signal of corneal graft rejection for COVID-19 Vaccine (ChAdOx1-S [recombinant]) - VAXZEVRIA (EPITT ref. No. 19791) was identified by PRAC in March 2022. AstraZeneca submitted the cumulative assessment of corneal graft rejection in association with VAXZEVRIA on 27 June 2022, and concluded that based on the available data from clinical, post-marketing, literature, and O/E analysis, currently there is insufficient evidence to suggest a causal association of corneal graft rejection with the use of VAXZEVRIA. Therefore, no changes to the European Union Summary of Product Characteristics or Risk Management Plan are warranted. On 02 September 2022, AstraZeneca received the PRAC recommendation (EMEA/H/C/PSUSA/189794/2022) and PRAC agreed with AstraZeneca's conclusion and

requested to discuss any new data, including data from the literature on Corneal graft rejection in the next PBRER.

Global Patient Safety Database

An interval search (01 June 2022 – 28 December 2022) of the AstraZeneca Global Safety Database for corneal graft rejection with VAXZEVRIA was performed using MedDRA version 25.1. The search strategy included the following preferred terms: Corneal graft failure, Corneal graft rejection, Ocular surface, Stem Cell Transplant Rejection, Transplant failure, and Transplant rejection. The search retrieved no new cases of corneal graft rejection reported to the AstraZeneca Global Patient Safety Database during the reporting period.

In the previous assessment presented to the PRAC response dated 29 June 2022, cumulatively (until 01 June 2022), there were 19 case reports of Corneal graft rejection reported to the AstraZeneca Global Patient Safety Database. There were 5 cases with follow up information during the interval search (01 June 2022 – 28 December 2022) with updates to demographic details (in one case the country of report updated to Northern Ireland) and reporter identification information added in all follow-up cases.

Literature

A literature search of the databases in Embase, InsightMeme and PubMed was conducted for relevant articles on corneal graft rejection in association with VAXZEVRIA from 01 June 2022 (DLP for the last analysis) to 28 December 2022 and no new relevant literature articles were retrieved.

The following combination of search terms were utilized:

'azd1222', 'azd-1222', 'VAXZEVRIA', 'covid-19 vaccine astrazeneca', 'chadox1 ncov 19', and 'covishield', oxford-astrazeneca covid-19 vaccine, chadox1 ncov-19 vaccine, and 'covid19 vaccine' (in general), 'comirnaty', 'tozinameran', 'bnt162B2', 'pfizer biontech COVID-19 vaccine', 'sputnik v', 'ad26.cov2', 'mrna 1273', 'moderna covid 19 vaccine', 'mrna-1273', 'nvx-cov2373 vaccine', 'sars-cov-2 vaccine', 'covid-19 vaccine', '2019 novel coronavirus vaccine', '2019-cov vaccine', and 'coronavirus 2019 vaccine', and 'Vaccine' (in general).

In addition, the following key words were utilized in conjunction with the search terms above:

'corneal graft failure', corneal graft rejection', 'ocular surface stem cell transplant rejection', 'transplant failure', 'transplant rejection', graft failure, graft rejection, and 'cornea transplantation'.

Cumulatively (until 01 June 2022), there were 7 literature articles (Balidis et al 2021, Parmar et al 2021, Rajagopal and Priyanka 2022, Ravichandran and Natarajan 2021, Molero-Senosiain et al 2022, Ann John et al 2022, Nahata et al 2022) of corneal graft rejection relevant to the safety topic and were discussed in the previous PRAC response, dated

29 June 2022. The review of the literature showed no safety concerns regarding corneal graft rejection with VAXZEVRIA.

Conclusion

Based on the review of the updated cumulative data, AstraZeneca remains in its position that there is insufficient evidence to suggest a causal association between corneal graft rejection and VAXZEVRIA. It is AstraZeneca's opinion that no changes to the CDS or RMP are warranted at this time. The topic will continue to be monitored as part of AstraZeneca's ongoing surveillance activities. AstraZeneca will not discuss the topic in future PBRERs, unless significant new safety information arises.

15.2.12 Histiocytic necrotizing lymphandenitis (HNL)

Background

On 01 September 2022, AstraZeneca received a request from PRAC to submit cumulative review of histiocytic necrotizing lymphadenitis associated with VAXZEVRIA in the next PSUR (DLP 28 December 2022). This signal was initially identified for Tozinameran (COVID-19 mRNA vaccine) – Comirnaty. As it is believed that the signal may also be relevant for VAXZEVRIA, PRAC has agreed that AstraZeneca should submit within the next PSUR (DLP 28 December 2022) a cumulative review of all cases concerning VAXZEVRIA associated with histiocytic necrotizing lymphadenitis from all sources, including any relevant articles from literature and to discuss probable mechanism(s) of action for the occurrence of vaccine-associated histiocytic necrotizing lymphadenitis following administration of VAXZEVRIA. The PRAC also requested that the MAH to discuss the need for any potential amendment to the product information and/or the risk management plan and make accordingly a proposal for changes to the relevant sections within this discussion.

Diagnostic criteria

Definitive diagnosis of histiocytic necrotizing lymphadenitis is made by histopathology of the Lymph node biopsy/excision.

3 stages are described based on histology (Kuo TT et al 1995, Kuo TT et al 2004):

- Proliferative: proliferation of plasmacytoid dendritic cells, immunoblasts and histiocytes
- Necrotizing: areas of necrosis with karyorrhectic debris
- Xanthomatous: foamy histiocytes predominate; may represent histologic variant

Global Patient Safety Database

A cumulative search until 28 December 2022 of the AstraZeneca Global Safety Database for Histiocytic necrotizing lymphadenitis (HNL) with VAXZEVRIA was performed using MedDRA version 25.1. The search strategy included the MedDRA HLT: Lymphoproliferative disorders NEC (excl. leukaemias and lymphomas) including the PTs Castleman's disease, Epstein Barr virus positive mucocutaneous ulcer, Epstein-Barr virus

associated lymphoproliferative disorder, Histiocytic necrotizing lymphadenitis, Lymphoproliferative disorder, Lymphoproliferative disorder in remission, Post-transplant lymphoproliferative disorder, and X-linked lymphoproliferative syndrome.

The search retrieved a total of 10 adverse events of HNL in 10 case reports. These cases were reported from the following countries; UK 5 (50.0%) case reports and 1 (10.0%) each in Australia, Botswana, Panama, Spain and Taiwan .

The distribution of these 10 events are presented in Table 93 below in descending order of frequency:

Table 93 Distribution of MedDRA PTs (n=10) pertaining to HNL with VAXZEVRIA received cumulatively through DLP

MedDRA PT	Serious	Non-serious	Grand Total
Histiocytic necrotising lymphadenitis	1	2	3
Lymphoproliferative disorder	2	1	3
Epstein Barr virus positive mucocutaneous ulcer	1	1	2
Lymphoproliferative disorder in remission	1	0	1
Post transplant lymphoproliferative disorder	1	0	1
Grand total	**6**	**4**	**10**

HNL Histiocytic necrotizing lymphadenitis; MedDRA. Medical Dictionary for Regulatory Activities; PT Preferred term

Upon review of these 10 case reports, 3 reports with PT of HNL were considered relevant for discussion and these 3 reports are included in the Table 94 below. The remaining 7 cases reported were not diagnosed as HNL which is the PT of focus for this evaluation. Also, there was no information reported in these cases that were suggestive of HNL

Table 94 Overview of HNL reports

Case ID / Country / Medically confirmed (Y/N) / Source	Age (Years) / Gender (M/F)	Medical History / Concomitant medications	Time to Onset (days) from AZ vaccine* / Dose Information	Histiocytic necrotising lymphadenitis PT	Other reported conditions	WHO-UMC Causality Assessment	Additional Comment
[redacted] [redacted]/N/Spontaneous	41/M	Not Reported/Ramipril, Aspirin, Ticagrelor, Rosuvastatine	6/Dose 1 & Dose 2	Histiocytic necrotising lymphadenitis	Not Reported	Possible with limited information	Although hospitalization was mentioned, further information on the course of event or corrective treatment is not available. No histopathology and information regarding patient's immune state prior to exposure to VAXZEVRIA was reported.
[redacted] [redacted]/N/Regulatory	44/F	Not Reported/Not Reported	19/Dose Unknown	Histiocytic necrotising lymphadenitis	Not Reported	Possible with limited information	Medical history and concomitant medications information were not reported. Information regarding alternative causality work up was not provided - the histopathology result provided could also be indicative of autoimmune disease eg SLE. The histopathology result falls under Proliferative stage of the disease, however immunoblasts were absent.

Table 94 Overview of HNL reports

Case ID / Country / Medically confirmed (Y/N) / Source	Age (Years) / Gender (M/F)	Medical History / Concomitant medications	Time to Onset (days) from AZ vaccine* / Dose Information	Histiocytic necrotising lymphadenitis PT	Other reported conditions	WHO-UMC Causality Assessment	Additional Comment
[redacted] Y/Literature	30/F	Not Reported/Not Reported	12/Dose 1 & Dose 2	Histiocytic necrotising lymphadenitis	Not Reported	Possible with limited information	Medical history and concomitant medications were not reported, information regarding alternative causality workups was not provided. However, the histopathology result provided could also indicate SLE and considering the fact that the patient is a female and in her early 30's a proper workup was not done.

AZ AstraZeneca; F female; HNL Histiocytic necrotizing lymphadenitis; M Male; PT Preferred term; SLE systemic lupus erythematosus; UMC Uppsala Monitoring Centre; UK United Kingdom; WHO World Health Organisation.

The events most commonly co-reported along with HNL were Thrombocytopenia (3), Asthenia, Malaise, Myalgia, and Transaminases increased (2 each).

WHO -UMC causality Assessment

WHO-UMC causality assessment was performed for all cases.

Table 95 Overview of WHO-UMC Causality Assessments / for case reports of HNL with VAXZEVRIA reported cumulatively up to 28 December 2022

WHO-UMC causality	Grand Total
Certain	0
Probable/Likely	0
Possible with risk factors/confounders	4
Possible with limited information	4
Unassessable/Unclassifiable with limited information	2
Unlikely	0
Conditional /Unclassified	0
Total	**10**

HNL Histiocytic necrotizing lymphadenitis; WHO World Health Organisation; UMC Uppsala Monitoring Centre

Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, or where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.

Amongst 10 cases of HNL, 4 (40%) were considered as Possible, 4 (40%) were identified with relevant risk/confounding factors and 2 (20%) were unassessable due to limited information. The relevant risk/confounder includes a previous history of a heart transplant, use of tacrolimus and mycophenolate, concurrent Systemic Lupus Erythematosus (SLE), Chronic Lymphocytic Leukaemia (CLL), and elderly patient.

Literature

A cumulative literature search of the databases in Embase, InsightMeme and PubMed was conducted for relevant articles on HNL in association with VAXZEVRIA.

The search identified 1 article for VAXZEVRIA and HNL. The article (Kirsebom et al 2022) described the condition of contralateral supraclavicular lymphadenopathy, did not fulfil the diagnostic criteria for HNL, and was not relevant to the review of this safety topic.

Mechanism of action articles review and summary cumulatively up to 28 December 2022

A search for other Covid-19 vaccines and HNL identified 8 articles. Two of the articles hypothesized the same mechanism of action (regarding genetic components) with regards to Covid-19 vaccines to cause HNL. The remaining 6 articles did not identify any new relevant safety information with regards to HNL.

Genetic predisposition (Eg, HLA-DPA1 and HLA-DPB1): It has been suggested that patients with genetic components such as HLA-DPA1 and HLA-DPB1 are usually predisposed to develop mainly T cells, especially cytotoxic T cells as immune responses. This may contribute to development of HNL in these patient when exposed to mRNA vaccine (unspecified protein) which induces a CD8+ T cell-related immune response in the draining of localized lymph nodes Kashiwada T et al 2022This hypothesized exuberant T cell-mediated immune responses was also referenced by Soub HA et al 2021, in people genetically susceptible to various nonspecific stimuli. This is suggested to be due to predisposition some HLA class II genes that are more frequently seen in Kikuchi-Fujimoto Disease (KFD) patients.

AZ comment: The mechanism of action for Covid-19 vaccines to cause HNL remains speculative and inconclusive.

Summary

Cumulatively, a total of 10 reports of HNL with the use of VAXZEVRIA have been received. Only 3 reports with PT of HNL were considered relevant for discussion, the other had AEs that are not consistent with HNL. 2 of the 3 cases were reported as serious and none had a seriousness criterion of Fatal or Life-threatening. Reported age was 30, 41 and 44 respectively.

2 of the events occurred after first dose and in 1 cases dose was unknown.

1 event reported outcome recovered and the event duration was reported as 54 days.

1 of the 3 cases was medically confirmed.

None of the cases met WHO-UMC causality criteria for Certain or Probable/Likely. Four were (40%) considered as Possible, 4 (40%) were identified with relevant risk/confounding factors and 2 (20%) were un-assessable due to limited information. Conclusion

This updated cumulative review found insufficient evidence for a new or emerging signal regarding Histiocytic Necrotizing lymphadenitis and VAXZEVRIA. No changes to the CDS or RMP are recommended, and the topic will not be discussed in future PBRERs, unless significant new safety information arises.

15.2.13 TGA (Therapeutic Goods Administration) request on Post-marketing Exposure Data

AstraZeneca received the following request from TGA upon review of the 6 monthly PSUR for VAXZEVRIA, covering the period of 29 December 2021 to 28 June 2022*:*

"The exposure data in this PSUR includes negative values which are derived by subtracting the previous report's cumulative value from the current cumulative value. It is difficult to interpret interval data when presented in this way. To assist with review, the sponsor should present interval data in a way that more accurately represents actual usage in future reports."

AstraZeneca Response:

Please see section 5.2.1.2.

16 SIGNAL AND RISK EVALUATION

16.1 Summary of safety concerns

At the beginning of the reporting period, the VAXZEVRIA safety specification (presented in the global AstraZeneca Core Risk Management Plan, Version no. 7.0, dated 22 February 2022 included the following important identified risks, important potential risks, and missing information (see Table 96):

Table 96 Summary of safety concerns – AstraZeneca Core Risk Management Plan for VAXZEVRIA (Version no. 7.0, dated 22 February 2022)

Risk category	Safety concern
Important identified risks	Thrombosis in combination with thrombocytopenia
Important potential risks	Cerebrovascular venous sinus thrombosis without thrombocytopenia
	Immune mediated neurological conditions
	Vaccine-associated enhanced disease (VAED)
Missing information	Use of VAXZEVRIA in pregnant and breastfeeding women
	Use of VAXZEVRIA in subjects with severe immunodeficiency
	Use of VAXZEVRIA in subjects with severe and/or uncontrolled underlying disease
	Use of VAXZEVRIA with other vaccines

16.2 Signal evaluation

Three validated signals were closed during the reporting period, immune thrombocytopenia (ITP) cutaneous vasculitis and Tinnitus. A summary of the signal evaluation is provided below.

16.2.1 Closed and rejected/refuted signals

There were no closed and rejected/refuted signals during the reporting period.

However post the DLP of the PBRER (28 December 2022). The signal of feeling hot was identified from the final pooled analysis of COV studies (DCO 3: 31 December 2021). The details of this signal are presented below.

16.2.1.1 Feeling hot

Table 97 Feeling hot

Characterisation	Summary
Source of the signal	Final pooled analysis of COV studies (COV001, 002, 003 and 005; DCO 3:31 December 2021)
Date detected/validated	22 December 2022
Date closed	17 January 2023
Reference document(s)	Not applicable
Regulatory Procedure Reference	Not applicable
Search criteria	PT: Feeling hot
Method(s) of evaluation	Review of events from COV001, 002, 003 and 005 and pooled analysis
Outcome of the evaluation	The event term "Feeling hot" is not recommended to include in the VAXERVIA CDS and the signal is refuted
Conclusions	Feeling hot resembles solicited events of Feverishness and Fever (PT: Pyrexia), which are listed as ADRs in the VAXZEVRIA CDS. It was noted that the observed numerical imbalance was mainly from the COV003 Study (169 (3.2%) in the AZD1222 arm compared to 74 (1.4%) in the control arm in the Dose 1 SD Safety Analysis Set). Taking in to consideration that the event of 'Feeling hot' is adequately covered in the VAXZEVRIA CDS with the listed events of Feverishness and Fever (PT: Pyrexia); "Feeling hot" need not be specifically included as an ADR in Section 4.8 of the VAXZEVRIA CDS.

MedDRA Medical Dictionary for Regulatory Activities, PT Preferred Term
Signal Feeling hot is closed after the DLP on 17 January 2023

16.2.2 Closed signals categorised as important potential risks

There were no closed signals categorised as important potential risks during the reporting period.

16.2.3 Closed signals categorised as important identified risks

There were no closed signals categorised as important identified risks during the reporting period.

16.2.4 Closed signals that are potential risks not categorised as important

There were no closed signals that are potential risks not categorised as important during the reporting period.

16.2.5 Closed signals that are identified risks not categorised as important

There were 3 signals (Tinnitus, Cutaneous vasculitis and Immune thrombocytopenia) that were closed during the reporting interval, please refer to Table 98, Table 99 , Table 100.

16.2.5.1 Tinnitus

Table 98 Tinnitus

Characterisation	Summary
Source of the signal	Regulatory Authority – Request in preliminary assessment report for 3rd PBRER (DLP 28 June 2022) to include "Tinnitus" in section 4.8 of the EU SmPC
Date detected	11 May 2022
Date closed	01 July 2022
Regulatory Procedure Reference	EMEA/H/C/PSUSA/00010912/202112
Search criteria	MedDRA PT: Tinnitus
Method(s) of evaluation	Comprehensive cumulative review of clinical and post-marketing reports and the literature (including case reviews and epidemiological studies). Medical review and causality assessment according to WHO-UMC causality criteria for medically confirmed cases. Quantitative Signal Detection System using EVDAS data and observed versus expected analysis), stratified by age and risk window 0-42 days, with incidence rates from Stohler et al 2019
Outcome of the evaluation	Update to include "Tinnitus" in section 4.8 in VAXZEVRIA CDS with frequency "uncommon" based on clinical trial data and section 4 of PIL
Conclusion	Based on the evaluation of currently available information from various sources, AstraZeneca considers that there is a reasonable possibility of a causal association between VAXZEVRIA and tinnitus. VAXZEVRIA CDS Section 4.8 (undesirable effects) was updated to include 'Tinnitus'. When used in accordance with the revised prescribing information, the benefits of VAXZEVRIA continue to outweigh the risks.

MedDRA Medical Dictionary for Regulatory Activities, PT Preferred Term, TGA Australian Therapeutic Goods Administration.

16.2.5.2 Cutaneous vasculitis

Table 99 Cutaneous vasculitis

Characterisation	Summary
Source of the signal	Literature Article, Regulatory Authority
Date detected	05 April 2022
Date closed	31 August 2022
Regulatory Procedure Reference	EMEA/H/C/PSUSA/00010912/202112

Table 99 Cutaneous vasculitis

Characterisation	Summary
Search criteria	A search was performed to identify any relevant cases of cutaneous vasculitis using the MedDRA (V25.0) SMQ of Vasculitis. A narrative review of cases with the following PTs from this SMQ was performed to identify the relevant cases: Vasculitis, Vasculitic rash, Hypersensitivity vasculitis, Vascular purpura, Urticarial vasculitis, Chronic pigmented purpura, Haemorrhagic vasculitis, Vasculitis necrotising, Capillaritis, and Nodular vasculitis.
Method(s) of evaluation	Comprehensive cumulative review of clinical and post-marketing reports and the literature (including case reviews and epidemiological studies). Quantitative Signal Detection System (Observed versus expected analysis), External Quantitative Signal Detection System (EVDAS), Literature review.
Outcome of the evaluation	CDS Section 4.8 (undesirable effects) was updated to include cutaneous vasculitis as an ADR (frequency: not known)
Conclusions	Based on the evaluation of currently available information from various sources, AstraZeneca has determined that there is a reasonable possibility of a causal association between VAXZEVRIA and CV. VAXZEVRIA CDS Section 4.8 (undesirable effects) was updated to include 'Cutaneous vasculitis' with frequency of "not known". When used in accordance with the revised prescribing information, the benefits of VAXZEVRIA continue to outweigh the risks.

MedDRA Medical Dictionary for Regulatory Activities, PT Preferred Term

16.2.5.3 Immune thrombocytopenia

Table 100 Immune thrombocytopenia

Characterisation	Summary
Source of the signal	Qualitative data analysis (Individual Case Safety Report or Case Series), Literature cases
Date detected	06 July 2022
Date closed	08 November 2022
Regulatory Procedure Reference	Not applicable
Search criteria	HLT: Thrombocytopenia and SMQ narrow: Haematopoietic thrombocytopenia, and SMQ: Haemorrhage terms (excluding laboratory terms).
Method(s) of evaluation	Quantitative Signal Detection System (Observed versus expected analyses), Literature review, Preclinical review, Clinical review, Qualitative data analysis (Individual Case Safety Report or Case Series), Epidemiology analyses
Outcome of the evaluation	CDS Section 4.4 (Special warnings and special precautions for use) updated to include relevant text on Immune thrombocytopenia and CDS Section 4.8 (undesirable effects) was updated to include Immune thrombocytopenia as an ADR (frequency: not known)

Table 100 Immune thrombocytopenia

Characterisation	Summary
Conclusions	Based on a review of available information, in particular spontaneous reports, AstraZeneca has determined that there is a reasonable possibility of a causal association between VAXZEVRIA and Immune thrombocytopenia. VAXZEVRIA CDS Section 4.8 (undesirable effects) was updated to include Immune thrombocytopenia as an ADR with frequency of "not known", and also to include relevant text in Section 4.4 (Special warnings and special precautions for use) of the CDS.

MedDRA Medical Dictionary for Regulatory Activities, PT Preferred Term

16.2.5.4 Decreased appetite

Table 101 Decreased appetite

Characterisation	Summary
Source of the signal	Final pooled analysis of COV studies (COV001, 002, 003 and 005; DCO 3: 31 December 2021)
Date detected	22 December 2022
Date closed	Ongoing
Reference document(s)	Not applicable
Regulatory Procedure Reference	Not applicable
Search criteria	MedDRA PT: Decreased appetite
Method(s) of evaluation	With a DCO of 31 December 2021, the "DC03" data was derived from the results of AstraZeneca's final pooled analysis of the safety, durability of efficacy, and immunogenicity of 2-dose primary intramuscular vaccinations with AZD1222, based on data from University of Oxford sponsored studies COV001, COV002, COV003 and COV005
Outcome of the evaluation	CDS Section 4.8 (undesirable effects) to be updated to include Decreased appetite as an ADR (frequency: uncommon)
Conclusions	CDS is currently in the progress to be updated to include Decreased appetite as ADR in Section 4.8 with frequency of 'uncommon'

MedDRA Medical Dictionary for Regulatory Activities, PT Preferred Term
Signal of Decreased appetite is ongoing and CDS update is in progress

16.3 Evaluation of risks and new information

This section presents data from the AstraZeneca global safety database obtained using search strategies inclusive of all available data in the database. Numbers presented here may differ from those presented in the Appendix 2 summary tabulations (also from the AstraZeneca global safety database), where the search strategies are specific to the requirements for the summary tabulations.

Period data may include case reports which have been received prior to this period but where follow-up information have been obtained during the reporting period.

16.3.1 New information on important potential risks

All important potential risks included in Section 16.1 are kept under close surveillance by AstraZeneca.

16.3.1.1 Cerebrovascular venous and sinus thrombosis without thrombocytopenia Global Patient Safety Database

A cumulative search through 28 December 2022 and period search (29 June 2022 to 28 December 2022) of the AstraZeneca Global Patient Safety Database was conducted using the following MedDRA (v25.1) HLT: Cerebrovascular venous and sinus thrombosis (CVST). To identify the cases of CVST without co-reported thrombocytopenia, the following were excluded from the search results: any cases with events from the HLT: Thrombocytopenia, SMQ: Hematopoietic thrombocytopenia (Narrow), or cases with platelet values less than 150,000 per microliter.

Reporting period (29 June 2022 – 28 December 2022)

After applying the above exclusion criteria, 37 cases (17 initial and 20 follow-up) of CVST without thrombocytopenia were retrieved. A majority of the cases, 8 (21.6%), were reported from the UK, followed by Brazil 5 (13.5%) and Germany with 5 (13.5%) cases.

The distribution of the preferred terms for CVST without co-reported Thrombocytopenia are presented in Table 102 below in descending order of frequency:

Table 102 Distribution of MedDRA PTs (n = 40) pertaining to CVST without co-reported Thrombocytopenia with VAXZEVRIA received during the reporting period.

MedDRA PT	Serious	Non-serious	Grand Total
Cerebral venous sinus thrombosis	24	0	24
Cerebral venous thrombosis	11	0	11
Superior sagittal sinus thrombosis	4	0	4
Cavernous sinus thrombosis	1	0	1
Grand total	40	0	40

CVST Cerebral Venous Sinus Thrombosis; MedDRA Medical Dictionary for Regulatory Activities; PT Preferred Term

The breakdown and overview of these 37 cases reporting 40 events of topic is presented in the Table 103 below

Table 103 Overview of CVST without co-reported thrombocytopenia Events/Cases during the reporting period.

Parameter	Break-down	Values (%)
	Total	40

Table 103 Overview of CVST without co-reported thrombocytopenia Events/Cases during the reporting period.

Parameter	Break-down	Values (%)
Event Count	Serious	40 (100%)
	Non serious	0
Case Count	Medically confirmed	20 (54%)
Case Report Source	Spontaneous	10 (27%)
	Literature	9 (24.3%)
	Regulatory	18 (48.7%)
Sex	Female N (%)	23 (62.2%)
	Male N (%)	9 (24.3%)
	Unknown/not reported N (%)	5
Age Group	0-17	1 (2.7%)
	18-49	23 (62.2%)
	50-59	6 (16.2%)
	60-69	5 (13.5%)
	Unk	2
	Median age (range)	42 years (17 to 63)
Event occurrence with dose	Dose 1 (%)	32 (86.4%)
	Dose 2 (%)	3 (8.2%)
	Dose 3 (%)	2 (5.4%)
Case level -TTO (days)[a]	0-14	16 (43.2%)
	15-28	1 (2.7%)
	29-42	1 (2.7%)
	43 and above	3 (8.1%)
	Unknown	16
	Median TTO (range)	8 (1 to 445 days)
Event Seriousness criteria	Medically important	11 (27.5%)
	Disability	0
	Hospitalization	18 (45%)
	Congenital anomaly	0
	Life-threatening	6 (15%)
	Death	5 (12.5%) (Initial-2; Follow-up-3)
AE Outcome	Recovered	7 (17.5%)
	Recovering	7 (17.5%)
	Recovered with sequelae	3 (7.5%)
	Not recovered	7 (17.5%)
	Fatal	5 (12.5%)
	Unknown	11

Table 103 Overview of CVST without co-reported thrombocytopenia Events/Cases during the reporting period.

Parameter	Break-down	Values (%)
Duration of recovered/recovered with sequelae events	Known duration (number of events)	2
	Range (days)	3-117
	Mean (days)	60
	Unknown duration (number of events)	8

[a] TTO was reported for 21 case reports (total number of cases) used to calculate the percentage.
Where multiple TTOs are present in a case, the most conservative TTO for the relevant event is chosen
percentages for all, calculated based on known values
AE Adverse Event; CVST Cerebral Venous Sinus Thrombosis; TTO Time To Onset

Cases with fatal outcome

The assessment of the fatal case reports identified during the reporting period is presented in the below Table 104. Out of 6 cases 3 were initial and 3 were follow-up. One case was reported from the US, however this is a case received via Social Media concerned a vaccinee from unknown origin (source country unknown).

Table 104 Summary of case reports with fatal outcome for CVST without Thrombocytopenia (N = 6) during the reporting period

Case ID/ Age/Gender/Medically confirmed (Y/N)/ Source/Country/	TTO[a]	Relevant Medical History/ Concomitant medications (Risk factors)	Autopsy (Y/N)/ Summary of Autopsy result	Cause of Death PTs	WHO UMC Causality Assessment	Comment for WHO Assessment
[redacted]/40/F/Y/ Spontaneous/Brazil	7	Abortion spontaneous; Decompressive craniectomy/Concomitant use of Estradiol	N	Haemorrhagic stroke; Cerebral venous thrombosis	Possible with Confounders	TTO is reasonable, case confounded by oral contraceptives usage pre vaccination.
[redacted]/37/Unk /N/Spontaneous/Germany	Unk	Not reported	N	Cerebral venous thrombosis	Unassessable with limited information	TTO unknown. Lack of information regarding medical history, concomitant medication, onset latency, event details and lab data/autopsy findings; preclude a comprehensive causality assessment.
[redacted]/27/M/N /Spontaneous/United States (Social media/Origin Country-Unknown)	Unk	Not reported	N	Cerebral haemorrhage	Unassessable with limited information	TTO unknown. Lack of information regarding medical history, concomitant medication, onset latency, event details and lab data/autopsy findings; preclude a comprehensive causality assessment.

Table 104 Summary of case reports with fatal outcome for CVST without Thrombocytopenia (N = 6) during the reporting period

Case ID/ Age/Gender/Medically confirmed (Y/N)/ Source/Country/	TTO[a]	Relevant Medical History/ Concomitant medications (Risk factors)	Autopsy (Y/N)/ Summary of Autopsy result	Cause of Death PTs	WHO UMC Causality Assessment	Comment for WHO Assessment
[redacted]/30/M/Y /Literature/Korea, Republic of	Unk	Not reported	N	Cerebral venous thrombosis	Unassessable with limited information	TTO unknown. Lack of information regarding medical history, concomitant medication, onset latency, event details and lab data/autopsy findings; preclude a comprehensive causality assessment.
[redacted]/Unk/F/ Y/Spontaneous/France	Unk	Anticoagulant therapy	N	Cerebral venous thrombosis	Unassessable with limited information	TTO unknown. Lack of information regarding precise type of anticoagulation patient was on and for what indication, any prior history of arterial/venous thrombosis, event onset latency, event details, lab data and autopsy findings; preclude a comprehensive causality assessment.

Table 104 Summary of case reports with fatal outcome for CVST without Thrombocytopenia (N = 6) during the reporting period

Case ID/ Age/Gender/Medically confirmed (Y/N)/ Source/Country/	TTO[a]	Relevant Medical History/ Concomitant medications (Risk factors)	Autopsy (Y/N)/ Summary of Autopsy result	Cause of Death PTs	WHO UMC Causality Assessment	Comment for WHO Assessment
[redacted]/27/M/Y /Spontaneous/United Kingdom	Unk	Not reported	N	Cerebral venous sinus thrombosis; Adverse drug reaction	Unassessable with limited information	TTO unknown. Lack of information regarding medical history, concomitant medication, onset latency, event details and lab data/autopsy findings; preclude a comprehensive causality assessment.

[a] Shortest time to onset for CVST events. TTO is for the event onset and not for date of death.

AE Adverse Event; CVST Cerebral Venous Sinus N No; Thrombosis; TTO Time To Onset; UMC Uppsala Monitoring Centre; WHO World Health Organization; Y Yes;

Recurrence case reports

There were no cases indicating a recurrence.

WHO -UMC causality Assessment

Causality assessment of all cases was performed using WHO- UMC causality assessment criteria with a risk window of 42 days.

Table 105 Overview of WHO-UMC Causality Assessments for case reports of CVST without Thrombocytopenia with VAXZEVRIA reported during the reporting period

WHO-UMC causality assessment	Grand Total
Possible with risk factors/confounders	6
Possible with limited information	13
Unassessable/Unclassifiable with limited information	13
Unassessable/Unclassifiable with risk factors/confounders	2
Unlikely	3
Total	**37**

Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, or where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.

UMC Uppsala Monitoring Centre; WHO World Health Organization

None of the cases met WHO-UMC criteria as 'Certain', 'Probable/Likely' and 'Conditional/Unclassified'.

There was available information on confounding comorbidities, other medical confounders or risk factors and confounding medications reported in 8 (21.6%) of the 37 cases. Out of the remaining 29 cases, 28 cases had no information on any confounding/risk factor and in 1 case there were no relevant risk factors identified. A single case may have more than one risk/confounding factor.

The confounding factors reported for the cases were concomitant use of contraceptives, history of obesity, COVID-19 illness prior to vaccine, Atrial fibrillation, Arterial thrombosis, chronic ischaemic heart disease and hypertension.

Observed Versus Expected (O/E) Analyses for all cases of CVST without Thrombocytopenia

The observed versus expected analyses for all cases of CVST without thrombocytopenia are carried out cumulatively using incidence rates from ACCESS: SIDIAP PCHOSP and Truven MarketScan (2019). The observed versus expected analysis for all cases of CVST without thrombocytopenia is presented with different risk windows (21 days, 30 days and 42 days) for all global reports in Table 106 and stratified by age for the EEA, UK, Australia and Brazil regions in Table 107 and by age and gender in UK (Table 108 and Table 109). Global analysis also included cases with an unknown time to onset, as a conservative approach. The incidence rates used were from SIDIAP_PCHOSP (Willame et al 2021 (A)) as that rate was used by the EMA, and this would permit a comparison of the O/E analysis conducted by EMA and AstraZeneca.

SIDIAP PCHOSP is a data source containing 5.7 million (80% of the population) in Catalonia and includes General Practitioner (GP) medical records, communication from specialists and hospitalization discharge diagnoses. SIDIAP PCHOSP is representative of the general population in terms of age, sex, and geographic distribution. Since CVST is a very rare event, a larger database was used in addition to SIDIAP PCHOSP. Truven MarketScan (US) was chosen since is a longitudinal database capturing outcomes from in- and outpatient visits and pharmaceuticals and contains almost 230 million unique patients. Moreover, it includes both commercial employer-based insurance and government-based insurance. In addition to its large sample size Truven MarketScan was used for consistency with background rates for CVST generated using MarketScan.

As a comparison to the above, the same observed versus expected analyses are carried out using incidence rates from Truven MarketScan. Those analyses for CVST are presented with different risk windows (21 days, 30 days and 42 days) for all global reports in Table 110, stratified by age in the EEA, UK, Australia and Brazil in Table 111 and by age and gender in the UK (Table 112 and Table 113).

Table 106 Observed versus expected analysis for CVST without thrombocytopenia (using SIDIAP_PC HOSP incident rate) for global reports

Age group	IR [a]	Exposure[b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
Overall (Global)	0.72	46611 5644	289	192.96	1.5 (1.33 - 1.68)	Observed significantly > expected	331	275.66	1.2 (1.07 - 1.34)	Observed significantly > expected	378	385.92	0.98 (0.88 - 1.08)	Observed < expected
Overall (Global) plus cases Unk TTO	0.72	46611 5644	454	192.96	2.35 (2.14 - 2.58)	Observed significantly > expected	496	275.66	1.8 (1.64 - 1.96)	Observed significantly > expected	543	385.92	1.41 (1.29 - 1.53)	Observed significantly > expected

[a] Incidence rate Source:Willame et al 2021 (A) from ES_SIDIAP_PCHOSP

[b] Exposure is to DLP 28 December 2022

[c] All cases to DLP 28 December 2022.

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days

CI Confidence Interval; CVST Cerebral Venous Sinus Thrombosis; E Expected; EEA European economic area; IR Incidence Rate; O Observed; TTO Time to onset; UK United Kingdom

Table 107 Observed versus expected analysis for CVST without thrombocytopenia (using SIDIAP_PC HOSP incident rates) stratified by age in the EEA +UK +Australia +Brazil

Age group	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
EEA+UK+Brazil+Australia Data														
18-49 Years	0.27	110094983	124	17.09	7.26 (6.03 - 8.65)	Observed significantly > expected	136	24.42	5.57 (4.67 - 6.59)	Observed significantly > expected	154	34.18	4.51 (3.82 - 5.28)	Observed significantly > expected
50-59 Years	1.57	58336094	53	52.66	1.01 (0.75 - 1.32)	Observed > expected	63	75.23	0.84 (0.64 - 1.07)	Observed < expected	71	105.32	0.67 (0.53 - 0.85)	Observed significantly < expected
60-69 Years	0.68	57960860	58	22.66	2.56 (1.94 - 3.31)	Observed significantly > expected	65	32.37	2.01 (1.55 - 2.56)	Observed significantly > expected	78	45.32	1.72 (1.36 - 2.15)	Observed significantly > expected
Over 70 Years	0.34	32376365	35	6.33	5.53 (3.85 - 7.69)	Observed significantly > expected	41	9.04	4.54 (3.25 - 6.15)	Observed significantly > expected	46	12.66	3.63 (2.66 - 4.85)	Observed significantly > expected

[a] Incidence rate Source: Willame et al 2021 (A) from ES_SIDIAP_PCHOSP

[b] Exposure is to DLP 28 December 2022

[c] All cases to DLP 28 December 2022

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CI Confidence Interval; CVST Cerebral Venous Sinus Thrombosis; E Expected; IR Incidence Rate; O Observed; TTO Time to onset; UK United Kingdom; EEA European economic area.

Table 108 Observed versus expected analysis for CVST without thrombocytopenia (using SIDIAP_PC HOSP incident rates) stratified by age and gender (FEMALE) in the UK

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female 40-49	0.77	4412245	12	1.95	6.15 (3.18 - 10.75)	Observed significantly > expected	12	2.79	4.3 (2.22 - 7.51)	Observed significantly > expected	13	3.91	3.32 (1.77 - 5.69)	Observed significantly > expected
Female over 80	1.67	1630324	1	1.57	0.64 (0.02 - 3.55)	Observed < expected	1	2.24	0.45 (0.01 - 2.49)	Observed < expected	3	3.13	0.96 (0.2 - 2.8)	Observed < expected

[a] Incidence rate Source:Willame et al 2021 (A), from ES_SIDIAP_PCHOSP\

[b] Exposure is to DLP 28 December 2022.

[c] All cases to DLP 28 December 2022.

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CI Confidence Interval; CVST Cerebral Venous Sinus Thrombosis; E Expected; IR Incidence Rate; O Observed; TTO Time to onset; UK United Kingdom; EEA European economic area.

Table 109 Observed versus expected analysis for CVST without thrombocytopenia (using SIDIAP_PC HOSP incident rates) stratified by age and gender (MALE) in the UK

Age group / Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases[c] cases[c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male 18-29	1.27	808938	2	0.59	3.39 (0.41 - 12.25)	Observed > expected	2	0.84	2.38 (0.29 - 8.6)	Observed > expected	4	1.18	3.39 (0.92 - 8.68)	Observed > expected
Male 40-49	0.72	4542157	5	1.88	2.66 (0.86 - 6.21)	Observed > expected	6	2.69	2.23 (0.82 - 4.85)	Observed > expected	7	3.76	1.86 (0.75 - 3.84)	Observed > expected
Male 50-59	0.9	6510960	6	3.37	1.78 (0.65 - 3.88)	Observed > expected	8	4.81	1.66 (0.72 - 3.28)	Observed > expected	12	6.74	1.78 (0.92 - 3.11)	Observed > expected
Male 60-69	2.49	4934728	4	7.06	0.57 (0.15 - 1.45)	Observed < expected	4	10.09	0.4 (0.11 - 1.02)	Observed significantly < expected	6	14.13	0.42 (0.16 - 0.92)	Observed significantly < expected
Male 70-79	1.68	3137304	3	3.03	0.99 (0.2 - 2.89)	Observed < expected	3	4.33	0.69 (0.14 - 2.02)	Observed < expected	3	6.06	0.5 (0.1 - 1.45)	Observed < expected
Male over 80	2.81	1025046	1	1.66	0.6 (0.02 - 3.36)	Observed < expected	1	2.37	0.42 (0.01 - 2.35)	Observed < expected	1	3.31	0.3 (0.01 - 1.68)	Observed < expected

[a] Incidence rate Source:Willame et al 2021 (A), from ES_SIDIAP_PCHOSP

[b] Exposure is to DLP 28 December 2022.

[c] All cases to DLP 28 December 2022

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CI Confidence Interval; CVST Cerebral Venous Sinus Thrombosis; E Expected; IR Incidence Rate; O Observed; TTO Time to onset; UK United Kingdom; EEA European economic area.

Table 110 Observed versus expected analysis for CVST without thrombocytopenia (using Truven 14 incident rates) for global reports

Age group	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion
Overall (Global)	1.5	466115644	289	402	0.72 (0.64 - 0.81)	Observed significantly < expected	331	574.28	0.58 (0.52 - 0.64)	Observed significantly < expected	378	803.99	0.47 (0.42 - 0.52)	Observed significantly < expected
Overall (Global) plus cases Unk TTO	1.5	466115644	454	402	1.13 (1.03 - 1.24)	Observed significantly > expected	496	574.28	0.86 (0.79 - 0.94)	Observed significantly < expected	543	803.99	0.68 (0.62 - 0.73)	Observed significantly < expected

[a] Incidence Rate (per/100,000 PY) from Truven Market Scan database (2019)
[b] Exposure is to DLP 28 December 2022.
[c] All cases to DLP 28 December 2022.
Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.
CI Confidence Interval; CVST Cerebral Venous Sinus Thrombosis; E Expected; IR Incidence Rate; O Observed; TTO Time to onset; UK United Kingdom; EEA European economic area

Table 111 Observed versus expected analysis for CVST without thrombocytopenia (using Truven 14 incident rates) for EEA+UK+Australia+Brazil

Age group	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of casesc	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of casesc	Expected number of cases	Over E ratio (95 % CI)	Conclusion
EEA+UK+Brazil+Australia Data														
18-49 Years	1.55	110094983	124	98.12	1.26 (1.05 - 1.51)	Observed significantly > expected	136	140.16	0.97 (0.81 - 1.15)	Observed < expected	154	196.23	0.78 (0.67 - 0.92)	Observed significantly < expected
50-59 Years	0.86	58336094	53	28.85	1.84 (1.38 - 2.4)	Observed significantly > expected	63	41.21	1.53 (1.17 - 1.96)	Observed significantly > expected	71	57.69	1.23 (0.96 - 1.55)	Observed > expected
60-69 Years	1.65	57960860	58	54.99	1.05 (0.8 - 1.36)	Observed > expected	65	78.55	0.83 (0.64 - 1.05)	Observed < expected	78	109.97	0.71 (0.56 - 0.89)	Observed significantly < expected
Over 70 Years	0.9	32376365	35	16.75	2.09 (1.46 -	Observed significantly > expected	41	23.93	1.71 (1.23 -	Observed significantly > expected	46	33.51	1.37 (1.01 -	Observed significantly > expected

Table 111 Observed versus expected analysis for CVST without thrombocytopenia (using Truven 14 incident rates) for EEA+UK+Australia+Brazil

Age group	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion	Observed number of casesc	Expected number of cases	O over E ratio (95 % CI)	Conclusion	Observed number of casesc	Expected number of cases	O over E ratio (95 % CI)	Conclusion
					2.91)				2.32)				1.83)	

[a] Incidence Rate (per/100,000 PY) from Truven Market Scan database (2019)

[b] Exposure is to DLP 28 December 2022.

[c] All cases to DLP 28 December 2022.

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CI Confidence Interval; CVST Cerebral Venous Sinus Thrombosis; E Expected; IR Incidence Rate; O Observed; TTO Time to onset; UK United Kingdom; EEA European economic area

Table 112 Observed versus expected analysis for CVST without thrombocytopenia (using Truven 14 incident rates) stratified by age and gender (Female) in the UK

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion
Female 18-29	2.46	1109488	3	1.57	1.91 (	Observed > expected	4	2.24	1.79 (	Observed > expected	4	3.14	1.27 (	Observed > expected

Table 112 Observed versus expected analysis for CVST without thrombocytopenia (using Truven 14 incident rates) stratified by age and gender (Female) in the UK

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion
					0.39 - 5.58)				0.49 - 4.57)				0.35 - 3.26)	
Female 30-39	2.23	1892968	3	2.43	1.23 (0.25 - 3.61)	Observed > expected	3	3.47	0.86 (0.18 - 2.53)	Observed < expected	5	4.85	1.03 (0.33 - 2.41)	Observed > expected
Female 40-49	1.84	4412245	12	4.67	2.57 (1.33 - 4.49)	Observed significantly > expected	12	6.67	1.8 (0.93 - 3.14)	Observed > expected	13	9.34	1.39 (0.74 - 2.38)	Observed > expected
Female 50-59	0.82	5944683	6	2.8	2.14 (0.79 - 4.66)	Observed > expected	8	4	2 (0.86 - 3.94)	Observed > expected	9	5.61	1.6 (0.73 - 3.05)	Observed > expected
Female 60-69	1.41	4783416	3	3.88	0.77 (	Observed < expected	5	5.54	0.9 (0.29	Observed < expected	6	7.76	0.77 (	Observed < expected

Table 112 Observed versus expected analysis for CVST without thrombocytopenia (using Truven 14 incident rates) stratified by age and gender (Female) in the UK

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion
					0.16 - 2.26)				- 2.11)				0.28 - 1.68)	
Female 70-79	0.71	3475875	3	1.42	2.11 (0.44 - 6.17)	Observed > expected	4	2.03	1.97 (0.54 - 5.05)	Observed > expected	4	2.84	1.41 (0.38 - 3.61)	Observed > expected
Female over 80	9.32	1630324	1	8.74	0.11 (0 - 0.64)	Observed significantly < expected	1	12.48	0.08 (0 - 0.45)	Observed significantly < expected	3	17.47	0.17 (0.04 - 0.5)	Observed significantly < expected

[a] Incidence Rate (per/100,000 PY) from Truven Market Scan database (2019)
[b] Exposure is to DLP 28 December 2022.
[c] All cases to DLP 28 December 2022
Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.
CI Confidence Interval; CVST Cerebral Venous Sinus Thrombosis; E Expected; IR Incidence Rate; O Observed; TTO Time to onset; UK United Kingdom; EEA European economic area

Table 113 Observed versus expected analysis for CVST without thrombocytopenia (using Truven 14 incident rates) stratified by age and gender (Male) in the UK

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion
Male 18-29	1.1	808938	2	0.51	3.92 (0.47 - 14.17)	Observed > expected	2	0.73	2.74 (0.33 - 9.9)	Observed > expected	4	1.02	3.92 (1.07 - 10.04)	Observed significantly > expected
Male 30-39	0.69	1415003	2	0.56	3.57 (0.43 - 12.9)	Observed > expected	2	0.8	2.5 (0.3 - 9.03)	Observed > expected	2	1.12	1.79 (0.22 - 6.45)	Observed > expected
Male 40-49	0.86	4542157	5	2.25	2.22 (0.72 - 5.19)	Observed > expected	6	3.21	1.87 (0.69 - 4.07)	Observed > expected	7	4.49	1.56 (0.63 - 3.21)	Observed > expected
Male 50-59	0.91	6510960	6	3.41	1.76 (0.65 - 3.83)	Observed > expected	8	4.87	1.64 (0.71 - 3.24)	Observed > expected	12	6.81	1.76 (0.91 - 3.08)	Observed > expected

Table 113 Observed versus expected analysis for CVST without thrombocytopenia (using Truven 14 incident rates) stratified by age and gender (Male) in the UK

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion
Male 60-69	1.92	4934728	4	5.45	0.73 (0.2 - 1.88)	Observed < expected	4	7.78	0.51 (0.14 - 1.32)	Observed < expected	6	10.9	0.55 (0.2 - 1.2)	Observed < expected
Male 70-79	2.49	3137304	3	4.49	0.67 (0.14 - 1.95)	Observed < expected	3	6.42	0.47 (0.1 - 1.37)	Observed < expected	3	8.98	0.33 (0.07 - 0.98)	Observed significantly < expected
Male over 80	6.64	1025046	1	3.91	0.26 (0.01 - 1.42)	Observed < expected	1	5.59	0.18 (0 - 1)	Observed significantly < expected	1	7.83	0.13 (0 - 0.71)	Observed significantly < expected

[a] Incidence Rate (per/100,000 PY) from Truven Market Scan database (2019)

[b] Exposure is to DLP 28 December 2022.

[c] All cases to DLP 28 December 2022.

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CI Confidence Interval; CVST Cerebral Venous Sinus Thrombosis ; E Expected; IR Incidence Rate; O Observed; TTO Time to onset; UK United Kingdom; EEA European economic area

When an overall rate of 0.72/100,000 person years (PY) from SIDIAP_HOSP is used, observed cases of CVST without thrombocytopenia are significantly more than expected for all risk windows except for risk window of 42 days. Observed cases were significantly more than expected for all risk windows when an unknown time to onset was included.

In comparison, when Truven 14 IR are used, observed cases are significantly less than expected for all the risk windows, when cases with unknown TTO are excluded. When cases with an unknown TTO are included to all risk windows as a conservative approach, observed cases are significantly more than expected for risk window 21 days, however observed cases were significantly less than expected for 30 and 42-days risk window (Table 110).

When the observed versus expected analysis was stratified by age in the EEA, UK, Australia and Brazil region using SIDIAP_HOSP rates, observed cases were less than expected for age groups 50-59 (for risk window 30 and 42 days). For all other age stratifications and risk windows of 21, 30 and 42 days in EEA, UK, Australia and Brazil region using SIDIAP_HOSP rates observed cases were either more or significantly more than expected (Table 107).

In comparison, when observed versus expected analysis was stratified by age in the EEA, UK, Australia and Brazil region using Truven 14 IRs, observed cases are more or significantly more than expected in all age groups from 18-69 and over 70 years for risk windows 21 days. In risk window of 30 days, observed cases are more or significantly more than expected in age groups from 50-59 and in age group over 70 years and observed cases are less than expected in age group 18-49 and 60-69 years for risk window of 30 days. For risk window of 42 days, observed cases were significantly less than expected for age groups of 18-49, 60-69 and observed cases were either more or significantly more than expected for age groups 50-59 and over 70 years (Table 111).

When stratified by age and gender in the UK, using Truven 14 IRs, the observed cases divided between males (Table 113) and females (Table 112) as follows:

For females, observed cases were more or significantly more than expected for the age groups 18-59 and 70-79 years and observed cases were less or significantly less than expected for the age groups 60-69 and over 80 for 21 days risk window. Observed cases were more or significantly more than expected for the age groups 18-29, 40-49, 50-59, 70-79 years and observed cases were less or significantly less than expected for the age groups 30-39, 60-69 and over 80 years for 30 days risk window. Observed cases were more or significantly more than expected for the age groups 18-59, 70-79 years and observed cases were less or significantly less than expected for the age groups 60-69 and over 80 years for 42 days risk window.

For males, observed cases were less or significantly less than expected for age groups 60-69, 70-79 and over 80 years age group for all risk windows (21, 30 and 42 days). For all other age stratifications observed cases were either more or significantly more than expected for all risk windows (21, 30 and 42 days).

Observed versus expected analyses for CVST without thrombocytopenia (with known normal platelet count)

Information on normal platelets was available in 112 of the 597 cases. In the remaining 485 of the 597 cases the post-vaccination platelet count was unknown, however no thrombocytopenia-related PTs were reported. The 112 cases were used for observed versus expected analysis in order to represent the dataset with known normal thrombocytes.

The observed versus expected analysis for all 112 cases of CVST without thrombocytopenia is presented with different risk windows (21 days, 30 days and 42 days) for global reports in Table 114 and stratified by age in the EEA, UK, Australia and Brazil region in Table 115 and age groups in UK Table 116. The incidence rates used were from SIDIAP PCHOSP (Willame et al 2021 (A)), as that rate was used by the EMA, and this would permit a comparison of the O/E analysis conducted by EMA and AstraZeneca. All stratifications are provided with and without cases that have an unknown time to onset.

The O/E analysis for CVST without thrombocytopenia (with known normal thrombocytes) showed that the number of observed cases were significantly lower than expected when overall cases were considered. With the stratified O/E analysis by age and gender, there were certain age and gender groups where the observed number was higher than expected. However, when a qualitative review was conducted, many of the cases were missing information such as medical history, concomitant medications, precluding a proper assessment to determine causal relationship.

Table 114 Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using SIDIAP_PC HOSP incident rate) for global reports

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion
Overall (Global)	0.72	466115644	49	192.96	0.25 (0.19 - 0.34)	Observed significantly < expected	63	275.66	0.23 (0.18 - 0.29)	Observed significantly < expected	75	385.92	0.19 (0.15 - 0.24)	Observed significantly < expected
Overall (Global) plus cases Unk TTO	0.72	466115644	73	192.96	0.38 (0.3 - 0.48)	Observed significantly < expected	87	275.66	0.32 (0.25 - 0.39)	Observed significantly < expected	99	385.92	0.26 (0.21 - 0.31)	Observed significantly < expected

[a] Incidence rate Source:Willame et al 2021 (A), from ES_SIDIAP_PCHOSP

[b] Exposure is to DLP 28 December 2022.

[c] All cases up to DLP 28 December 2022.

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CI Confidence Interval, CVST Cerebrovascular venous and sinus thrombosis, E Expected; IR Incidence Rate; O Observed; TTO Time To Onset; Unk Unknown

Table 115 Observed versus expected analysis for CVST without thrombocytopenia (using SIDIAP_PC HOSP incident rates) (with known normal platelet count) stratified by age in the EEA +UK +Australia +Brazil

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion
EEA+UK+Brazil+Australia Data														
18-49 Years	0.34	110094983	19	21.52	0.88 (0.53 - 1.38)	Observed < expected	21	30.75	0.68 (0.42 - 1.04)	Observed < expected	23	43.04	0.53 (0.34 - 0.8)	Observed significantly < expected
50-59 Years	1.57	58336094	12	52.66	0.23 (0.12 - 0.4)	Observed significantly < expected	17	75.23	0.23 (0.13 - 0.36)	Observed significantly < expected	19	105.32	0.18 (0.11 - 0.28)	Observed significantly < expected
60-69 Years	0.68	57960860	6	22.66	0.26 (0.1 - 0.58)	Observed significantly < expected	9	32.37	0.28 (0.13 - 0.53)	Observed significantly < expected	12	45.32	0.26 (0.14 - 0.46)	Observed significantly < expected
Over 70 Years	0.34	32376365	7	6.33	1.11 (0.44 -	Observed > expected	10	9.04	1.11 (0.53 -	Observed > expected	13	12.66	1.03 (0.55 -	Observed > expected

Table 115 Observed versus expected analysis for CVST without thrombocytopenia (using SIDIAP_PC HOSP incident rates) (with known normal platelet count) stratified by age in the EEA +UK +Australia +Brazil

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion
					2.28)				2.03)				1.76)	
18-49 Years plus cases Unk TTO	0.34	110094983	26	21.52	1.21 (0.79 - 1.77)	Observed > expected	28	30.75	0.91 (0.61 - 1.32)	Observed < expected	30	43.04	0.7 (0.47 - 1)	Observed significantly < expected
50-59 Years plus cases Unk TTO	1.57	58336094	16	52.66	0.3 (0.17 - 0.49)	Observed significantly < expected	21	75.23	0.28 (0.17 - 0.43)	Observed significantly < expected	23	105.32	0.22 (0.14 - 0.33)	Observed significantly < expected
60-69 Years plus cases Unk TTO	0.68	57960860	8	22.66	0.35 (0.15 - 0.7)	Observed significantly < expected	11	32.37	0.34 (0.17 - 0.61)	Observed significantly < expected	14	45.32	0.31 (0.17 - 0.52)	Observed significantly < expected

Table 115 Observed versus expected analysis for CVST without thrombocytopenia (using SIDIAP_PC HOSP incident rates) (with known normal platelet count) stratified by age in the EEA +UK +Australia +Brazil

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion
Over 70 Years plus cases Unk TTO	0.34	32376365	12	6.33	1.9 (0.98 - 3.31)	Observed > expected	15	9.04	1.66 (0.93 - 2.74)	Observed > expected	18	12.66	1.42 (0.84 - 2.25)	Observed > expected

[a] Incidence rate Source:Willame et al 2021 (A), from ES_SIDIAP_PCHOSP

[b] Exposure is to DLP 28 December 2022.

[c] All cases up to DLP 28 December 2022.

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CI Confidence Interval, CVST Cerebrovascular venous and sinus thrombosis, E Expected; IR Incidence Rate; O Observed; TTO Time To Onset; Unk Unknown

Table 116 Observed versus expected analysis for CVST without thrombocytopenia (using SIDIAP_PC HOSP incident rates) (with known normal platelet count) stratified by age in the UK

Age group	IR[a]	Exposure b	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion
18-49 UK	0.34	14181834	12	2.77	4.33 (2.24 - 7.57)	Observed significantly > expected	13	3.96	3.28 (1.75 - 5.61)	Observed significantly > expected	15	5.54	2.71 (1.52 - 4.47)	Observed significantly > expected
50-59 UK	1.57	12455887	9	11.24	0.8 (0.37 - 1.52)	Observed < expected	12	16.06	0.75 (0.39 - 1.31)	Observed < expected	14	22.49	0.62 (0.34 - 1.04)	Observed < expected
60-69 UK	0.68	9718273	3	3.8	0.79 (0.16 - 2.31)	Observed < expected	5	5.43	0.92 (0.3 - 2.15)	Observed < expected	7	7.6	0.92 (0.37 - 1.9)	Observed < expected
70-79 UK	0.67	6613249	4	2.55	1.57 (0.43 - 4.02)	Observed > expected	5	3.64	1.37 (0.45 - 3.21)	Observed > expected	5	5.1	0.98 (0.32 - 2.29)	Observed < expected

Table 116 Observed versus expected analysis for CVST without thrombocytopenia (using SIDIAP_PC HOSP incident rates) (with known normal platelet count) stratified by age in the UK

Age group	IR[a]	Exposure b	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion
Over 80 UK	1.49	2655389	1	2.27	0.44 (0.01 - 2.45)	Observed < expected	1	3.25	0.31 (0.01 - 1.71)	Observed < expected	3	4.55	0.66 (0.14 - 1.93)	Observed < expected
18-49 UK plus cases Unk TTO	0.34	14181834	15	2.77	5.42 (3.03 - 8.93)	Observed significantly > expected	16	3.96	4.04 (2.31 - 6.56)	Observed significantly > expected	18	5.54	3.25 (1.93 - 5.13)	Observed significantly > expected
50-59 UK plus cases Unk TTO	1.57	12455887	13	11.24	1.16 (0.62 - 1.98)	Observed > expected	16	16.06	1 (0.57 - 1.62)	Observed < expected	18	22.49	0.8 (0.47 - 1.26)	Observed < expected
60-69 UK plus cases	0.68	9718273	5	3.8	1.32 (0.43 -	Observed > expected	7	5.43	1.29 (0.52 -	Observed > expected	9	7.6	1.18 (0.54 -	Observed > expected

Table 116 Observed versus expected analysis for CVST without thrombocytopenia (using SIDIAP_PC HOSP incident rates) (with known normal platelet count) stratified by age in the UK

Age group	IR[a]	Exposure[b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion
Unk TTO					3.07)				2.66)				2.25)	
70-79 UK plus cases Unk TTO	0.67	6613249	5	2.55	1.96 (0.64 - 4.58)	Observed > expected	6	3.64	1.65 (0.6 - 3.59)	Observed > expected	6	5.1	1.18 (0.43 - 2.56)	Observed > expected
Over 80 UK plus cases Unk TTO	1.49	2655389	2	2.27	0.88 (0.11 - 3.18)	Observed < expected	2	3.25	0.62 (0.07 - 2.22)	Observed < expected	4	4.55	0.88 (0.24 - 2.25)	Observed < expected

[a] Incidence rate Source:Willame et al 2021 (A), from ES_SIDIAP_PCHOSP

[b] Exposure is to DLP 28 December 2022.

[c] All cases up to DLP 28 December 2022.

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CI Confidence Interval, CVST Cerebrovascular venous and sinus thrombosis, E Expected; IR Incidence Rate; O Observed; TTO Time To Onset; Unk Unknown

As a comparison to the above, the same observed versus expected analyses are carried out using incidence rates from Truven MarketScan. That approach is aligned with incidence rates routinely used for TTS O/E monitoring. In particular, the time window for exclusion of patients with TCP (either -7/+7 or-1/+14) was consistent with the one used for TTS. In this analysis, a conservative approach in terms of ICD10 codes for CVST (I63.6 and I67.6) was used. Also, the analysis included only incident (no CVST claims within 12 months prior to index) inpatient claims. Those analyses for CVST are presented with different risk windows (21 days, 30 days, and 42 days) for all global reports in Table 117, stratified by age in the EEA, UK, Australia and Brazil region in Table 118, stratified by age in UK in Table 119 and gender (Female and Male) in the UK (Table 120 and Table 121). All stratifications also included cases with an unknown TTO, as a conservative approach.

The O/E analysis for CVST without thrombocytopenia (with known normal thrombocytes) using incidence rates from Truven MarketScan showed that the number of observed cases were significantly lower than expected when overall and also cases from EEA, UK, Brazil and Australia were considered. With the stratified O/E analysis by age and gender, there were certain age and gender groups (50-59 years in UK for all risk windows including unknown TTO, 18-49 years in UK for risk window of 21 days, only when unknown TTO is considered) where the observed number was higher than expected. However, when a qualitative review was conducted, many of the cases were missing information such as medical history, concomitant medications, precluding a proper assessment to determine causal relationship.

Table 117 Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) for global reports

Age group	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
Overall (Global)	1.5	466115644	49	402	0.12 (0.09 - 0.16)	Observed significantly < expected	63	574.28	0.11 (0.08 - 0.14)	Observed significantly < expected	75	803.99	0.09 (0.07 - 0.12)	Observed significantly < expected
Overall (Global) plus cases Unk TTO	1.5	466115644	73	402	0.18 (0.14 - 0.23)	Observed significantly < expected	87	574.28	0.15 (0.12 - 0.19)	Observed significantly < expected	99	803.99	0.12 (0.1 - 0.15)	Observed significantly < expected

[a] Incidence Rate (per/100,000 PY) from Truven Market Scan database (2019)

[b] Exposure is to DLP 28 December 2022.

[c] All cases to DLP 28 December 2022.

Truven 14: CVST (I63.6 or I67.6) inpatient without TCP within -1/14 days (incident)

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CVST Cerebral Venous Sinus Thrombosis; IR Incidence Rate; TTO Time To Onset

Table 118 Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) for EEA+UK+Australia+Brazil

Age group	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
EEA+UK+Brazil+Australia Data														
18-49 Years	1.55	110094983	19	98.12	0.19 (0.12 - 0.3)	Observed significantly < expected	21	140.16	0.15 (0.09 - 0.23)	Observed significantly < expected	23	196.23	0.12 (0.07 - 0.18)	Observed significantly < expected
50-59 Years	0.86	58336094	12	28.85	0.42 (0.21 - 0.73)	Observed significantly < expected	17	41.21	0.41 (0.24 - 0.66)	Observed significantly < expected	19	57.69	0.33 (0.2 - 0.51)	Observed significantly < expected
60-69 Years	1.65	57960860	6	54.99	0.11 (0.04 - 0.24)	Observed significantly < expected	9	78.55	0.11 (0.05 - 0.22)	Observed significantly < expected	12	109.97	0.11 (0.06 - 0.19)	Observed significantly < expected
Over 70 Years	0.9	32376365	7	16.75	0.42 (0.17 - 0.86)	Observed significantly < expected	10	23.93	0.42 (0.2 - 0.77)	Observed significantly < expected	13	33.51	0.39 (0.21 - 0.66)	Observed significantly < expected
18-49 Years plus cases Unk TTO	1.55	110094983	26	98.12	0.26 (0.17 - 0.39)	Observed significantly < expected	28	140.16	0.2 (0.13 - 0.29)	Observed significantly < expected	30	196.23	0.15 (0.1 - 0.22)	Observed significantly < expected

Table 118 Observed versus expected analysis for CVST without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) for EEA+UK+Australia+Brazil

Age group	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
50-59 Years plus cases Unk TTO	0.86	58336094	16	28.85	0.55 (0.32 - 0.9)	Observed significantly < expected	21	41.21	0.51 (0.32 - 0.78)	Observed significantly < expected	23	57.69	0.4 (0.25 - 0.6)	Observed significantly < expected
60-69 Years plus cases Unk TTO	1.65	57960860	8	54.99	0.15 (0.06 - 0.29)	Observed significantly < expected	11	78.55	0.14 (0.07 - 0.25)	Observed significantly < expected	14	109.97	0.13 (0.07 - 0.21)	Observed significantly < expected
Over 70 Years plus cases Unk TTO	0.9	32376365	12	16.75	0.72 (0.37 - 1.25)	Observed < expected	15	23.93	0.63 (0.35 - 1.03)	Observed < expected	18	33.51	0.54 (0.32 - 0.85)	Observed significantly < expected

[a] Incidence Rate (per/100,000 PY) from Truven Market Scan database (2019)

[b] Exposure is to DLP 28 December 2022.

[c] All cases to DLP 28 December 2022.

Truven 14: CVST (I63.6 or I67.6) inpatient without TCP within -1/14 days (incident)

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CVST Cerebral Venous Sinus Thrombosis; IR Incidence Rate; TTO Time To Onset

Table 119 Observed versus expected analysis for CVST (Cerebrovascular venous and sinus thrombosis) without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) stratified by age in the UK

Age group	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
18-49 UK	1.55	14181834	12	12.64	0.95 (0.49 - 1.66)	Observed < expected	13	18.06	0.72 (0.38 - 1.23)	Observed < expected	15	25.28	0.59 (0.33 - 0.98)	Observed significantly < expected
50-59 UK	0.86	12455887	9	6.16	1.46 (0.67 - 2.77)	Observed > expected	12	8.8	1.36 (0.7 - 2.38)	Observed > expected	14	12.32	1.14 (0.62 - 1.91)	Observed > expected
60-69 UK	1.65	9718273	3	9.22	0.33 (0.07 - 0.95)	Observed significantly < expected	5	13.17	0.38 (0.12 - 0.89)	Observed significantly < expected	7	18.44	0.38 (0.15 - 0.78)	Observed significantly < expected
70-79 UK	1.53	6613249	4	5.82	0.69 (0.19 - 1.76)	Observed < expected	5	8.31	0.6 (0.2 - 1.4)	Observed < expected	5	11.64	0.43 (0.14 - 1)	Observed < expected
Over 80 UK	8.21	2655389	1	12.53	0.08 (0 - 0.44)	Observed significantly < expected	1	17.91	0.06 (0 - 0.31)	Observed significantly < expected	3	25.07	0.12 (0.02 - 0.35)	Observed significantly < expected
18-49 UK plus cases Unk TTO	1.55	14181834	15	12.64	1.19 (0.66 - 1.96)	Observed > expected	16	18.06	0.89 (0.51 - 1.44)	Observed < expected	18	25.28	0.71 (0.42 - 1.13)	Observed < expected

Table 119 Observed versus expected analysis for CVST (Cerebrovascular venous and sinus thrombosis) without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) stratified by age in the UK

Age group	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion	Observed number of cases [c]	Expected number of cases	O over E ratio (95% CI)	Conclusion
50-59 UK plus cases Unk TTO	0.86	12455887	13	6.16	2.11 (1.12 - 3.61)	Observed significantly > expected	16	8.8	1.82 (1.04 - 2.95)	Observed significantly > expected	18	12.32	1.46 (0.87 - 2.31)	Observed > expected
60-69 UK plus cases Unk TTO	1.65	9718273	5	9.22	0.54 (0.18 - 1.27)	Observed < expected	7	13.17	0.53 (0.21 - 1.1)	Observed < expected	9	18.44	0.49 (0.22 - 0.93)	Observed significantly < expected
70-79 UK plus cases Unk TTO	1.53	6613249	5	5.82	0.86 (0.28 - 2)	Observed < expected	6	8.31	0.72 (0.26 - 1.57)	Observed < expected	6	11.64	0.52 (0.19 - 1.12)	Observed < expected
Over 80 UK plus cases Unk TTO	8.21	2655389	2	12.53	0.16 (0.02 - 0.58)	Observed significantly < expected	2	17.91	0.11 (0.01 - 0.4)	Observed significantly < expected	4	25.07	0.16 (0.04 - 0.41)	Observed significantly < expected

[a] Incidence Rate (per/100,000 PY) from Truven Market Scan database (2019)

[b] Exposure is to DLP 28 December 2022.

[c] All cases to DLP 28 December 2022.

Truven 14: CVST (I63.6 or I67.6) inpatient without TCP within -1/14 days (incident)

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CVST Cerebral Venous Sinus Thrombosis; IR Incidence Rate; TTO Time To Onset

Table 120 Observed versus expected analysis for CVST (Cerebrovascular venous and sinus thrombosis) without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) stratified by gender (Female) in the UK

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion
Female 18-29	2.46	1109488	1	1.57	0.64 (0.02 - 3.55)	Observed < expected	1	2.24	0.45 (0.01 - 2.49)	Observed < expected	1	3.14	0.32 (0.01 - 1.77)	Observed < expected
Female 30-39	2.23	1892968	2	2.43	0.82 (0.1 - 2.97)	Observed < expected	2	3.47	0.58 (0.07 - 2.08)	Observed < expected	2	4.85	0.41 (0.05 - 1.49)	Observed < expected
Female 40-49	1.84	4412245	4	4.67	0.86 (0.23 - 2.19)	Observed < expected	4	6.67	0.6 (0.16 - 1.54)	Observed < expected	5	9.34	0.54 (0.17 - 1.25)	Observed < expected
Female 50-59	0.82	5944683	4	2.8	1.43 (0.39 -	Observed > expected	5	4	1.25 (0.41 -	Observed > expected	6	5.61	1.07 (0.39 -	Observed > expected

Table 120 Observed versus expected analysis for CVST (Cerebrovascular venous and sinus thrombosis) without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) stratified by gender (Female) in the UK

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion
					3.66)				2.92)				2.33)	
Female 60-69	1.41	4783416	1	3.88	0.26 (0.01 - 1.44)	Observed < expected	3	5.54	0.54 (0.11 - 1.58)	Observed < expected	4	7.76	0.52 (0.14 - 1.32)	Observed < expected
Female 70-79	0.71	3475875	2	1.42	1.41 (0.17 - 5.09)	Observed > expected	3	2.03	1.48 (0.3 - 4.32)	Observed > expected	3	2.84	1.06 (0.22 - 3.09)	Observed > expected
Female over 80	9.32	1630324	0	8.74	0 (0 - 0.42)	Observed significantly < expected	0	12.48	0 (0 - 0.3)	Observed significantly < expected	2	17.47	0.11 (0.01 - 0.41)	Observed significantly < expected
Female 18-29 plus	2.46	1109488	1	1.57	0.64 (0.02	Observed < expected	1	2.24	0.45 (0.01	Observed < expected	1	3.14	0.32 (0.01	Observed < expected

Table 120 Observed versus expected analysis for CVST (Cerebrovascular venous and sinus thrombosis) without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) stratified by gender (Female) in the UK

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion
cases Unk TTO					- 3.55)				- 2.49)				- 1.77)	
Female 30-39 plus cases Unk TTO	2.23	1892968	2	2.43	0.82 (0.1 - 2.97)	Observed < expected	2	3.47	0.58 (0.07 - 2.08)	Observed < expected	2	4.85	0.41 (0.05 - 1.49)	Observed < expected
Female 40-49 plus cases Unk TTO	1.84	4412245	6	4.67	1.28 (0.47 - 2.8)	Observed > expected	6	6.67	0.9 (0.33 - 1.96)	Observed < expected	7	9.34	0.75 (0.3 - 1.54)	Observed < expected
Female 50-59 plus cases Unk TTO	0.82	5944683	5	2.8	1.79 (0.58 - 4.17)	Observed > expected	6	4	1.5 (0.55 - 3.26)	Observed > expected	7	5.61	1.25 (0.5 - 2.57)	Observed > expected

Table 120 Observed versus expected analysis for CVST (Cerebrovascular venous and sinus thrombosis) without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) stratified by gender (Female) in the UK

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	O over E ratio (95 % CI)	Conclusion
Female 60-69 plus cases Unk TTO	1.41	4783416	3	3.88	0.77 (0.16 - 2.26)	Observed < expected	5	5.54	0.9 (0.29 - 2.11)	Observed < expected	6	7.76	0.77 (0.28 - 1.68)	Observed < expected
Female 70-79 plus cases Unk TTO	0.71	3475875	2	1.42	1.41 (0.17 - 5.09)	Observed > expected	3	2.03	1.48 (0.3 - 4.32)	Observed > expected	3	2.84	1.06 (0.22 - 3.09)	Observed > expected
Female over 80 plus cases Unk TTO	9.32	1630324	1	8.74	0.11 (0 - 0.64)	Observed significantly < expected	1	12.48	0.08 (0 - 0.45)	Observed significantly < expected	3	17.47	0.17 (0.04 - 0.5)	Observed significantly < expected

[a] Incidence Rate (per/100,000 PY) from Truven Market Scan database (2019)

[b] Exposure is to DLP 28 December 2022.

[c] All cases to DLP 28 December 2022.

Truven 14: CVST (I63.6 or I67.6) inpatient without TCP within -1/14 days (incident)

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.
CVST Cerebral Venous Sinus Thrombosis; IR Incidence Rate; TTO Time To Onset

Table 121 Observed versus expected analysis for CVST (Cerebrovascular venous and sinus thrombosis) without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) stratified by gender (Male) in the UK

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95% CI)	Conclusion
Male 18-29	1.1	808938	1	0.51	1.96 (0.05 - 10.92)	Observed > expected	1	0.73	1.37 (0.03 - 7.63)	Observed > expected	2	1.02	1.96 (0.24 - 7.08)	Observed > expected
Male 30-39	0.69	1415003	1	0.56	1.79 (0.05 - 9.95)	Observed > expected	1	0.8	1.25 (0.03 - 6.96)	Observed > expected	1	1.12	0.89 (0.02 - 4.97)	Observed < expected
Male 40-49	0.86	4542157	3	2.25	1.33 (0.27 - 3.9)	Observed > expected	4	3.21	1.25 (0.34 - 3.19)	Observed > expected	4	4.49	0.89 (0.24 - 2.28)	Observed < expected
Male 50-59	0.91	6510960	5	3.41	1.47 (0.48 -	Observed > expected	7	4.87	1.44 (0.58 -	Observed > expected	8	6.81	1.17 (0.51 - 2.31)	Observed > expected

Table 121 Observed versus expected analysis for CVST (Cerebrovascular venous and sinus thrombosis) without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) stratified by gender (Male) in the UK

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95% CI)	Conclusion
					3.42)				2.96)					
Male 60-69	1.92	4934728	2	5.45	0.37 (0.04 - 1.33)	Observed < expected	2	7.78	0.26 (0.03 - 0.93)	Observed significantly < expected	3	10.9	0.28 (0.06 - 0.8)	Observed significantly < expected
Male 70-79	2.49	3137304	2	4.49	0.45 (0.05 - 1.61)	Observed < expected	2	6.42	0.31 (0.04 - 1.13)	Observed < expected	2	8.98	0.22 (0.03 - 0.8)	Observed significantly < expected
Male over 80	6.64	1025046	1	3.91	0.26 (0.01 - 1.42)	Observed < expected	1	5.59	0.18 (0 - 1)	Observed significantly < expected	1	7.83	0.13 (0 - 0.71)	Observed significantly < expected

Table 121 Observed versus expected analysis for CVST (Cerebrovascular venous and sinus thrombosis) without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) stratified by gender (Male) in the UK

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95% CI)	Conclusion
Male 18-29 plus cases Unk TTO	1.1	808938	1	0.51	1.96 (0.05 - 10.92)	Observed > expected	1	0.73	1.37 (0.03 - 7.63)	Observed > expected	2	1.02	1.96 (0.24 - 7.08)	Observed > expected
Male 30-39 plus cases Unk TTO	0.69	1415003	1	0.56	1.79 (0.05 - 9.95)	Observed > expected	1	0.8	1.25 (0.03 - 6.96)	Observed > expected	1	1.12	0.89 (0.02 - 4.97)	Observed < expected
Male 40-49 plus cases Unk TTO	0.86	4542157	4	2.25	1.78 (0.48 - 4.55)	Observed > expected	5	3.21	1.56 (0.51 - 3.63)	Observed > expected	5	4.49	1.11 (0.36 - 2.6)	Observed > expected
Male 50-59 plus	0.91	6510960	8	3.41	2.35 (1.01 -	Observed significantly > expected	10	4.87	2.05 (0.98 -	Observed > expected	11	6.81	1.62 (0.81 - 2.89)	Observed > expected

Table 121 Observed versus expected analysis for CVST (Cerebrovascular venous and sinus thrombosis) without thrombocytopenia (with known normal platelet count) (using Truven 14 incident rates) stratified by gender (Male) in the UK

Age group/ Gender	IR [a]	Exposure [b]	Risk Window 21 Days				Risk Window 30 Days				Risk Window 42 Days			
			Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95 % CI)	Conclusion	Observed number of cases[c]	Expected number of cases	Over E ratio (95% CI)	Conclusion
cases Unk TTO					4.62)				3.78)					
Male 60-69 plus cases Unk TTO	1.92	4934728	2	5.45	0.37 (0.04 - 1.33)	Observed < expected	2	7.78	0.26 (0.03 - 0.93)	Observed significantly < expected	3	10.9	0.28 (0.06 - 0.8)	Observed significantly < expected
Male 70-79 plus cases Unk TTO	2.49	3137304	3	4.49	0.67 (0.14 - 1.95)	Observed < expected	3	6.42	0.47 (0.1 - 1.37)	Observed < expected	3	8.98	0.33 (0.07 - 0.98)	Observed significantly < expected
Male over 80 plus cases Unk TTO	6.64	1025046	1	3.91	0.26 (0.01 - 1.42)	Observed < expected	1	5.59	0.18 (0 - 1)	Observed significantly < expected	1	7.83	0.13 (0 - 0.71)	Observed significantly < expected

[a] Incidence Rate (per/100,000 PY) from Truven Market Scan database (2019)
[b] Exposure is to DLP 28 December 2022.
[c] All cases to DLP 28 December 2022.

Truven 14: CVST (I63.6 or I67.6) inpatient without TCP within -1/14 days (incident)

Only cases observed within 0-21, 0-30 and 0-42 days were included; Risk window: 21, 30 and 42 days.

CVST Cerebral Venous Sinus Thrombosis; IR Incidence Rate; TTO Time To Onset

Literature

A periodic literature search of the databases in Embase, InsightMeme and PubMed was conducted for relevant articles on CVST without Thrombocytopenia in association with VAXZEVRIA.

The search yielded 287 articles of which 5 articles were considered relevant for further evaluation and presentation. The remaining articles were not considered as relevant and therefore will not be discussed (as they discussed CVST in the context of Vaccine-Induced Thrombotic Thrombocytopenia (VITT), TTS, or CVST with thrombocytopenia; contained information on unspecified COVID-19 vaccines; or did not provide sufficient information to make a meaningful assessment).

Study articles identified during the reporting period:

Krzywicka et al 2022 reported an age-stratified risk of CVST with and without thrombocytopenia after SARS-CoV-2 vaccination. They estimated the absolute risk of CVST with and without thrombocytopenia within 28 days of a first dose of four SARS-CoV-2 vaccinations using data from the European Medicines Agency's EudraVigilance database (until 13 June 2021). As a denominator, they used data on vaccine delivery from 31 European countries. For 22.8 million adults from 25 countries, they estimated the absolute risk of CVST after the first dose of VAXZEVRIA per age category. The absolute risk of CVST with and without thrombocytopenia, within 28 days of first-dose vaccination was 7.5 (95% confidence interval [CI] 6.9–8.3), 0.7 (95% CI 0.2–2.4), 0.6 (95% CI 0.5–0.7), and 0.6 (95% CI 0.3–1.1) per million of first doses of VAXZEVRIA, Ad26.COV2.S, BNT162b2, and mRNA- 1273, respectively. In recipients of VAXZEVRIA, the absolute risk of CVST without thrombocytopenia, was the highest in the 18- to 24-year-old group (3.7 per million, 95% CI 1.0–13.3). The overall absolute risk of CVST without thrombocytopenia for VAXZEVRIA vaccination, 3.2 (95% CI 2.8–3.7) per million, was the highest of all vaccines. The remaining 3 vaccines showed absolute risks of 0.6 (95% CI 0.3–1.1), 0.5 (95% CI 0.4–0.7), and 0.0 (95% CI 0.0–1.3) for mRNA-1273, BNT162b2, and Ad26.COV2.S, respectively. The age-stratified risk of CVST without thrombocytopenia after VAXZEVRIA vaccination, was the highest in the 18- to 24-year-old group (3.7 [95% CI 1.0–13.3]) and the lowest in the 60- to 69-year-old and ≥70-year-old groups (1.1 [95% CI 0.6–2.0] and 1.1 [95% CI 0.5–2.6]). They found an increased rate of CVST without thrombocytopenia in recipients of VAXZEVRIA compared to the other vaccines.

AZ Comment: The main strength of this study is its multinational population-based approach, implemented in the European setting of pharmacovigilance, which includes centralized and updated registries of both vaccine delivery and adverse reactions. However, the findings in this report are subject to several limitations. Underreporting of thrombocytopenia among earlier cases with CVST is plausible, particularly before March 2021 when details of this new condition were not yet known. In addition, reporting bias associated with increased surveillance of vaccine recipients, and particularly younger people, cannot be excluded. Moreover, reporting practices likely differed over time, per

country, and per vaccine. Second, age stratified data on vaccine delivery were available for only 25 European countries, leading to the exclusion of a substantial number of reports that originated from other European countries. The overall risk analysis was based on 61.7 million first doses of VAXZEVRIA vaccine administered, whereas the age-stratified analysis was based on 22.8 million administered first doses of the VAXZEVRIA vaccine. Lastly, the data collected refer only to European countries (EEA countries and the United Kingdom); thus, the risk estimates might not be generalizable to the entire population of persons who have received SARS-CoV-2 vaccines.

Perry et al 2021 in a multicentre cohort study, did direct comparison between 70 patients with VITT-associated cerebral venous thrombosis and 25 patients who developed cerebral venous thrombosis after vaccination but did not have VITT, in addition to secondary comparisons with a large historical cohort with cerebral venous thrombosis. They included data between 01 April 2021 and 20 May 2021, of 99 patients from collaborators in 43 hospitals across the UK. Four patients were excluded because they did not have definitive evidence of cerebral venous thrombosis on imaging. Of the remaining 95 patients, 70 had VITT and 25 did not. The median age of the VITT group (47 years, IQR 32–55) was lower than in the non-VITT group (57 years; 41–62; p=0·0045). Patients with VITT-associated cerebral venous thrombosis had more intracranial veins thrombosed (median three, IQR 2–4) than non-VITT patients (two, 2–3; p=0·041) and more frequently had extracranial thrombosis (31 [44%] of 70 patients) compared with non-VITT patients (one [4%] of 25 patients; p=0·0003). The primary outcome of death or dependency occurred more frequently in patients with VITT-associated cerebral venous thrombosis (33 [47%] of 70 patients) compared with the non-VITT control group (four [16%] of 25 patients; p=0·0061). Their results showed that, when they are compared with those without VITT, patients with VITT-associated cerebral venous thrombosis were younger, had fewer venous thrombosis risk factors, and were more likely to have been given the ChAdOx1 vaccine. They developed more extensive cerebral venous thrombosis with more veins or sinuses thrombosed, and multiple intracerebral haemorrhage was more common. They were more likely to have concurrent extracranial venous or arterial thromboses. Their outcomes at the end of hospital admission were worse, with higher rates of death and disability. The ratio of patients with VITT to patients without VITT was 2.8:1, as expected from the estimated incidence of VITT-associated cerebral venous thrombosis in individuals receiving a first dose of the VAXZEVRIA vaccine (12·3 per million) and the expected background incidence of cerebral venous thrombosis in the same subpopulation during the 4-month study period (4·4 per million), suggesting that cerebral venous thrombosis was probably unrelated to vaccination in most or all of their non-VITT cases.

AZ Comment: This is a detailed study of comparison between VITT-associated cerebral venous thrombosis, with a well-matched control group consisting of patients presenting to UK hospitals with cerebral venous thrombosis after vaccination against COVID-19 but without evidence of VITT. This study shows that the clinical phenotype, severity, and outcome of VITT-associated cerebral venous thrombosis is distinct from that of non- VITT cerebral venous thrombosis. However, this study has some limitations. The number of patients in each group in this study was small, because of the rarity of these conditions. The

study was underpowered for some of the comparisons made between the VITT and non-VITT groups. Comparison of the patients with the much larger historical ISCVT cohort might have been confounded by the higher age of patients in this study, attributable to COVID-19 vaccination policy in the UK. Although this study will generate important hypotheses for future research, we cannot draw inferences about other populations of patients with cerebral venous thrombosis after COVID-19 vaccination.

(Two articles included from the same author included in the below summary)

Sánchez van Kammen, Heldner et al 2021 in a descriptive analysis of a retrospective consecutive sample of 865 patients with cerebral venous sinus thrombosis (CVST) from 1987 to 2018 (prior to COVID-19 pandemic), reported that, baseline thrombocytopenia was observed in 8.4% of patients, and heparin-induced thrombocytopenia (HIT) was diagnosed in 0.1%. In a convenience sample subset of 93 patients with plasma available for additional laboratory analysis (including 8 who had thrombocytopenia), none had platelet factor 4 (PF 4)/heparin antibodies. They concluded that in patients with cerebral venous sinus thrombosis prior to the COVID-19 pandemic, baseline thrombocytopenia was uncommon, and heparin-induced thrombocytopenia and platelet factor 4/heparin antibodies were rare.

In another article published by the same author (Sánchez van Kammen, Aguiar de Sousa et al 2021), a cohort study used data from an international registry of consecutive patients with CVST within 28 days of SARS-CoV-2 vaccination included between 29 March 2021 and 18 June 2021, from 81 hospitals in 19 countries. For reference, data from patients with CVST between 2015 and 2018 (prior to COVID-19 pandemic) were derived from an existing international registry. Clinical characteristics and mortality rate were described for adults with (1) CVST in the setting of SARS-CoV-2 vaccine–induced immune thrombotic thrombocytopenia, (2) CVST after SARS-CoV-2 vaccination not fulling criteria for TTS, and (3) CVST unrelated to SARS-CoV-2 vaccination.

Of 116 patients with postvaccination CVST, 78 (67.2%) had TTS, of whom 76 had been vaccinated with ChAdOx1 nCov-19; 38 (32.8%) had no indication of TTS. The control group included 207 patients with CVST before the COVID-19 pandemic. A total of 63 of 78 (81%), 30 of 38 (79%), and 145 of 207 (70.0%) patients, respectively, were female, and the mean (SD) age was 45 (14), 55 (20), and 42 (16) years, respectively. Concomitant thromboembolism (TE) occurred in 25 of 70 patients (36%) in the TTS group, 2 of 35 (6%) in the no TTS group, and 10 of 206 (4.9%) in the control group, and in-hospital mortality rates were 47% (36 of 76; 95% CI, 37-58), 5% (2 of 37; 95% CI, 1-18), and 3.9% (8 of 207; 95% CI, 2.0-7.4), respectively. Only one patient in the TTS group and 1 in the no TTS group were COVID-19 positive. In the TTS group 93% patients had moderate to severe thrombocytopenia and 91% tested positive for anti PF-4 antibodies. In this study, patients with CVST after recent SARS-CoV-2 vaccination who fulfilled the criteria for TTS had a severe clinical profile, with high rates of coma and intracerebral haemorrhage at presentation, high rates of concomitant thromboembolism, and death due to brain herniation occurring in approximately half of all patients. This clinical profile was distinct from both patients with post vaccination CVST who did not fulfil the criteria for TTS as well as a control group of patients with CVST from prior to the COVID-19

pandemic. In contrast, patients with post vaccination CVST who did not fulfil the TTS criteria were largely similar to those in the control group with CVST before the COVID-19 pandemic, with regard to clinical manifestations, outcome and prognosis.

AZ Comment: The first study shows that prior to the COVID-19 pandemic, baseline thrombocytopenia was uncommon in CVST patients (8%), and platelet factor 4/heparin antibodies were rare. From the second study one can infer that probably the cases of CVST without thrombocytopenia (non-TTS CVST) are coincidental and comparable to CVST cases prior to the COVID-19 pandemic. However, the study has several limitations. First, the lack of central adjudication of CVST diagnosis and study outcome measures is a possible source of imprecision and bias. The authors have focused their analysis mainly on hard end points, such as mortality. Second, information was available up to hospital discharge only, precluding evaluation of the long-term consequences of CVST, which should be the focus of future studies. Third, differences in patients with post vaccination CVST and the historical control group should be considered. For example, many countries used different SARS-CoV-2 vaccines for different age groups, and pregnant women were partly excluded from SARS-CoV-2 vaccination at the time of study recruitment. Furthermore, the post vaccination CVST cohort included patients from countries not included in the historical control group, each with their own unique health care context. The limited sample size precluded them from performing a secondary analysis comparing only cases from similar countries.

Kan et al 2022 applied basic disproportionality analysis to identify trends in reporting embolic and thrombotic events (ETEs) after COVID-19 vaccination in the spontaneous Vaccine Adverse Event Reporting System (VAERS) based on the vaccine type in the United States. In this retrospective, pharmacovigilance study, they analysed the VAERS reports from 01 January 2020 to 18 June 2021, and performed signal detection and time-to-onset analysis of adverse events by calculating the reported odds ratio (ROR) to understand ETE trends after COVID-19 vaccination based on the vaccine type. The exposure to COVID-19 vaccination, was stratified by two platforms: mRNA and adenovirus viral vector vaccines. Between 01 January 2020 and 18 June 2021; 345,779 individuals were reported to have received COVID-19 vaccinations according to VAERS, of which 8,849 (2.6%) were reported to have thromboembolism. Out of 8849, 7144 ETEs were reported for mRNA and 1705 ETEs for adenovirus vector-based vaccines. Nine adverse events associated with ETEs were reported following the administration of viral vector vaccines (lower limit of the 95% CI of the ROR was >1). In particular, CVST and superficial thrombophlebitis showed a high ROR. The median time to ETE onset was 6 (interquartile range (IQR): 2–17) days for mRNA vaccines, and 11 (interquartile range: 4–21) days for viral vector vaccines. This analysis suggested a stronger CVST signal for Adenovirus (ADV – JCOVDEN) compared to mRNA-based (COMIRNATY, ELASOMERAN/SPIKEVAX) COVID-19 vaccines.

AZ Comment: The authors acknowledged several limitations to the study. VAERS is designed for passive surveillance and includes Adverse Events (AE) that are spontaneously reported by consumers eg, patients, Healthcare professionals, or manufacturers. The inherent reporting bias due to underreporting (owing to lack of awareness/compliance with reporting

requirements) and overreporting (owing to increased awareness due to media coverage, among others) are major limitations to any analysis conducted in VAERS. Furthermore, the spontaneous datasets routinely miss key information for proper stratification eg, demographics (age and gender), and risk factors such as medical history and concomitant medications and pre-empt any conclusions on causal relationship. VAERS data covers only the US, where the use of adenovirus COVID-19 vaccines was rather short/limited. More importantly, the AstraZeneca vaccine was never used in the USA. Thus, the disproportionality analysis, which was used to assess the risk of ETEs following adenovirus COVID-19 vaccines in this study, may not be appropriate to allow reliable assessment.

Overall comment on literature section: Thrombocytopenia was uncommon in CVST cases prior to the COVID-19 pandemic. CVST without thrombocytopenia has a milder phenotype (in terms of presentation, severity, and outcome). This is comparable to the CVST cases seen prior to the pandemic. The study by Kan et al 2022 and the other literature articles discussed above did not establish a definitive causal relationship between VAXZEVRIA and CVST in absence of TCP.

Summary

AstraZeneca continued to review the safety information for CVST without thrombocytopenia from sources including clinical trials, post-marketing reports, and the published literature for the reporting period.

There were no case reports indicating recurrence (after the first and second dose of the vaccine). There are 597 and 37 cases for the cumulative and reporting period respectively. Out of the 597 cases, 99 % of the reported cases were serious, 51 (8.5%) had a seriousness criteria of Fatal, and 131 (21.9%) Life-threatening. Median age was 51 years. There was a preponderance for female gender (60.8%) versus males (35%), and 68.5% cases were in age group 18-64 years. Cumulatively, 29 (56.8%) out of all 51 fatal cases were reported in females. There was no significant difference noted between the cumulative and reporting period in terms of the safety patterns and distribution of cases.

Of the total number of case reports cumulatively, 353 (59.1%) were medically confirmed.

Cumulatively, One (1) case met WHO-UMC causality criteria for Probable/Likely and 1 case for Conditional/Unclassified. 373 were considered as Possible, Out of 373, 145 (38.8%) were identified with relevant risk/confounding factors.

A review of the published literature did not identify any new safety information on this topic in association with VAXZEVRIA.

The results of observed versus expected analysis showed observed cases were more than expected in the general population globally. The age stratifications suggest that the O/E ratio is higher in younger age groups than in the older age groups and that the O/E ratio is higher in females than in males. However, it is important to note that O/E analyses are complementary to routine signal detection methods, and are not designed to determine a

causal relationship; confounding factors were not considered in O/E (such as possible COVID-19 infections or other possible causes for CVST without thrombocytopenia).

CVST without thrombocytopenia is an important potential risk in the VAXZEVRIA Core Risk Management Plan and the topic will continue to be kept under close surveillance by AstraZeneca.

Conclusion

From the data identified during the reporting period and also taking into account the cumulative experience, AstraZeneca considers that there is currently insufficient evidence of a reasonable possibility of causal relationship between VAXZEVRIA and CVST without thrombocytopenia. CVST without thrombocytopenia is included in section 4.4 (section 4.4 Warnings and Precautions) of the CDS to inform prescribers that these events may require different treatment approaches than TTS. Healthcare professionals should consult applicable guidance. No changes to the CDS or product leaflets are warranted at this time.

AstraZeneca will continue to monitor safety information for CVST without thrombocytopenia as an important potential risk and take further actions as deemed appropriate.

16.3.1.2 Immune-mediated neurological conditions

Immune-mediated neurological condition is considered as an important potential risk for VAXZEVRIA as per the AstraZeneca Core RMP.

During the reporting interval of the PBRER, AstraZeneca had received assessment report from the PRAC (EMEA/H/C/PSUSA/00010912/202206), requesting ADEM to be addressed in the next PSUR on 'Acute Disseminated Encephalomyelitis' which is discussed in section 15.2.1.

Reviews of specific topics relating to Immune-mediated neurological conditions/ Nervous system disorders, including immune-mediated neurological conditions with VAXZEVRIA, including Encephalitis, and Transverse myelitis (TM), as requested by PRAC for inclusion in the previous PBRER (DLP 28 June 2022) are continued in this PBRER.

During the period covered by this report (29 June 2022 – 28 December 2022), a total of 2609 cases from literature, interventional studies, non-interventional studies and spontaneous sources were reported within the concept of immune-mediated neurological disorders. Out of the 2609 cases, 873 (33.5%) were medically confirmed (serious 429 (49.14%), non-serious 444 (50.86%)) and 1736 (66.5%) were consumer reports (serious 561 (32.32%), non-serious 1175 (67.68%)). The 2609 cases had 3135 PTs. The most commonly reported PTs were Paraesthesia (1289), Hypoaesthesia (924), Guillain-Barre syndrome (GBS) (189), Neuralgia (176), Sensory disturbance (116), Sensory loss (59), Neuropathy peripheral (53), Multiple sclerosis (30), Myelitis transverse (28), Encephalitis (25), Small fibre neuropathy (23), Optic neuritis (18), Polyneuropathy (18), Chronic inflammatory demyelinating polyradiculoneuropathy (17), Demyelination (17), Acute disseminated encephalomyelitis

(15), Multiple sclerosis relapse (11), Neuritis (10), Noninfective encephalitis (10), Miller Fisher syndrome (9), Myelitis (9), Peripheral sensory neuropathy (8), Encephalitis autoimmune (7), Encephalopathy (7), Demyelinating polyneuropathy (6), Myelin oligodendrocyte glycoprotein antibody-associated disease (6), Encephalomyelitis (5), Myelopathy (4), Posterior reversible encephalopathy syndrome (4), Limbic encephalitis (3), Loss of proprioception (3), Neuromyelitis optica spectrum disorder (3), Autoimmune encephalopathy (2), Clinically isolated syndrome (2), Encephalitis brain stem (2), Hypertensive encephalopathy (2), Multifocal motor neuropathy (2), Peripheral motor neuropathy (2), Peripheral sensorimotor neuropathy (2), Relapsing-remitting multiple sclerosis (2), Acute motor axonal neuropathy (1), Acute motor-sensory axonal neuropathy (1), Acute polyneuropathy (1), Amyotrophy (1), Axonal and demyelinating polyneuropathy (1), Axonal neuropathy (1), Encephalitis post immunisation (1), Hypoxic-ischaemic encephalopathy (1), Immune-mediated encephalitis (1), Immune-mediated neurological disorder (1), Immune-mediated neuropathy (1), Neuropathic muscular atrophy (1), Noninfective encephalomyelitis (1), Paroxysmal extreme pain disorder (1), Secondary progressive multiple sclerosis (1), Sensorimotor disorder (1), Tick paralysis (1).

Cumulatively till 28 December 2022, a total of 38164 cases from literature, clinical studies, non-interventional studies and spontaneous sources were reported within the concept of immune-mediated neurological disorders. Out of the 38164 cases, 8340 (21.9%) were medically confirmed (3552 (42.6%) serious, 4788 (57.4%) non-serious) and 29824 were consumer reports (14439 (48.4%) serious, 15385 (51.6%) non-serious.

Literature review in the reporting period: A literature search for reporting interval (29 June 2022 to 28 December 2022) of the databases in Embase, InsightMeme and PubMed was conducted for relevant articles on topic in association with VAXZEVRIA.

The search yielded 81 articles of which 2 articles were considered relevant for further evaluation and presentation.

Study articles identified cumulatively / during the reporting period:

García-Grimshaw et al 2022 performed a retrospective study through passive epidemiological surveillance, aiming to report GBS incidence as Adverse Event Following Immunization (AEFI) among adult (> 18 years) recipients of 81,842,426 doses of seven COVID-19 vaccines between 24 December 2020 and 29 October 2021.

Authors identified that according to the Mexican Health Ministry, in 2019, the nationwide reported GBS incidence as 0.71 cases per 100,000 person-years. In the study, the authors recognized 31,095 case reports from the Mexican epidemiological surveillance system. Out of 31,095 reports, 816 of them (2%) were considered serious, and among those, 111 reports were identified with potential GBS (as per Asbury criteria), where 11 cases were excluded since had an alternative diagnosis; having in total 97 cases with confirmed GBS (observed incidence of 1.19 per 1,000,000 cases). Majority were related with male patients (53.6%), and the median age was 44. It was mentioned that the overall observed GBS incidence was 1.19

(95% CI 0.97-1.45) cases per 1.000.000 administered doses, being the higher observed incidences recognized from JCOVEN (3.86 cases per 1.000.000), following with COMINARTY (1.92 cases per 1.000.000), then VAXZEVRIA (0.96 cases per 1.000.000), this last, with lower incidence than reported in the United Kingdom National Immunoglobulin Database (8,7 per 1,000,000 first doses administered).

Subsequently, as a conclusion, the authors agreed that GBS was a very infrequent AEFI among recipients of all vaccines against SARS-CoV-2.

AstraZeneca comment:

The company acknowledges the authors' findings of a very small frequency of GBS among recipients of COVID-19 vaccines including VAXZEVRIA. The article relied on an unusually large population of vaccine recipients in relationship with several COVID-19 vaccines. The observed incidence of GBS in following Mexican Health Ministry was less than the expected incidence. Due to limitation of this study design, any further characterization in particular GBS patterns, was not reported by the authors. An indirect comparison of incidence rates in Mexico versus incidence rates in UK, as reported by the authors is considered imprecise, based on differences in environmental factors. The AE of GBS is already included in the existing language on demyelinating disorders in the section 4.4 of the CDS.

Tamborska et al 2022 conducted a UK-wide, open-access, online system surveillance study from 01 January 2021 to 30 June 2021; open to any clinician to report neurological adverse events following any SARS-CoV-2 vaccination, aiming to capture clinical and demographic information on the cases of GBS following SARS-CoV-2 vaccines, and to evaluate the causal association. Article focused on a total of 70 reports of GBS following COVID-19 vaccines, 67 (96%) of them (65 with 1st dose and 2 with 2nd dose) received VAXZEVRIA, and 3 (4%) COMIRNATY (all 1st dose). Median age of the patients was 59 years, in majority patients were male (51%), and the median time to onset was 15 days. Since the published Brighton Collaboration Criteria do not apply for all GBS variants, a modified Brighton criteria (BC) collaboration was created and used by authors to identify the level of certainty. From the 70 reports, 33 fulfilled the criteria for BC 1 and 28 fulfilled for BC 2. No patients fulfilled for BC 3. Considering the WHO-UMC causality assessment, the authors also provided a modified algorithm, since there is no previous literature confirming an association between GBS and SARS-CoV-2 vaccines. Considering the proposed causality assessment criteria, authors provided the assessment of 'Probable' to 56 reports (80%) out of 70 cases, since vaccinees experienced GBS within 6 weeks after vaccination, and no other causes were found; 12 reports (17%) were considered 'Possible' (2 of them with COMIRNATY), either because timeframe was plausible but not typical or due to other possible cause for GBS, and 2 reports (1 of them with COMIRNATY) were considered 'Unlikely' due to proven alternative cause related with GBS. The authors also correlated the information with Patone et al 2021 article, suggesting an increased risk of GBS from 2 weeks after the 1st dose of VAXZEVRIA, with an incidence rate ratio of 2.90 (95% CI 21.5 to 3.95) at 15-21 days, providing an estimate 38 excess GBS cases per 10million vaccines, compared with 145 excess cases per 10million people infected with SARS-CoV-2. In conclusion, authors

considered that most reports of GBS followed 1st dose with VAXZEVRIA, and despite it was not possible to refuse causation, the contemplation of the absence of alternative aetiologies, different than expected age distribution and the presence of unusual clinical features support a causal link.

AstraZeneca comment:

The company acknowledges the authors' suggestion regarding VAXZEVRIA's first dose being associated with GBS risk.

However, the company also considers some limitation as a possible reporting bias for the online surveillance open to only clinicians, use of a non-validated diagnosis classification criteria and non-validated causality criteria (possibility of assessors' bias), and in addition, the article didn't provide sufficient case details to replicate classification and causality assessment. Also, in congruence with authors extrapolated the findings of Patone et al 2021, article however, in this article COVID-19 infections could not be ruled out as a possibility in the cases included in the study.

Overall Conclusion for Immune Mediated Neurological Conditions:

It is AstraZeneca's opinion that no further changes to the VAXZEVRIA CDS, RMPs, corresponding local labels or product leaflets are warranted based on the review of currently available information. Immune-mediated neurological conditions will continue to be closely monitored as part of AstraZeneca's ongoing surveillance efforts for the important potential risk of immune-mediated neurological conditions.

16.3.1.2.1 Encephalitis, including fatal

Review of Cases (Interval period 29 June 2022 – 28 December 2022)

A search of the AstraZeneca global safety database was conducted for the reporting period (29 June 2022 to 28 December 2022) for adverse event reports of encephalitis using the narrow MedDRA SMQ: Noninfective Encephalitis (excluding PT of Acute disseminated encephalomyelitis) and HLT: Encephalopathy with VAXZEVRIA.

The above search identified 70 case reports (25 were initial case reports and 45 were follow-up reports), in vaccinees who received VAXZEVRIA. Cumulatively, till 28 December 2022, there are 385 cases of encephalitis received, out of which 13 cases were reported with fatal outcome. The below summary will present the data received during the reporting interval.

Out of the 70 reports, 16 (22.9%) were from Germany, 10 (14.3%) cases were reported from the United Kingdom, 7 (10.0 %) cases each from Brazil and India, 5 (7.1%) cases from Poland, 4 (5.7%) cases from Canada, 3 (4.3 %) cases each were reported from Australia, France, Mexico, United States, 1 (1.4%) case each from Austria, China, Cyprus, Greece, Italy, Republic of Korea, Peru, Slovenia, Spain.

Table 122 Distribution of MedDRA PTs (n = 77) pertaining to Encephalitis with VAXZEVRIA received during the reporting period

MedDRA PT	Serious	Non-serious	Grand Total
Encephalitis	25	0	25
Noninfective encephalitis	10	0	10
Encephalitis autoimmune	7	0	7
Encephalopathy	7	0	7
Myelin oligodendrocyte glycoprotein antibody-associated disease	6	0	6
Encephalomyelitis	5	0	5
Posterior reversible encephalopathy syndrome	4	0	4
Limbic encephalitis	3	0	3
Autoimmune encephalopathy	2	0	2
Encephalitis brain stem	2	0	2
Hypertensive encephalopathy	2	0	2
Encephalitis post immunisation	1	0	1
Hypoxic-ischaemic encephalopathy	1	0	1
Immune-mediated encephalitis	1	0	1
Noninfective encephalomyelitis	1	0	1

MedDRA Medical Dictionary for Regulatory Activities; PT Preferred Term

The breakdown and overview of these 70 cases reporting 77 events of topics were presented in the below Table 123.

Table 123 Overview of Encephalitis events/cases for the interval period

Parameter	Break-down	Values (%)
Case Count	Medically confirmed	43 (61.42%)
Case Report Source	Interventional Clinical study	00 (0.00 %)
	Non-interventional study	00 (0.00 %)
	Spontaneous[a]	50 (51.02%)
	Literature	20 (20.41%)
	Regulatory	28 (28.57%)
Sex	Female N (%)	36 (51.43%)
	Male N (%)	27 (38.57%)
	Unknown/not reported N (%)	07 (10.00%)
Age Group	18-65 years	53 (75.7%)
	>65 Years	08 (11.4%)
	Unknown	09 (12.9%)
	Median age (range)	45 years (19 to 75)

Table 123 Overview of Encephalitis events/cases for the interval period

Parameter	Break-down	Values (%)
Event occurrence with dose[b]	Dose 1 (%)	42 (89.36%)
	Dose 2 (%)	05 (10.64%)
	Dose 3 (%)	00 (0.00%)
	Dose 4 (%)	00 (0.00%)
	Multiple Doses	00 (0.00%)
	Unknown dose	23
Case level -TTO (days)	0-1	03 (4.29%)
	2-42	34 (48.57%)
	>42 days	05 (7.14%)
	Unknown	28 (40.0%)
	Median TTO (range)	11 (0 to 405)
AE Outcome	Recovered	15 (21.43%)
	Recovering	09 (12.86%)
	Recovered with sequelae	04 (5.71%)
	Not recovered	15 (21.43%)
	Fatal [c]	02 (2.86%)[c]
	Unknown	25 (35.71%)
Duration of recovered/recovered with sequelae events	Range (days)[d]	05 to 619
	Mean (days)	19
	Unknown duration (number of events)	10

[a] Spontaneous case counts also includes regulatory source counts.
[b] Known dose information used to calculate the percentage for the case reports.
[c] Two fatal events were reported in 2 cases (2 follow up cases).
[d] Event recovery duration information is present only in 9 cases.
AE Adverse Event; TTO Time To Onset

The frequently co-reported events in case reports for Encephalitis during the reporting period included Fatigue, Headache, Pyrexia, Hypoaesthesia, and Confusional state.

Events with fatal outcome

Of the 70 total events reported, 2 (2.85%) events were reported with a fatal outcome, both medically confirmed. Summary of these case reports with details are presented below.

[redacted] A literature case was received from Australia concerning a 75-year-old female patient, who experienced a fatal event of Acute Haemorrhagic Necrotizing Encephalopathy (ANE). The patient had a medical history of eosinophilic granulomatosis with polyangiitis (EGPA), hypertension, ischemic heart disease, hypercholesterolemia, monoclonal gammopathy and hospitalization (dates not reported). The patient was on concomitant cefalexin for a presumed urinary tract infection (UTI), hydrochlorothiazide,

amlodipine and simvastatin. Past drug therapy included corticosteroids and azathioprine (unspecified indication). The patient presented to the hospital with an altered level of consciousness and dysarthria 2 days after receiving her first dose of the VAXZEVRIA. Patient was dysarthric with no other lateralizing neurological signs. Patient had two successive generalized tonic clonic seizures which resulted in a sustained drop in conscious state necessitating endotracheal intubation and broad-spectrum antimicrobial agents were commenced for possible infective encephalitis, together with levetiracetam as treatment for seizures. Computed tomography (CT) brain, CT angiogram, CT venogram and CT perfusion imaging were normal. Cerebrospinal fluid (CSF) cell counts were within normal limits with a markedly elevated CSF protein of 2.98 g/L (reference range 0.15-0.45 g/L). Electroencephalogram (EEG) showed diffuse slowing and frequent triphasic waves consistent with widespread cortical dysfunction. Cerebral magnetic resonance imaging (MRI) showed extensive bilateral and symmetrical T2 hyperintense abnormalities in the thalami and medial temporal lobes, along with scattered punctate foci of diffusion restriction and petechial haemorrhage. Repeat scan 4 days later showed progression of disease. Testing of the patient's serum for SARS CoV-2 antibodies was negative. Extensive testing for other viral, autoimmune, and paraneoplastic antibodies was unrevealing. It was reported that, the clinical presentation and investigations were most consistent with acute haemorrhagic necrotizing encephalopathy (ANE) which was treated with intravenous immunoglobulins followed by nasogastric prednisolone. The patient passed away 1 month after illness onset. It was not known whether an autopsy was performed. The cause of death was acute haemorrhagic necrotizing encephalopathy.

AZ comment: The case was assessed as level 2 as per BCC criteria since patient had neurological symptoms such as altered level of consciousness and dysarthria along with positive EEG and MRI findings. The TTO of 2 days is considered as reasonable. The WHO UMC causality in this case was assessed as possible with confounders. The confounders were medical history of EGPA, monoclonal gammopathy, concurrent UTI, hypertension and ischemic heart disease.

[redacted] This case was received from a HCP concerning a 70-years old female vaccinee from Brazil, who had a fatal event of encephalitis. The vaccinee experienced onset of encephalitis 6 days following VAXZEVRIA (unspecified dose) and after an unspecified duration and clinical course experienced a fatal outcome. The medical history was not reported, however the vaccinee was on multiple medications usually prescribed for diabetes (insulin and oral anti-diabetic drugs), hypertension (enalapril, amlodipine, hydrochlorothiazide), dyslipidemia (valsartan), cardiovascular pathology (propranolol, warfarin). The vaccinee was also on cocaine (as reported). Limited etiological work-up was done (complete blood counts, liver function tests (LFT), renal function tests, serum electrolytes, inflammation markers, MRI, angiography, virology markers (Anti-HCV), syphilis, rheumatoid factor and ANCA) without any information on biopsy or autopsy. The significant positive findings were T2/ Fluid-Attenuated Inversion Recovery (FLAIR) hypersignal foci in the bilateral periventricular white matter without diffusion restriction ('probably related to 'microangiopathy', aneurysms in carotid vessels and anaemia.

AZ comment: The diagnostic certainty can be conservatively considered as BCC3 based on suggestive radiological findings and encephalopathy. The TTO of encephalitis onset is reasonable. Elderly age, possible chronic co-morbid conditions of diabetes, hypertension, dyslipidemia, Cardiovascular Disease (CVD) as suggested by concomitant medications and suggested radiological finding of angiopathy in backdrop of carotid aneurysms can be considered as possible confounders for morbidity and mortality. However, due to insufficient information on autopsy details, cocaine use details and exact clinical course of encephalitis, the WHO-UMC causality is assessed as Possible with limited information.

Review of cases using BCC and causality assessment using WHO-UMC Criteria

Brighton Collaboration Criteria

All the cases during the interval period have been reviewed and analysed using Brighton Collaboration (BCC) classification, summarized along with cumulative data in below sections.

The Brighton collaboration criteria for diagnostic certainty (Law B 2021) was used for the review of the data available in the case reports during the interval period (29 June 2022 – 28 December 2022).

The BCC and WHO-UMC causality assessment performed for these cases is provided in the following Table 124.

Table 124 Overview of BCC and WHO-UMC Causality Assessments / for case reports of (Encephalitis) with VAXZEVRIA reported during the reporting period

WHO-UMC/BCC Level	Level 1	Level 2	Level 3	Level 4	Level 5	Grand Total
Certain	0	0	0	0	0	0
Probable/Likely	0	0	0	0	0	0
Possible with risk factors/confounders	0	1	3	1	0	5
Possible with limited information	0	4	11	15	0	30
Unassessable/Unclassifiable with limited information	0	1	3	21	1	26
Unassessable/Unclassifiable with risk factors/confounders	0	0	1	0	0	1
Unlikely	0	0	1	7	0	8
Conditional /Unclassified	0	0	0	0	0	0
Total	**0**	**6**	**19**	**44**	**1**	**70**

BCC Brighton Collaboration Criteria, UMC Uppsala Monitoring Centre; WHO World Health Organization

Six cases fulfilled BCC Level 2 criteria, 19 cases Level 3 criteria, 44 cases were considered in level 4 and 1 case did not fulfil BCC criteria for certainty (Level 5 criteria). There are no certain or probable cases based on WHO-UMC causality assessment criteria.

Brighton Collaboration Level 2

Summary of cases fulfilling Brighton collaboration level 2 for encephalitis reported during the interval period (29 June 2022 – 28 December 2022).

Six out of the 70 cases fulfilled Brighton collaboration level 2. Three (3) case reports concerned females, and other 3 were reported in male vaccinees. The age range was 23-75 years.

In these 6 cases, the TTO range was between 2 to 10 days. The median TTO was 09 days. In 4 cases there was limited information about medical history, family history, concomitant medications to make a comprehensive causality assessment. In 1 case there were confounders noted like concurrent UTI, hypertension, ischemic heart disease, and monoclonal gammopathy. In the remaining one case, the WHO-UMC causality was considered as unassessable/unclassifiable due to unknown TTO.

Brighton Collaboration Level 3

Summary of Cases fulfilling Brighton collaboration level 3 for encephalitis reported during the interval period (29 June 2022 – 28 December 2022).

Nineteen (19) out of 70 cases fulfilled Brighton collaboration level 3. Eight (8) case reports concerned females, and 11 were reported in male vaccinees. The age range was 25-73 years.

In these 19 cases, the TTO range was between 6 to 215 days. The median TTO was 13 days. In 11 cases there was limited information medical history, family history, concomitant medications to make a comprehensive causality assessment, 3 cases are noted with confounders, 4 cases were unassessable/ unclassifiable as the TTO is unknown, and remaining 1 case was unlikely as the TTO is 215 days.

Brighton Collaboration Level 4

Based on the review, 44 out of 70 cases were classified as Brighton collaboration level 4. These cases did not fulfil criteria for a level 3, 2, or 1 certainty as there was insufficient information to confirm the diagnosis or medical assessment of the cases.

Brighton Collaboration Level 5

Based on the review, 1 out of 70 cases was classified as Brighton collaboration level 5 (ie, Encephalitis was excluded due to an alternative diagnosis). In this case, auto-immune thyroiditis was reported, and there was no event of encephalitis.

Observed vs. Expected Analysis

The observed versus expected analysis for all cases of encephalitis reported cumulatively till DLP 28 December 2022 is presented with three risk windows (14 days, 30 days, and 42 days) in Table 125. This includes all reported cases irrespective of the Brighton collaboration criteria level. The risk window of 2-42 days was included from the Brighton case definition

(Law B 2021). The background incidence rates used are from a meta-analysis of ACCESS rates (Meningoencephalitis, 2010-2013 and 2017-2019) The outcome of observed versus expected analysis of all cases for encephalitis suggested that observed cases were significantly less than expected. The observed versus expected analysis of cases for encephalitis showed that observed cases occurred significantly less frequently than expected for all age stratifications in EEA/UK, Brazil, and Australia. Most cases in all age groups from EEA/UK, Brazil and Australia showed insufficient information to make any causality assessment and only few cases met the Brighton Collaboration Criteria Level 1, 2 or 3.

O/E analysis showed that observed cases occurred significantly less than expected with all stratifications.

Table 125 Observed Versus Expected Analysis for all cases reporting encephalitis (Global reports) reported cumulatively till DLP 28 December 2022

Adverse Events	Risk window	IR	Exposure[a]	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Overall Incidence Rate Encephalitis	14	9.1	466115644	146	1625.85	0.09 (0.08 - 0.11)	Observed significantly < expected
Overall Incidence Rate Encephalitis	30	9.1	466115644	181	3483.97	0.05 (0.04 - 0.06)	Observed significantly < expected
Overall Incidence Rate Encephalitis	42	9.1	466115644	214	4877.56	0.04 (0.04 - 0.05)	Observed significantly < expected
Overall Incidence Rate Encephalitis cases including unknown TTO	42	9.1	466115644	346	4877.56	0.07 (0.06 - 0.08)	Observed significantly < expected

[a] Exposure until 28 December 2022; Incidence rate (IR) source: Meta-analysis of ACCESS rates (Meningoencephalitis, 2010-2013 and 2017-2019)

CI Confidence Interval, DLP Data Lock Point E Expected, IR Incidence rate, O Observed; ; TTO Time To Onset

An observed versus expected analysis of cases stratified by age range and regions (EU/UK. Brazil and Australia) with different Risk windows are presented in Table 126.

Table 126 Observed Versus Expected Analysis for encephalitis cases stratified by age for EEA/UK, Brazil & Australia reported cumulatively till DLP 28 December 2022

Adverse Events	Risk window	IR[a]	Exposure[b]	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
EEA UK, Brazil & Australia Encephalitis Age 18-49	14	7.48	110094983	56	315.66	0.18 (0.13 - 0.23)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 18-49	30	7.48	110094983	66	676.41	0.1 (0.08 - 0.12)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 18-49	42	7.48	110094983	77	946.97	0.08 (0.06 - 0.1)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 50-59	14	8.66	58336094	19	193.64	0.1 (0.06 - 0.15)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 50-59	30	8.66	58336094	27	414.95	0.07 (0.04 - 0.09)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 50-59	42	8.66	58336094	34	580.93	0.06 (0.04 - 0.08)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 60-69	14	9.87	57960860	33	219.28	0.15 (0.1 - 0.21)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 60-69	30	9.87	57960860	44	469.89	0.09 (0.07 - 0.13)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 60-69	42	9.87	57960860	50	657.84	0.08 (0.06 - 0.1)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 70+	14	10.71	32376365	20	132.91	0.15 (0.09 - 0.23)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 70+	30	10.71	32376365	21	284.81	0.07 (0.05 - 0.11)	Observed significantly < expected
EEA UK, Brazil & Australia Encephalitis Age 70+	42	10.71	32376365	25	398.74	0.06 (0.04 - 0.09)	Observed significantly < expected

[a] Source: Incidence rate (IR) source: Meta-analysis of ACCESS rates Meningoencephalitis, 2010-2013 and 2017-2019)

[b] Exposure until 28 December 2022 for EEA/UK, Brazil, and Australia.

CI Confidence Interval; CPRD Clinical Practice Research Database; E Expected; EEA European Economic Area; IR: Incidence rate; O Observed; TTO Time to onset; UK United Kingdom; CI Confidence Interval; CPRD Clinical Practice Research Database

An O/E analysis of cases meeting case definition according to Brighton Criteria (BC) for Level 1, 2 or 3, based on clinical course, examination such as brain histopathology, clinical features, and evaluations (Law B 2021) are presented in Table 127.

Table 127 Observed Versus Expected Analysis for encephalitis cases meeting the Brighton Criteria Level 1, 2 or 3 and stratified by age for EEA/UK Brazil & Australia regions reported cumulatively till DLP 28 December 2022.

Adverse Events	Risk window	IR [a]	Exposure [b]	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
EEA UK, Brazil & Australia; BCC 1-3; Age 18 -49	14	7.48	110094983	11	315.66	0.03 (0.02 - 0.06)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 18 -49	30	7.48	110094983	15	676.41	0.02 (0.01 - 0.04)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 18 -49	42	7.48	110094983	16	946.97	0.02 (0.01 - 0.03)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 50-59	14	8.66	58336094	1	193.64	0.01 (0 - 0.03)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 50-59	30	8.66	58336094	1	414.95	0 (0 - 0.01)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 50-59	42	8.66	58336094	3	580.93	0.01 (0 - 0.02)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 60-69	14	9.87	57960860	5	219.28	0.02 (0.01 - 0.05)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 60-69	30	9.87	57960860	7	469.89	0.01 (0.01 - 0.03)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 60-69	42	9.87	57960860	7	657.84	0.01 (0 - 0.02)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 70+	14	10.71	32376365	5	132.91	0.04 (0.01 - 0.09)	Observed significantly < expected

Table 127 Observed Versus Expected Analysis for encephalitis cases meeting the Brighton Criteria Level 1, 2 or 3 and stratified by age for EEA/UK Brazil & Australia regions reported cumulatively till DLP 28 December 2022.

Adverse Events	Risk window	IR [a]	Exposure [b]	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
EEA UK, Brazil & Australia; BCC 1-3; Age 70+	30	10.71	32376365	5	284.81	0.02 (0.01 - 0.04)	Observed significantly < expected
EEA UK, Brazil & Australia; BCC 1-3; Age 70+	42	10.71	32376365	5	398.74	0.01 (0 - 0.03)	Observed significantly < expected

[a] Incidence rate (IR) source: Meta-analysis of ACCESS rates (Meningoencephalitis, 2010-2013 and 2017-2019)

[b] Exposure until 28 December 2022 for EEA/UK, Brazil, and Australia.

CI Confidence Interval, E Expected, EEA European Economic Area; IR Incidence rate, O Observed PY Person Years; TTO Time to onset; UK United Kingdom.

Literature review during the reporting period

During the reporting period, nine (9) relevant articles were identified. These included 13 cases of encephalitis/ encephalopathy with VAXZEVRIA which are included in the AstraZeneca safety database review above [redacted] These cases are reviewed and discussed as part of safety database review.

There were no other relevant articles identified in the reporting period concerning encephalitis and VAXZEVRIA.

Summary

Encephalitis is known to occur naturally at an overall annual incidence up to 10 cases per 100,000 persons (Willame et al 2021 (A)). Incidence is highly variable dependent upon age, demographics, season, causative agent, and presence of epidemic illness. The natural aetiology is multifactorial but includes infectious, toxic, neoplastic, autoimmune, and metabolic causes (Wang et al 2022 [A]).

Of the 70 cases received during the reporting period, 53 (75.7%) of vaccinees were from the age group of 18-<65 (adult) and median age was found to be 47 years. In 42 (60.00%) cases, the events were reported to have occurred after the first dose, 5 (7.14%) case reports after the second dose of vaccine, and dose was not reported in 23 (32.86%) case reports. There was no report of recurrence of events.

Review of all cases during the interval period revealed no clear pattern in clinical presentation or medical history. There is a wide range in time to onset (TTO) of cases from

vaccination (0-405 days). The median TTO for all the cases was 11 days. Thirty-four (34) (48.57%) out of 70 cases were within the risk window of 2-42 days. All the 70 cases were serious. Case fatality rate is variable and dependent on causative factor (Wang et al 2022 [A]). The review of 2 case reports with fatal outcome did not identify any substantial evidence of a causal association between encephalitis and VAXZEVRIA. No changes were identified for interval data considering both safety patterns and volumes.

Based on Brighton Collaboration criteria approach, out of the 70 cases, 6 fulfilled level 2 criteria, 19 fulfilled level 3 criteria, 44 fulfilled level 4 criteria, and 1 case fulfilled level 5 criteria. 5 (7.14%) cases were evaluated with alternative causal factors noted and the remaining cases were evaluated with limited information to make any comprehensive causality assessment. The review of post authorization case reports did not find any evidence of a causal association between encephalitis and VAXZEVRIA.

The observed versus expected analysis of cumulative cases for encephalitis showed that observed cases occurred significantly less frequently than expected for all cases (385) and cases with BCC 1-3 (69), all age stratifications in EEA/UK, Brazil, and Australia, and risk windows. The contribution of under-reporting cannot be estimated, but observed cases are significantly below expected and do not indicate any disproportionality.

Overall, the clinical pattern of case presentation and numbers of reports are broadly consistent with what might be expected from the natural epidemiology of encephalitis, and there was no specific biological mechanism for development of encephalitis post vaccination with VAXZEVRIA.

Conclusion

From the data identified during the reporting period and taking into account the cumulative experience, there is currently insufficient evidence of a causal association between encephalitis and VAXZEVRIA.

VAXZEVRIA CDS Section 4.4 (Special warnings and special precautions for use) includes warnings on Neurological events: “Very rare events of demyelinating disorders, including Guillain-Barré syndrome (GBS), have been reported following vaccination with VAXZEVRIA. A causal relationship has not been established. As with other vaccines, the benefits and potential risks of vaccinating individuals with VAXZEVRIA should be considered”. In addition, encephalitis (immune mediated neurological condition/ nervous system disorders, including immune mediated neurological conditions.) is considered as an Important potential risk in the Core and EU RMPs for VAXZEVRIA. No further updates to the VAXZEVRIA CDS or RMP are warranted at this time. As such, the topic will continue to be to be closely monitored as part of AstraZeneca’s ongoing surveillance for the important potential risk of immune-mediated neurological conditions.

16.3.1.2.2 Transverse Myelitis

An interval search from 29 June 2022 to 28 December 2022 of the AstraZeneca Global Safety Database for Transverse myelitis with VAXZEVRIA was performed using MedDRA

version 25.1. The search strategy included: PTs: Myelitis transverse, Myelitis, and Acute necrotizing myelitis, and LLT: MOG-transverse myelitis.

The search retrieved a total of 37 events (9 events of myelitis and 28 events of Myelitis transverse) in 35 case reports reported predominantly from the following countries: United Kingdom (22.9%), Brazil (20.0%), Germany (17.1%), India (11.4%). 24 were initial and 11 were follow-up reports.

The breakdown and overview of these 35 cases reporting events of TM is presented in the below Table 128.

Table 128 Overview of Events/Cases for the interval

Parameter	Category	Values (%)[b]
Event Count	Total	37
	Serious	33 (89.2%)
	Non serious	4 (10.8%)
Case Count	Medically confirmed	21 (60%)
Case Report Source	Interventional Clinical study[c]	1 (2.9%)
	Non-interventional study	2 (5.7%)
	Spontaneous	13 (37.1%)
	Literature	6 (17.1%)
	Regulatory	13 (37.1%)
Sex	Female N (%)	17 (48.6%)
	Male N (%)	17 (48.6%)
	Unknown/not reported N (%)	1 (2.9%)
Age Group	15-24	0
	25-44	31.40%
	45-64	22.90%
	65+	11.40%
	Median age (range)	48 years (25 to 76)
Event occurrence with dose	Dose 1 (%)	16(45.7%)
	Dose 2 (%)	6 (18.8%)
	Dose 3 (%)	1(2.86%)
	Dose 4 (%)	0
	Multiple Doses	0
	Unknown dose	12
Case level - TTO (days)[a]	0-14	10 (28.6%)
	15-28	6 (17.1%)
	29-42	2 (5.7%)
	43 and above	7 (20.0%)

Table 128 Overview of Events/Cases for the interval

Parameter	Category	Values (%)[b]
	Median TTO (range)	21 (0 to 390)
Event Seriousness criteria	Medically important	18 (34.6%)
	Disability	7 (13.5%)
	Hospitalization	23 (44.2%)
	Congenital anomaly	0
	Life-threatening	3 (5.8%)
	Death	1 (1.9%)
AE Outcome	Recovered	2 (5.4%)
	Recovering	11 (29.6%)
	Recovered with sequelae	1 (2.7%)
	Not recovered	16 (43.2%)
	Fatal	1 (2.7%)
	Unknown	6

[a] TTO was reported for 22 case reports (total number of cases) used to calculate the percentage. Where multiple TTOs are present in a case, the most conservative TTO for the relevant event is chosen

[b] percentages for all, calculated based on known values

[c] There was one case from the COV002 study. The only new information received during the interval was unblinding information.

AE Adverse Event; TTO Time To Onsets

Events with fatal outcome

Of the 37 total events received during the interval period, a single event (2.7%) of myelitis transverse in 35 cases was reported with a fatal outcome. The event was medically confirmed and has been summarised below:

Case ID [redacted]

The report, concerning fifty nine year old male subject from Brazil, who post 5 days after AstraZeneca vaccination - presented to hospital with a history of 3 days of progressive, symmetrical and ascending loss of strength in the lower limbs. Examination revealed a Glasgow Coma Scale 15, isocoric and photoreactive pupils, no signs of meningeal irritation, grade 5 muscle strength in the upper limbs, grade 0 in the lower limbs with areflexia in the lower limbs and decrease of superficial and deep sensitivity in them. Symptoms were unresponsive to pulse methyl prednisolone and persisted and 11 days later horizontal choreic movements of the head, intention tremor in the upper limbs, significant dysmetria and nystagmus developed. CSF tested twice was non-specific. Further clinical course was complicated by cutaneous, urinary and pulmonary infections (unspecified chronologic course). It was reported that the patient died due from the events of sepsis, transverse myelitis, ADEM and cerebellar syndrome after about 110 days post hospitalization.

AstraZeneca comment: The case reported event of transverse myelitis however the diagnostic certainty was not met as per BCC diagnostic certainty algorithm for Transverse myelitis (BCC5). The case has been conservatively assessed as ADEM BCC3. The latency of 2 days to AE onset is reasonable, however due to insufficient information on infectious or neoplastic workup, the WHO-UMC causality association to the AE onset is considered as Possible with limited information. Development of Sepsis post treatment can possibly be attributed to methylprednisolone therapy and this could be a possible confounder for the fatality.

Recurrence case reports

There were no cases indicating a recurrence in the reporting period.

WHO -UMC and Brighton Collaboration Classification Assessment

The Brighton collaboration classification (BCC) for diagnostic certainty (Law B 2021 [C]) was used for review of information available in all case reports. Cases were categorised as Brighton Collaboration Level 1- 5 for acute myelitis based on clinical history, examination, and laboratory investigation results. Causality assessment of all cases was performed using WHO- UMC causality assessment criteria with a risk window of 42 days.

The BCC and WHO-UMC assessment performed for these cases is provided in the following Table 129.

Table 129 Overview of BCC and WHO-UMC Causality Assessments / for case reports of Transverse myelitis with VAXZEVRIA reported during the reporting period

WHO-UMC/BCC Level	Level 1	Level 2	Level 3	Level 4	Level 5	Grand Total
Certain	0	0	0	0	0	0
Probable/Likely	0	0	0	0	0	0
Possible with risk factors/confounders	0	1	0	0	0	1
Possible with limited information	0	4	4	7	4	19
Unassessable/Unclassifiable	0	0	0	5	3	8
Unlikely	0	1	0	6	0	7
Conditional /Unclassified	0	0	0	0	0	0
Total	**0**	**6**	**4**	**18**	**7**	**35**

Cases were considered to have "risk factors/confounders" where the event could also be explained by the vaccinee's diseases, or where relevant risk factors were present, or concomitant medications that could potentially contribute to the development of the event were reported.

BCC Brighton Collaboration Criteria; UMC Uppsala Monitoring Centre ; WHO World Health Organization

There were no cases assessed as certain or probable in the reporting period.

Review of cases as per BCC classification in the reporting period of the PBRER

The BCC (Law B 2021 [C]) was used for the review of the data available in the case reports. Based on this approach, out of the 35 cases: none of the cases fulfilled BCC Level 1 criteria; 6 cases fulfilled BCC Level 2 criteria; 4 cases fulfilled BCC Level 3 criteria; 18 cases fulfilled BCC Level 4 criteria and 7 cases fulfilled BCC Level 5 criteria.

In addition to the BCC, the published Brighton Case Definition for Acute Myelitis (Law B 2021 [C]) was also referenced during the review of the cases for the assessment of evidence related to associated risk factors (eg, comorbidities, infections, vaccines and malignancies).

The cases fulfil BCC levels 1-5 based on the available information on clinical course, clinical examination, and diagnostic investigations

BCC Level 1 for Transverse myelitis: None

BCC Level 2 for Transverse myelitis

Six out of the 35 case reports fulfilled BCC level 2 criteria. The cases fulfil this classification by clinical course, examination, and radiological features.

Out of these 6 cases, 4 reports were reported in females and 2 were reported in males and the age range was 25-76 years. The median age was 60 years.

Four of the 6 cases had time to onset from vaccination within 42 days. In one case the time to onset was unknown. The median time to onset was 9 days.

Out of these 6 cases, 3 cases reported to have occurred after receiving the first dose and one case after dose 3. The dose was unknown in remaining cases.

Out of the 6 cases fulfilling BCC Level 2, 4 ([redacted]) were assessed as Possible (with limited information) and one (2021A831965) as Unlikely as per WHO-UMC Causality assessment criteria.

Predominantly (5 out of 6 cases) presented with bowel/bladder dysfunction in addition to sensory and motor involvement of extremities. This also roughly correlated with involvement of multiple vertebral segments.

Majority of cases had lymphocyte predominance (3 out of 6 cases reporting cell count differentials) versus polymorphic picture (2 out of 6 cases reporting cell count differentials).

Information on oligoclonal bands in TM cases was reported in 2 cases (1 negative and 1 positive).

Information on serum or CSF levels on anti-neuronal antibodies (eg: MOG-Ab, NMO-Ab, AQP4-Ab) was reported in 4 out of 6 cases and it was normal in all. To summarize, either there was limited information or CSF picture including neuronal antibodies had a varied presentation to identify any possible singular immune etiopathogenetic role of AstraZeneca COVID-19 vaccine.

BCC Level 3 for Transverse myelitis

Four out of the 35 case reports fulfilled BCC level 3 criteria. The cases fulfil this classification by clinical course, examination features, and investigations.

Out of these 4 cases, three reports were reported in females and one was reported in a male vaccinee. The age distribution as reported in 3 cases was 31 years, 31 years, 32 years, unknown. The distribution of time to onset was 10 days, unknown dose number; 21 days, dose 1; 25 days, dose 2; 11 days, unknown dose number.

All the 4 cases fulfilling BCC Level 3 were assessed as Possible (with limited information) as per WHO Causality assessment criteria. The limited information was a lack of comprehensive etiological work-up (especially for infectious aetiologies), medical history and concomitant medications.

The CSF results presented a varied picture with respect to extent of pleocytosis (mild in one case, moderate in 2 cases with lymphocyte predominance). Information on serum or CSF levels on anti-neuronal antibodies (eg: MOG-Ab, NMO-Ab, AQP4-Ab) was reported in 1 out of 4 cases and was normal. Information on oligoclonal bands was reported in one case (normal). To summarize, either there was limited information or CSF picture including neuronal antibodies had a varied presentation to identify any singular etiopathogenetic possible role of VAXZEVRIA.

BCC Level 4 for Transverse Myelitis

A total of 18 cases fulfilled BCC Level 4 criteria, Limited information to make any causality assessment was noted in 5 of the cases, 7 cases were assessed as “Possible” (with limited information) and the remaining 6 cases were assessed as “Unlikely” as per WHO Causality assessment criteria.

BCC Level 5 for Transverse Myelitis

A total of 7 case reports fulfilled BCC level 5 criteria. Limited information to make any causality assessment was noted in 3 of the cases and the remaining 4 cases were assessed as “Possible (with limited information)” as per WHO Causality assessment criteria.

Observed Versus Expected (O/E) Analyses

An O/E analysis of transverse myelitis was conducted cumulatively.

Willame et al 2021 (B) have as part of ADVANCE EUROPE given incidence rates for transverse myelitis, stratified by age. The rates are slightly lower than other rates found corresponding to a more conservative estimate for background rates. An appendix to the same article by Willame et al 2021 (B) has given incidence rates stratified by age and gender.

Global overall rates based on the rates from ADVANCED Europe are presented in Table 131. The observed numbers are presented both including and excluding cases with an unknown time to onset and stratified by cases fulfilling Brighton collaboration criteria levels 1-3 (BCC 1-3).

The risk window for myelitis as a product related reaction for inactivated or subunit vaccines is likely similar to ADEM, where the recommended risk window for individuals is 2-42 days. A risk window of 42 days was used for this analysis, ie, cases that have the time to onset of 42 days or less from receiving the vaccine until the event occurred are counted in the observed numbers.

The O/E analysis for the cumulative cases of transverse myelitis globally with risk window of 42 days is presented with results in Table 130:

Table 130 Observed versus Expected Analysis for Transverse Myelitis Overall and for Brighton Collaboration cases

Age group/Gender	Risk window (days)	Back-ground rates	Exposure [a]	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Overall	42	0.97	466115644	218	519.92	0.42 (0.37 - 0.48)	Observed significantly < expected
Overall +Unk TTO	42	0.97	466115644	339	519.92	0.65 (0.58 - 0.73)	Observed significantly < expected
Overall BCC 1-3	42	0.97	466115644	55	519.92	0.11 (0.08 - 0.14)	Observed significantly < expected
Overall +Unk TTO BCC 1-3	42	0.97	466115644	64	519.92	0.12 (0.09 - 0.16)	Observed significantly < expected

[a] Exposure until 28 December 2022. All global reports are included in observed numbers. Exposure numbers are from United Kingdom, EEA, Australia, Canada, Philippines and Brazil. Exposure numbers from India are not included

BCC, Brighton collaboration criteria; CI, Confidence Interval; TTO: Time to onset; Unk, Unknown

Observed versus expected analyses stratified by age in the UK, using rates from ADVANCED Europe (Willame et al 2021 (B)) are presented in Table 131. The observed numbers are presented both including and excluding cases with an unknown time to onset and stratified by cases fulfilling Brighton collaboration criteria levels 1-3 (BCC 1-3).

Table 131 Observed versus expected analysis, stratified by age, BCC and with and without cases with an unknown TTO in the UK

Age Group	Risk Window	Background rates	Exposure[a]	Observed number of cases	Expected number of cases	O over E ratio	Background rates
15-24 years	42	0.64	871148	3	0.64	4.69 (0.97 - 13.7)	Observed > expected
25-44 years	42	1.36	8438999	25	13.2	1.89 (1.23 - 2.8)	Observed significantly > expected
45-64 years	42	1.23	22877522	32	32.36	0.99 (0.68 - 1.4)	Observed < expected
65 years +	42	0.76	13443624	33	11.75	2.81 (1.93 - 3.94)	Observed significantly > expected
15-24 years including cases with an unknown TTO	42	0.64	871148	4	0.64	6.25 (1.7 - 16)	Observed significantly > expected
25-44 years Including cases with an Unknown TTO	42	1.36	8438999	36	13.2	2.73 (1.91 - 3.78)	Observed significantly > expected
45-46 Years Including cases with an Unknown TTO	42	1.23	22877522	55	32.36	1.7 (1.28 - 2.21)	Observed significantly > expected
65 Years + Including cases with an Unknown TTO	42	0.76	13443624	53	11.75	4.51 (3.38 - 5.9)	Observed significantly > expected

Table 131 Observed versus expected analysis, stratified by age, BCC and with and without cases with an unknown TTO in the UK

Age Group	Risk Window	Background rates	Exposure[a]	Observed number of cases	Expected number of cases	O over E ratio	Background rates
15-24 years BCC 1-3	42	0.64	871148	0	0.64	0 (0 - 5.76)	Observed < expected
25-44 Years BCC 1-3	42	1.36	8438999	6	13.2	0.45 (0.17 - 0.99)	Observed significantly < expected
45-64 Years BCC 1-3	42	1.23	22877522	9	32.36	0.28 (0.13 - 0.53)	Observed significantly < expected
65 Years + BCC 1-3	42	0.76	13443624	2	11.75	0.17 (0.02 - 0.61)	Observed significantly < expected
15-24 years BCC 1-3 including cases with an unknown TTO	42	0.64	871148	0	0.64	0 (0 - 5.76)	Observed < expected
25-44 years BCC 1-3 including cases with an unknown TTO	42	1.36	8438999	8	13.2	0.61 (0.26 - 1.19)	Observed < expected
45-64 years BCC 1-3 including cases with an unknown TTO	42	1.23	22877522	11	32.36	0.34 (0.17 - 0.61)	Observed significantly < expected
65 years + BCC 1-3 including cases with an unknown TTO	42	0.76	13443624	4	11.75	0.34 (0.09 - 0.87)	Observed significantly < expected

[a] Exposure until 28 December 2022
BCC, Brighton Criteria; CI, Confidence Interval; TTO: Time to onset; Unk, Unknown

Observed versus expected analyses stratified by age and gender in the United Kingdom, using UK incidence rates from Willame et al 2021 (B), ie, UK The Health Improvement Network (UK_THIN), are presented in Table 132. The observed numbers are presented both including and excluding cases with an unknown time to onset.

Table 132 Observed versus expected analysis, stratified by age and gender in the UK in the context of the UK THIN background rates

Age group/Gender	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio	Risk window
Female 15-24 years UK THIN	42	1.2	501314	1	0.69	1.45 (0.04 - 8.07)	Observed > expected
Female 25-44 years UK THIN	42	2.6	4541193	18	13.58	1.33 (0.79 - 2.09)	Observed > expected
Female 45-64 years UK THIN	42	1.9	10983490	15	24	0.62 (0.35 - 1.03)	Observed < expected
Female 65 years+ UK THIN	42	0.8	7188495	18	6.61	2.72 (1.61 - 4.3)	Observed significantly > expected
Female Overall UK THIN	42	1.6	23252503	52	42.78	1.22 (0.91 - 1.59)	Observed > expected
Female 15-24 years UKTHIN + Unk TTO	42	1.2	501314	2	0.69	2.9 (0.35 - 10.47)	Observed > expected
Female 25-44 years UKTHIN + Unk TTO	42	2.6	4541193	27	13.58	1.99 (1.31 - 2.89)	Observed significantly > expected

Table 132 Observed versus expected analysis, stratified by age and gender in the UK in the context of the UK THIN background rates

Age group/Gender	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio	Risk window
Female 45-64 years UKTHIN + Unk TTO	42	1.9	10983490	25	24	1.04 (0.67 - 1.54)	Observed > expected
Female 65 years+ UKTHIN + Unk TTO	42	0.8	7188495	26	6.61	3.93 (2.57 - 5.76)	Observed significantly > expected
Female Overall UKTHIN + Unk TTO	42	1.6	23252503	80	42.78	1.87 (1.48 - 2.33)	Observed significantly > expected
Male 15-24 years UK THIN	42	0.7	368837	2	0.3	6.67 (0.81 - 24.08)	Observed > expected
Male 25-44 years UK THIN	42	1.5	3890126	7	6.71	1.04 (0.42 - 2.15)	Observed > expected
Male 45-64 years UK THIN	42	1.4	11873029	17	19.11	0.89 (0.52 - 1.42)	Observed < expected
Male 65 years + UK THIN	42	0.9	6228335	14	6.45	2.17 (1.19 - 3.64)	Observed significantly > expected
Male Overall UK THIN	42	1.1	22377923	40	28.31	1.41 (1.01 - 1.92)	Observed significantly > expected
Male 15-24 years UKTHIN +Unk TTO	42	0.7	368837	2	0.3	6.67 (0.81 - 24.08)	Observed > expected

Table 132 Observed versus expected analysis, stratified by age and gender in the UK in the context of the UK THIN background rates

Age group/Gender	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio	Risk window
Male 25-44 years UKTHIN +Unk TTO	42	1.5	3890126	8	6.71	1.19 (0.51 - 2.35)	Observed > expected
Male 45-64 years UKTHIN +Unk TTO	42	1.4	11873029	30	19.11	1.57 (1.06 - 2.24)	Observed significantly > expected
Male 65 years + UKTHIN +Unk TTO	42	0.9	6228335	25	6.45	3.88 (2.51 - 5.72)	Observed significantly > expected
Male Overall UKTHIN +Unk TTO	42	1.1	22377923	65	28.31	2.3 (1.77 - 2.93)	Observed significantly > expected

CI, Confidence Interval; E, Expected; O, Observed TTO: Time to onset; Unk, Unknown; UK, United Kingdom

An observed versus expected analysis, including cases fulfilling Brighton collaboration levels 1-3, stratified by age and gender in the UK are provided below, using background rates from UK THIN are presented in Table 133.

Table 133 Observed versus expected analysis, stratified by age and gender, BCC levels 1-3 in the UK in the context of the UK THIN background rates

Age group/Gender	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female 15-24 years UK THIN BCC 1-3	42	1.2	501314	0	0.69	0 (0 - 5.35)	Observed < expected
Female 25-44 years UK THIN BCC 1-3	42	2.6	4541193	6	13.58	0.44 (0.16 - 0.96)	Observed significantly < expected
Female 45-64 years UK THIN BCC 1-3	42	1.9	10983490	2	24	0.08 (0.01 - 0.3)	Observed significantly < expected

Table 133 Observed versus expected analysis, stratified by age and gender, BCC levels 1-3 in the UK in the context of the UK THIN background rates

Age group/Gender	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female 65 years+ UK THIN BCC 1-3	42	0.8	7188495	0	6.61	0 (0 - 0.56)	Observed significantly < expected
Female Overall UK THIN BCC 1-3	42	1.6	23252503	8	42.78	0.19 (0.08 - 0.37)	Observed significantly < expected
Female 15-24 years UKTHIN +Unk TTO BCC 1-3	42	1.2	501314	0	0.69	0 (0 - 5.35)	Observed < expected
Female 25-44 years UKTHIN +Unk TTO BCC 1-3	42	2.6	4541193	8	13.58	0.59 (0.25 - 1.16)	Observed < expected
Female 45-64 years UKTHIN +Unk TTO BCC 1-3	42	1.9	10983490	3	24	0.12 (0.03 - 0.37)	Observed significantly < expected
Female 65 years + UKTHIN +Unk TTO BCC 1-3	42	0.8	7188495	1	6.61	0.15 (0 - 0.84)	Observed significantly < expected
Female Overall UKTHIN +Unk TTO BCC 1-3	42	1.6	23252503	12	42.78	0.28 (0.14 - 0.49)	Observed significantly < expected
Male 15-24 years UK THIN BCC 1-3	42	0.7	368837	0	0.3	0 (0 - 12.3)	Observed < expected
Male 25-44 years UK THIN BCC 1-3	42	1.5	3890126	0	6.71	0 (0 - 0.55)	Observed significantly < expected
Male 45-64 years UK THIN BCC 1-3	42	1.4	11873029	7	19.11	0.37 (0.15 - 0.75)	Observed significantly < expected

Table 133 Observed versus expected analysis, stratified by age and gender, BCC levels 1-3 in the UK in the context of the UK THIN background rates

Age group/Gender	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male 65 years + UK THIN BCC 1-3	42	0.9	6228335	2	6.45	0.31 (0.04 - 1.12)	Observed < expected
Male Overall UK THIN BCC 1-3	42	1.1	22377923	9	28.31	0.32 (0.15 - 0.6)	Observed significantly < expected
Male 15-24 years UKTHIN +Unk TTO BCC 1-3	42	0.7	368837	0	0.3	0 (0 - 12.3)	Observed < expected
Male 25-44 years UKTHIN +Unk TTO BCC 1-3	42	1.5	3890126	0	6.71	0 (0 - 0.55)	Observed significantly < expected
Male 45-64 years UKTHIN +Unk TTO BCC 1-3	42	1.4	11873029	8	19.11	0.42 (0.18 - 0.82)	Observed significantly < expected
Male 65 years + UKTHIN +Unk TTO BCC 1-3	42	0.9	6228335	3	6.45	0.47 (0.1 - 1.36)	Observed < expected
Male Overall UKTHIN +Unk TTO BCC 1-3	42	1.1	22377923	11	28.31	0.39 (0.19 - 0.7)	Observed significantly < expected

BCC Brighton collaboration criteria; CI Confidence Interval; E Expected; O Observed; TTO Time to Onset; UK United Kingdom; UKTHIN United Kingdom The Health Improvement Network; Unk Unknown;

Observed versus expected analyses stratified by Dose number, age and gender, BCC in the United Kingdom, using UK incidence rates from Willame et al 2021 (B), ie, UK The Health Improvement Network (UK_THIN), are presented in Table 134.

Table 134 Observed versus expected analyses stratified by Dose number, age and gender, BCC in UK

Gender /Age group / Dose #	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male/ 15-24 years/ Dose 1	42	0.7	188508	0	0.15	0 (0 - 24.59)	Observed < expected
Male/ 25-44 years/ Dose 1	42	1.5	1980408	6	3.42	1.75 (0.64 - 3.82)	Observed > expected
Male/ 45- 64 years/ Dose 1	42	1.4	5990807	12	9.64	1.24 (0.64 - 2.17)	Observed > expected
Male/ 65 yrs +/ Dose 1	42	0.9	3126893	8	3.24	2.47 (1.07 - 4.87)	Observed significantly > expected
Male/ Overall/ Dose 1	42	1.1	11286808	26	14.28	1.82 (1.19 - 2.67)	Observed significantly > expected
Male/ 15-24 years/ Dose 1/ BCC 1-3	42	0.7	188508	0	0.15	0 (0 - 24.59)	Observed < expected
Male/ 25-44 years/ Dose 1/ BCC1-3	42	1.5	1980408	0	3.42	0 (0 - 1.08)	Observed < expected
Male/ 45- 64 years/ Dose 1/ BCC 1-3	42	1.4	5990807	5	9.64	0.52 (0.17 - 1.21)	Observed < expected
Male/ 65 yrs +/ Dose 1/ BCC 1-3	42	0.9	3126893	0	3.24	0 (0 - 1.14)	Observed < expected
Male/ Overall/ Dose 1/ BCC-1-3	42	1.1	11286808	5	14.28	0.35 (0.11 - 0.82)	Observed significantly < expected
Male/ 15-24 years/ Dose 2	42	0.7	180329	0	0.15	0 (0 - 24.59)	Observed < expected
Male/ 25-44 years/ Dose 2	42	1.5	1909718	0	3.29	0 (0 - 1.12)	Observed < expected
Male/ 45- 64 years/ Dose 2	42	1.4	5882222	4	9.47	0.42 (0.12 - 1.08)	Observed < expected

Table 134 Observed versus expected analyses stratified by Dose number, age and gender, BCC in UK

Gender /Age group / Dose #	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Male/ 65 yrs +/ Dose 2	42	0.9	3101442	3	3.21	0.93 (0.19 - 2.73)	Observed < expected
Male/ Overall/ Dose 2	42	1.1	11073845	7	14.01	0.5 (0.2 - 1.03)	Observed < expected
Male/ 15-24 years/ Dose 2/ BCC 1-3	42	0.7	180329	0	0.15	0 (0 - 24.59)	Observed < expected
Male/ 25-44 years/ Dose 2/ BCC 1-3	42	1.5	1909718	0	3.29	0 (0 - 1.12)	Observed < expected
Male/ 45- 64 years/ Dose 2/ BCC 1-3	42	1.4	5882222	1	9.47	0.11 (0 - 0.59)	Observed significantly < expected
Male/ 65 yrs +/ Dose 2/ BCC 1-3	42	0.9	3101442	1	3.21	0.31 (0.01 - 1.74)	Observed < expected
Male/ Overall/ Dose 2/ BCC 1-3	42	1.1	11073845	2	14.01	0.14 (0.02 - 0.52)	Observed significantly < expected
Female/ 15-24 years/ Dose 1	42	1.2	255760	1	0.35	2.86 (0.07 - 15.92)	Observed > expected
Female/ 25-44 years/ Dose 1	42	2.6	2310305	12	6.91	1.74 (0.9 - 3.03)	Observed > expected
Female/ 45- 64 years/ Dose 1	42	1.9	5537396	9	12.1	0.74 (0.34 - 1.41)	Observed < expected
Female/ 65 yrs +/ Dose 1	42	0.8	3610734	10	3.32	3.01 (1.44 - 5.54)	Observed significantly > expected
Female/ Overall/ Dose 1	42	1.6	11714377	32	21.55	1.48 (1.02 - 2.1)	Observed significantly > expected
Female/ 15-24 years/ Dose 1/ BCC 1-3	42	1.2	255760	0	0.35	0 (0 - 10.54)	Observed < expected

Table 134 Observed versus expected analyses stratified by Dose number, age and gender, BCC in UK

Gender /Age group / Dose #	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female/ 25-44 years/ Dose 1/ BCC 1-3	42	2.6	2310305	3	6.91	0.43 (0.09 - 1.27)	Observed < expected
Female/ 45- 64 years/ Dose 1/ BCC 1-3	42	1.9	5537396	1	12.1	0.08 (0 - 0.46)	Observed significantly < expected
Female/ 65 years +/ Dose 1/ BCC 1-3	42	0.8	3610734	0	3.32	0 (0 - 1.11)	Observed < expected
Female/ Overall/ Dose 1/ BCC 1-3	42	1.6	11714377	4	21.55	0.19 (0.05 - 0.48)	Observed significantly < expected
Female/ 15-24 years/ Dose 2	42	1.2	245554	0	0.34	0 (0 - 10.85)	Observed < expected
Female/ 25-44 years/ Dose 2	42	2.6	2230888	2	6.67	0.3 (0.04 - 1.08)	Observed < expected
Female/ 45- 64 years/ Dose 2	42	1.9	5446094	3	11.9	0.25 (0.05 - 0.74)	Observed significantly < expected
Female/ 65 years +/ Dose 2	42	0.8	3577761	1	3.29	0.3 (0.01 - 1.69)	Observed < expected
Female/ Overall/ Dose 2	42	1.6	11500418	6	21.16	0.28 (0.1 - 0.62)	Observed significantly < expected
Female/ 15-24 years/ Dose 2/ BCC 1-3	42	1.2	245554	0	0.34	0 (0 - 10.85)	Observed < expected
Female/ 25-44 years/ Dose 2 / BCC 1-3	42	2.6	2230888	1	6.67	0.15 (0 - 0.84)	Observed significantly < expected
Female/ 45- 64 years/ Dose 2 / BCC 1-3	42	1.9	5446094	0	11.9	0 (0 - 0.31)	Observed significantly < expected

Table 134 Observed versus expected analyses stratified by Dose number, age and gender, BCC in UK

Gender /Age group / Dose #	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Female/ 65 years +/ Dose 2 / BCC 1-3	42	0.8	3577761	0	3.29	0 (0 - 1.12)	Observed < expected
Female/ Overall/ Dose 2 / BCC 1-3	42	1.6	11500418	1	21.16	0.05 (0 - 0.26)	Observed significantly < expected

BCC, Brighton collaboration criteria; CI, Confidence Interval; E Expected; O Observed TTO: Time to onset; UK United Kingdom; Unk, Unknown

Observed versus expected analyses stratified by Dose number, age and gender, BCC in the United Kingdom, using UK incidence rates from Willame et al 2021 (B), ie, ADVANCED Europe, are presented in Table 135. The observed numbers are presented both including and excluding cases with an unknown time to onset and stratified by cases fulfilling Brighton collaboration criteria levels 1-3 (BCC 1-3).

Table 135 Observed versus expected analysis, stratified by Dose, age, BCC in the UK

Age Group/Dose	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
15-24 years/ Dose 1	42	0.64	444378	1	0.33	3.03 (0.08 - 16.88)	Observed > expected
25-44 years/ Dose 1	42	1.36	4291068	18	6.71	2.68 (1.59 - 4.24)	Observed significantly > expected
45- 64 years/ Dose 1	42	1.23	11528448	21	16.31	1.29 (0.8 - 1.97)	Observed > expected
65 Years + Dose 1	42	0.76	3126893	19	2.73	6.96 (4.19 - 10.87)	Observed significantly > expected
Overall/ Dose 1	42	0.97	24725401	59	27.58	2.14 (1.63 - 2.76)	Observed significantly > expected

Table 135 Observed versus expected analysis, stratified by Dose, age, BCC in the UK

Age Group/Dose	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
15-24 years/ Dose 1/ BCC 1-3	42	0.64	444378	0	0.33	0 (0 - 11.18)	Observed < expected
25-44 years/ Dose 1/ BCC1-3	42	1.36	4291068	3	6.71	0.45 (0.09 - 1.31)	Observed < expected
45- 64 years/ Dose 1/ BCC 1-3	42	1.23	11528448	6	16.31	0.37 (0.14 - 0.8)	Observed significantly < expected
65 yrs +/ Dose 1/ BCC 1-3	42	0.76	3126893	0	2.73	0 (0 - 1.35)	Observed < expected
Overall/ Dose 1/ BCC-1-3	42	0.97	24725401	9	27.58	0.33 (0.15 - 0.62)	Observed significantly < expected
15-24 years/ Dose 2	42	0.64	425986	0	0.31	0 (0 - 11.9)	Observed < expected
25-44 years/ Dose 2	42	1.36	4140925	2	6.48	0.31 (0.04 - 1.11)	Observed < expected
45- 64 years/ Dose 2	42	1.23	11328542	7	16.02	0.44 (0.18 - 0.9)	Observed significantly < expected
65 years +/ Dose 2	42	0.76	6679268	4	5.84	0.68 (0.19 - 1.75)	Observed < expected
Overall/ Dose 2	42	0.97	24141350	13	26.93	0.48 (0.26 - 0.83)	Observed significantly < expected
15-24 years/ Dose 2/ BCC 1-3	42	0.64	425986	0	0.31	0 (0 - 11.9)	Observed < expected

Table 135 Observed versus expected analysis, stratified by Dose, age, BCC in the UK

Age Group/Dose	Risk window	Background rates	Exposure	Observed number of cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
25-44 years/ Dose 2/ BCC 1-3	42	1.36	4140925	1	6.48	0.15 (0 - 0.86)	Observed significantly < expected
45- 64 years/ Dose 2/ BCC 1-3	42	1.23	11328542	1	16.02	0.06 (0 - 0.35)	Observed significantly < expected
65 years +/ Dose 2/ BCC 1-3	42	0.76	6679268	1	5.84	0.17 (0 - 0.95)	Observed significantly < expected
Overall/ Dose 2/ BCC 1-3	42	0.97	24141350	3	26.93	0.11 (0.02 - 0.33)	Observed significantly < expected

BCC, Brighton collaboration classification criteria; CI, Confidence Interval; E Expected; EEA, European Economic Area O Observed TTO: Time to onset; Unk, Unknown; UK, United Kingdom.

Observed vs expected analysis summary:

When the observed versus expected analysis is carried out overall for global reports for all ages and genders, the number of observed cases is significantly less than expected for all stratifications provided.

When stratified by age only in the UK using the ADVANCE EUROPE rates, observed cases are significantly more than expected for age groups 25-44 years regardless of whether cases with an unknown time to onset are included or not. For the age group 15-24 years, observed cases are more than expected, however the disproportionality was significant when cases with unknown TTO are included. For the age group 45-64 years observed cases are less than expected when cases with an unknown TTO are not included. For the older age group (65+) observed cases are significantly more than expected when cases with an unknown TTO are not included as well as when cases with an unknown TTO are included. When the cases without an unknown TTO are included for all age groups, observed cases are more than expected with a significant disproportionality.

When only cases of transverse myelitis fulfilling BCC levels 1-3 are included, observed cases are significantly less than/less than expected for all stratifications.

The observed cases for females in the UK using the rate from United Kingdom The Health Improvement Network (UKTHIN) are more than expected. When stratified by age and gender, observed cases for females were greater than expected in all the age groups except for

45-64 years, without the result being significant. In the 65+ years group, observed cases were significantly more than expected. Observed cases were significantly more than expected for females overall when rate from UKTHIN and when cases with unknown TTO were included. Observed cases were more than expected, with a significant disproportionality in the 25-44 and 65+ year groups when cases with unknown TTO are included and were more than expected, without a significant disproportionality in the 15-24 and the 45-64 year groups.

When only cases fulfilling BCC levels 1-3 are included, observed cases are either less or significantly less than expected for all age stratifications (result is not significant for the youngest age group, 15-24 years, however, there are no observed cases with BCC 1-3 in that age group).

When stratified by age and gender, the observed cases for males are significantly more than expected for males overall when cases with and without an unknown TTO are included. When the UKTHIN rates are used, the 15-24 years group and the 25-44 years group have observed cases more than expected. Observed cases were significantly more than expected in the older (65+) age group. When cases with unknown TTO were included, however, all age groups had observed higher than expected with or without a significant disproportionality.

When males are stratified by BCC levels 1-3, observed cases were less/significantly less than expected in all age groups, regardless of whether unknown TTO was included.

Cases were also stratified by dose. For Dose 1 Overall, the observed cases were significantly less than expected. When Dose 1 cases in males were stratified using UK THIN background rates, the cases were either more or less than expected in all age stratifications, with an exception of the older (65+) age group in which there was a significant disproportionality. Overall the observed number of cases was significantly more than expected (26 cases to 14.28). Cases fulfilling BCC 1-3 criteria showed observed cases were significantly less than expected in males overall. For the other age groups observed cases were less than expected.

Cases in female patients after dose 1 stratified using the same UK THIN background rates had a significant disproportionality in the older age group (65+) and was significantly more than expected overall. When the cases were stratified by BCC 1-3, the observed cases were significantly less than expected (overall in females and in the 45-64 years age group).

When stratified by age only in the UK using the ADVANCE EUROPE rates, the observed cases were more than expected in all age groups except the 25-44 years range where it was significantly more than expected for the first dose (18 observed, 6.71 expected). When stratified by cases fulfilling BCC 1-3, observed cases were significantly less than/less than expected.

For Dose 2, overall, the observed cases were significantly less than expected with and without unknown TTO cases and the same when stratified by BCC 1-3. With the UK THIN background rates, observed cases were overall significantly less than expected in males and

females after dose 2. This was also significantly less than observed for cases stratified by dose, age and BCC in the UK using ADVANCE EUROPE rates.

Literature

A periodic literature search of the databases in Embase, InsightMeme and PubMed was conducted for relevant articles on topic in association with VAXZEVRIA.

The search did not yield any articles that were considered relevant for further evaluation and presentation.

Summary

The pathogenesis TM is thought to be immune-mediated from infection, para-infectious processes, autoimmune disease, or paraneoplastic processes. The exact mechanism of TM following immunization is unknown.

There were 10 cases of TM (fulfilling at least BCC 3 criteria) received during the reporting period, of these, 9 were assessed to be classified as "Possible" according to WHO-UMC causality criteria (as either "Possible" with limited information/ "Possible" with confounders). Seven of the 9 cases were classified as "Possible" with Limited Information based solely on the TTO parameter (reasonable TTO considered) as there was insufficient case information (such as vaccinees' medical history, comorbidities, concomitant medications, etiological work-up etc). For the remaining four cases the event could also be explained by the vaccinees' diseases or other medications.

In addition, an observed versus expected analysis of cumulative cases meeting Brighton collaboration criteria levels 1-3 showed that the observed number of TM cases fulfilling case definition are either less than or significantly less than the number of expected cases in all risk windows.

Conclusion

The information from this updated periodic review found insufficient evidence for a new or emerging signal regarding Transverse Myelitis and VAXZEVRIA. No changes to the CDS or RMP are recommended for Transverse Myelitis. As such, the topic will continue to be to be closely monitored as part of AstraZeneca's ongoing surveillance efforts for the important potential risk of immune mediated neurological conditions.

16.3.1.3 Vaccine-associated enhanced disease (VAED) / including vaccine-associated enhanced respiratory disease (VAERD)

During the period covered by this PBRER, the important potential risk of "Vaccine-associated enhanced disease, (VAED)", has been reclassified and removed from the list of safety concerns (Core RMP V8 dated 10 November 2022).

The review of the topic VAED/VAERD for this covering period of the PBRER is presented below:

Review of Cases

A cumulative search (29 December 2020 to 28 December 2022) and interval search (29 June 2022 to 28 December 2022) of the AstraZeneca Global Patient Safety Database was conducted for adverse event reports of Vaccine-associated enhanced disease (VAED) / Vaccine-associated enhanced respiratory disease (VAERD) in association with the use of VAXZEVRIA. The search was conducted using the following MedDRA (version 25.1) Preferred Terms: Acute lung injury; Acute respiratory failure; Autoimmune myositis; Breakthrough COVID-19; Coagulopathy; Coronavirus pneumonia; COVID-19 pneumonia; Cytokine abnormal; Cytokine release syndrome; Cytokine storm; Cytokine increased; Fibrinogen degradation products increased; Immune-mediated lung disease; Immune-mediated myositis; The International Society on Thrombosis and Haemostasis (ISTH) score for disseminated intravascular coagulation; Mechanical ventilation; Multiple organ dysfunction syndrome; Organ failure; Pneumonia; Pneumonitis; Post-acute COVID-19 syndrome; Pulmonary haemorrhage; Respiratory failure; SARS-CoV-2 sepsis; Septic coagulopathy; Septic cerebral embolism; Vaccine associated enhanced disease; Vaccine associated enhanced respiratory disease; Vaccine derived SARS-CoV-2 infection.

Interval Period (29 June 2022 to 28 December 2022)

During the interval period covered by this report, 320 events from 304 cases (175 initial and 129 follow-up) were retrieved under this AESI concept, which includes Pneumonia (108), Breakthrough COVID-19 (76), Post-acute COVID-19 syndrome (32), COVID-19 pneumonia (26), Coagulopathy (22), Respiratory failure (20), Acute respiratory failure (9), Multiple organ dysfunction syndrome (6), Pneumonitis (6), Pulmonary haemorrhage (4), Autoimmune myositis (3), Cytokine increased (3), Vaccine associated enhanced respiratory disease (2), Cytokine abnormal (1), Organ failure (1), SARS-CoV-2 sepsis (1).

Among these 304 cases, the majority were from spontaneous sources (211, 69.4%), followed by literature (50, 16.4%), non-interventional studies (38, 12.5%), and AZ-sponsored clinical trials (5, 1.6%). Of these 304 cases, 186 cases (118 serious and 68 non-serious) were medically confirmed. There were 69 (22.7%) case reports from elderly (≥65 years of age) vaccinees, 167 (54.9%) from adult (18 - 64 years of age) vaccinees, 7 (2.3%) from paediatric (0 – 17 years of age) vaccinees and age was unknown in 61 (20.1%) vaccinees. The outcome of potential VAED/VAERD events was fatal in 35 of the total 304 (11.5%) cases reported during the interval period.

Cumulative data through 28 December 2022

There have been 2420 case reports of potential VAED/VAERD which included 2537 events. These events include Pneumonia (981), COVID-19 pneumonia (400), Coagulopathy (393), Respiratory failure (204), Pneumonitis (109), Breakthrough COVID-19 (100), Multiple organ

dysfunction syndrome (97), Acute respiratory failure (81), Post-acute COVID-19 syndrome (76), Pulmonary haemorrhage (31), Organ failure (15), Cytokine storm (12), Autoimmune myositis (7), Mechanical ventilation (5), Vaccine associated enhanced disease (5), Immune-mediated myositis (4), Acute lung injury (3), Cytokine increased (3), Cytokine release syndrome (3), Vaccine associated enhanced respiratory disease (3), SARS-CoV-2 sepsis (2), Coronavirus pneumonia (1), Cytokine abnormal (1), and Vaccine derived SARS-CoV-2 infection (1). In 404 cases, the event occurred after Dose 2 and in 14 after the Booster/Dose 3. The Time to Onset for the 2537 events is between day of vaccination and 690 days. In total, 176 patients were associated with medical history of immunocompromised conditions like, Pneumonia, Pneumonitis, Respiratory failure, Coagulopathy, Multiple organ dysfunction syndrome, Acute respiratory failure, COVID-19 pneumonia, Mechanical ventilation etc.

Among these 2420 cases, the majority were from spontaneous sources (2266, 93.6%), followed by literature (78, 3.2%), non-interventional studies (67, 2.8%), and AZ-sponsored clinical trials (9, 0.4%). Of these 2420 cases, 1176 cases were reported from females and 1146 from males; and in the remaining 98 cases, gender was unknown. Among total cases, 1164 (1041 serious and 123 non-serious) were medically confirmed cases with the use of VAXZEVRIA. There were 888 (36.7%) case reports from elderly (≥65 years of age) vaccinees, 1291 (53.3%) from adult (18 - 64 years of age) vaccinees, 8 (0.3%) from paediatric (0 – 17 years of age) vaccinees, and age was unknown in 233 (9.6%) vaccinees. In 388 of the 2420 cases, the outcome of events was reported as fatal.

Literature

A search of the Embase and InsightMeme.com databases was undertaken covering the interval period to identify literature on VAED/VAERD with COVID-19 vaccines, including VAXZEVRIA.

A total of 155 (137 from Embase and 18 from InsightMeme) search results were obtained. Of these, none identified any new safety information or discussions of the mechanism of action relevant to the review of this topic.

Summary

On review of 304 cases of VAED/VAERD received during the reporting period, a majority (215 out of 304, 70.7%) of them were reported as serious, of which 118 cases were medically confirmed, and 35 out of 304 (11.5%) cases reported fatal outcomes. These cases had insufficient information on dose latency, medical history, concomitant medications, baseline medical condition prior to vaccination, clinical course, diagnostic and etiologic workup, and storage and transport conditions of the vaccine, which precluded a proper causal assessment. No hypothesized mechanism/pathways have been identified to date. No new safety information on this topic was identified through the review of the literature.

At the end of the reporting period, the important potential risk VAED/VAERD is reclassified and removed from the list of safety concerns and the justification for removal is presented below:

VAED including VAERD is a theoretical risk highlighted by the Regulators based on the previous preclinical models, although it has not been observed in clinical studies nor in the post-authorization experience with any COVID-19 vaccine. On the contrary, more COVID-19 related morbidity and mortality has been observed in unvaccinated populations globally. Cumulatively up to 28 June 2022, 2139 case reports (88% reported as serious) of potential VAED/VAERD were retrieved from the post-marketing setting, however there were no confirmed reports of VAED/VAERD. There is insufficient evidence of a reasonable possibility of a causal association between VAED/VAERD and VAXZEVRIA and the risk is neither considered as 'potential' nor 'important' and hence removed from the list of safety concerns. Updated data from the post-marketing experience (with > 2.2 billion doses administered globally) do not support the initial supposition and there is no reasonable expectation that additional pharmacovigilance activity could further characterize the risk. This risk will continue to be monitored through routine pharmacovigilance activities.

Conclusion

Based on the evaluation of the available data during the reporting period and considering the cumulative experience, the important potential risk of VAED/VAERD is removed from the list of safety concerns.

16.3.2 New information on important identified risks

16.3.2.1 Thrombosis in combination with thrombocytopenia / TTS

All Important identified risks included in Section 16.1 are kept under close surveillance by AstraZeneca.

Thrombosis in combination with thrombocytopenia / Thrombosis with thrombocytopenia syndrome

A cumulative search till 28 December 2022 of the AstraZeneca Global Safety Database for Thrombosis in combination with thrombocytopenia with VAXZEVRIA was performed using MedDRA version 25.1.

The search strategy included: A cumulative search of the AstraZeneca safety database was undertaken for AE reports under the HLT: Thrombocytopenia and SMQ: Hematopoietic Thrombocytopenia Narrow co-reported with events identified from the SMQ: Embolic and thrombotic events with VAXZEVRIA. This search criteria were also applied to retrieve case reports of Thrombosis with thrombocytopenia syndrome (TTS) following both first and second dose of VAXZEVRIA. Also, cases of CVST from Section (16.3.2.1) with platelet count less than 150 $x10^9$/ L were included.

The search resulted in a total of 2647 individual cases (cumulative up to 28 December 2022), and three case was considered potential duplicate on further review. The below analysis was focused on 2644 unique reports. Of the 2644 cases, 2632 (99.5%) were serious and 12 were non serious, 1918 case reports were medically confirmed and 726 were consumer reports and 1794 case reports were from regulatory, 427 from spontaneous, 467 from literature sources and 1 from Post-marketing/non-interventional study. There were 287 cases reported with thrombosis in combination with thrombocytopenia after Dose 2. There were 19 cases occurred after administration of a Dose 3/booster (either of AZD1222 or an mRNA vaccine): 15 after an AZD1222 booster, and 4 after an mRNA booster. The 4 cases after an mRNA booster are not further discussed here as they do not concern the use of AZD1222 as a booster.

During the reporting interval (28 June 2022 to 28 December 2022), there were 322 cases (12% of the total cumulative cases) reported. Of the 322 case reports 260 were initial reports [224 concerning Dose 1, 27 concerning Dose 2, 8 cases concerning Dose 3 and 1 case concerning Dose 4). There were 62 follow-up reports [55 concerning Dose 1, 4 concerning Dose 2 and 3 concerning Dose 3). Further analysis in this report is focused on the cumulative report.

Eight hundred thirty-two 31.4 % (832/2644) originated from UK and the other cases (≥ 20) were from the following countries: Australia (442), Germany (333), Brazil (175), Italy (134), Canada (85), France (69), India (62), Spain (61), Netherlands (60), Belgium (43), Austria (27), Sweden (25), Poland (24), Norway (22), Taiwan (20).

Eighteen percent 18% (482/2644) of the cases reported fatal outcome compared to the 17% (414/2392) fatal outcome reported in the previous PBRER (DLP: 28 June 2022). Fatality/survival rate cumulatively for each month up to 28 December 2022 is presented in Table 148 and Figure 2.

Time to onset (TTO) to TTS event was available in 75 % (1994/2644) case reports and ranged from 0 day to 313 days; median TTO was 12 days. TTO for events within 14, 21 and 42 days by Dose 1, Dose 2, Dose 3 and fatal reports are presented in Table 136. Overall, there were more fatal reports for TTO within 14 and 21 days. Seventy-four percent of the fatal report occurred with 14 days compare to 64% for all cases and 88% of the fatal report occurred with 21 days compare to 80% for all cases.

Table 136 Time to onset for thrombosis in combination with thrombocytopenia cases

	All cases N (%)	Dose 1 N (%)	Dose 2 N (%)	Dose 3 N (%)	Fatal reports N (%)
Time to onset available	1994(75)	1752(75)	231(80)	11(58)	350(73)
14 days	1292(64)	1160(66)	123(53)	9(82)	261(74)
21 days	1603(80)	1442(82)	151(65)	10(90)	309(88)
42 days	1866(94)	1659(95)	197(85)	0(0)	337(96)

Percentage represents percent of total number of cases each dose and fatal report.

Of the 2644 case reports, the reported venous thrombotic sites included CVST (HLT: Cerebrovascular venous and sinus thrombosis) in 643 (24%) cases. Of the 2644 case reports, 122 (5.0%) had the co-reported events from the HLT: Coagulopathies (including 60 cases with DIC) and 905 (34%) case reports had co-reported bleeding event from the narrow SMQ: Haemorrhage terms (excl laboratory terms). The most common (≥10) bleeding events included Cerebral haemorrhage (222), Haemorrhage (78), Haemorrhage intracranial (70), Subarachnoid haemorrhage (66), Disseminated intravascular coagulation (60), Contusion (58), Petechiae (53), Thrombotic thrombocytopenic purpura (49), Haemoptysis (27), Haemorrhagic stroke (26), Haematoma (24), Cerebral haematoma (23), Adrenal haemorrhage (20) Epistaxis (16) Haemorrhagic transformation stroke (15), Rectal haemorrhage (14), Subdural haematoma (12), Ecchymosis (12), Haemorrhagic infarction (12), Haematuria (11), and Purpura (10).

A total of 389 case reports contained PTs from the SMQ: Embolic and thrombotic events, arterial; 1359 reports contained PTs from the SMQ: Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous, and 1764 reports contained PTs from the SMQ: Embolic and thrombotic events, venous. Thrombosis events by site and age group and gender is presented in Table 137. The Table 138 includes all events irrespective of Dose 1, Dose 2 or Dose 3. One case may contain >1 reported thrombosis event; hence the event count is more than the case count. There are 527 events in 389 case reports for SMQ: Embolic and thrombotic events, arterial. The most common (≥30) arterial Embolic and thrombotic events included Ischaemic stroke (52), Peripheral artery thrombosis (50), Thrombotic thrombocytopenic purpura (49), Aortic thrombosis (41) Arterial thrombosis (32), Acute myocardial infarction (31), Carotid artery thrombosis (31), Myocardial infarction (30). There are 1763 events in 1359 case reports for SMQ: Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous. This included most common events (>30) Thrombosis with thrombocytopenia syndrome (531), Thrombosis (435), Cerebrovascular accident (93), Hemiparesis (88), Embolism (74), Cerebral infarction (71), Disseminated intravascular coagulation (60), Cerebral thrombosis (58), Heparin-induced thrombocytopenia (41), Hemiplegia (32).

There are 2608 events in 1764 case reports for SMQ: Embolic and thrombotic events, venous. This included most common events (>30) Pulmonary embolism (747), Cerebral venous sinus

thrombosis (462), Deep vein thrombosis (428), Portal vein thrombosis (187), Cerebral venous thrombosis (134), Superior sagittal sinus thrombosis (70), Venous thrombosis (56), Mesenteric vein thrombosis (56), Jugular vein thrombosis (53), Splenic vein thrombosis (43), Visceral venous thrombosis (38), Hepatic vein thrombosis (36), Superficial vein thrombosis (31), Transverse sinus thrombosis (31)

Table 137 Embolic and thrombotic events in thrombosis with thrombocytopenia case reports age group and gender

PT/Gender	Age - 18-29 Yrs			Age - 30-39 Yrs			Age - 40-49 Yrs			Age - 50-59 Yrs			Age - 60-69 Yrs			Age - 70-79 Yrs			Age - 80+ Yrs			Age Unknown			Grand Total
	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Arterial																									
Ischaemic stroke	2	2		6	2		4	1		11	3		7	5		4	1		1	2		1			52
Peripheral artery thrombosis				2	3		3	8		8	6		11	2		3	2					2			50
Thrombotic thrombocytopenic purpura	4	1		2	1		5	2		2	5		8	3		3	4		2	1		4	1	1	49
Aortic thrombosis				2	2		5	3		4	5		6	7		3	1			1		2			41
Arterial thrombosis	1	1		2	1		2			3	3	1	7	7		2				1		1			32
Acute myocardial infarction		1		1	2		2	5		1	5		3	3		3	4					1			31
Carotid artery thrombosis	2	2		4	7		1	3		3	1		5	1								2			31
Myocardial infarction	1			2	1			4		2	4		2	7		2	4							1	30
Cerebral artery thrombosis				3			1	4		6	2		1	1		1	1					1			21
Transient ischaemic attack					1		2				1			7			4			1			1		17
Peripheral artery occlusion								4		1	1		5	2		2									15
Coronary artery thrombosis				1			1	5		2	2						1								12

Table 137 Embolic and thrombotic events in thrombosis with thrombocytopenia case reports age group and gender

PT/Gender	Age - 18-29 Yrs			Age - 30-39 Yrs			Age - 40-49 Yrs			Age - 50-59 Yrs			Age - 60-69 Yrs			Age - 70-79 Yrs			Age - 80+ Yrs			Age Unknown			Grand Total
	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Cerebral artery occlusion							1			6			3			1									11
Pulmonary artery thrombosis					1			1		3	1		2	1											9
Aortic embolus				1							2		2	1		2						1			9
Splenic artery thrombosis				2				1		1			1	2			1								8
Peripheral embolism	1	1						1		1	2		1	1											8
Carotid artery occlusion				1			1	1		2			2				1								8
Mesenteric artery thrombosis		1									1		2	2									1		7
Thrombotic microangiopathy							1	1					4									1			7
Ischaemic cerebral infarction							2				3		1	1											7
Embolism arterial								2		1			2	2											7
Acute coronary syndrome					1					2	1			1											5
Renal artery thrombosis											2			1			2								5
Peripheral arterial occlusive disease		1									1		1			1						1			5

Table 137 Embolic and thrombotic events in thrombosis with thrombocytopenia case reports age group and gender

PT/Gender	Age - 18-29 Yrs			Age - 30-39 Yrs			Age - 40-49 Yrs			Age - 50-59 Yrs			Age - 60-69 Yrs			Age - 70-79 Yrs			Age - 80+ Yrs			Age Unknown			Grand Total
	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Lacunar infarction					1						1			2						1					5
Amaurosis fugax																						3	1		4
Hepatic artery thrombosis					1		1						1									1			4
Retinal artery occlusion				2				1																	3
Pulmonary artery occlusion								1					2												3
Arterial occlusive disease													1			2									3
Vertebral artery thrombosis	1						1																1		3
Subclavian artery thrombosis							1															1			2
Iliac artery occlusion													1	1											2
Mesenteric artery stenosis													2												2
Cerebral artery embolism	1															1									2
Leriche syndrome														1											1
Cerebrovascular insufficiency					1																				1

Table 137 Embolic and thrombotic events in thrombosis with thrombocytopenia case reports age group and gender

PT/Gender	Age - 18-29 Yrs			Age - 30-39 Yrs			Age - 40-49 Yrs			Age - 50-59 Yrs			Age - 60-69 Yrs			Age - 70-79 Yrs			Age - 80+ Yrs			Age Unknown			Grand Total
	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Femoral artery embolism													1												1
Hepatic artery occlusion					1																				1
Retinal artery thrombosis																1									1
Renal artery occlusion														1											1
Stress cardiomyopathy							1																		1
Internal capsule infarction																1									1
Thromboembolectomy													1												1
Basilar artery thrombosis																							1		1
Coronary artery occlusion											1														1
Vertebral artery occlusion													1												1
Truncus coeliacus thrombosis																1									1
Mesenteric arterial occlusion											1														1
Coronary artery bypass				1																					1

Table 137 Embolic and thrombotic events in thrombosis with thrombocytopenia case reports age group and gender

PT/Gender	Age - 18-29 Yrs			Age - 30-39 Yrs			Age - 40-49 Yrs			Age - 50-59 Yrs			Age - 60-69 Yrs			Age - 70-79 Yrs			Age - 80+ Yrs			Age Unknown			Grand Total
	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Blindness transient				1																					1
Renal embolism													1												1
Atrial Total	**13**	**10**	**0**	**33**	**26**	**0**	**35**	**48**	**0**	**59**	**54**	**1**	**87**	**62**	**0**	**33**	**26**	**0**	**3**	**7**	**0**	**22**	**6**	**2**	**527**
Mixed																									
Thrombosis with thrombocytopenia syndrome	50	29		54	32		45	35		43	27	1	46	36	1	15	16		2	7		20	8	64	531
Thrombosis	12	2	1	24	19		40	31		41	38		37	38	1	19	27		5	8		34	19	39	435
Cerebrovascular accident	2			8	2		8	7		7	3		13	3		5	10		9	4		4	6	2	93
Hemiparesis	6	5		6	6		10	6		10	12		10	5		4	1		3			1	3		88
Embolism	3	1		5	2		6	7		4	11		4	7		6	5		1	3		3	5	1	74
Cerebral infarction	3	4		6	5		8	5		6	6		11	3		3	3		1	4		2	1		71
Disseminated intravascular coagulation	2	4		5	5		3	3		6	3		7	3		12	2		1			3		1	60
Cerebral thrombosis	4	6		6	6		4			11	5		4	1			3		3			3	1	1	58
Heparin-induced thrombocytopenia	2	1		4	4		5	3		1	3		2	7		3	1		2	1		1		1	41
Hemiplegia	8	3		2	2		3	2		3	1		5			2	1								32
Haemorrhagic stroke		4		4	1		2	1		2	3		6	1			1					1			26
Splenic infarction		1		4				2		3	2		5	2		2				1					22
Renal infarct		1		3			2	4			3		2	3			1			1					20

Table 137 Embolic and thrombotic events in thrombosis with thrombocytopenia case reports age group and gender

PT/Gender	Age - 18-29 Yrs			Age - 30-39 Yrs			Age - 40-49 Yrs			Age - 50-59 Yrs			Age - 60-69 Yrs			Age - 70-79 Yrs			Age - 80+ Yrs			Age Unknown			Grand Total
	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Haemorrhagic transformation stroke				3	1		2	1					3	1		1			2			1			15
Haemorrhagic infarction	3			4			1	1					1	1								1			12
Cardiac ventricular thrombosis	1							1			1		1	1		1	1			1		1	2		11
Intracardiac thrombus								4		1	2			1		2				1					11
Haemorrhagic cerebral infarction	2						2	1		2	1		2												10
Monoparesis	1	1		2				1		2			1						1						9
Infarction				2			1			3			1	1						1					9
Thrombosis mesenteric vessel				1			2	2		1	1			1											8
Thrombotic stroke							4				1					2	1								8
Intestinal infarction				2			1	1		1	1		1	1											8
Haemorrhagic adrenal infarction				3	1						1		1				1		1						8
Cerebral ischaemia							1			1	1			3			1								7
Hepatic vascular thrombosis				1			1	1						2			1							1	7
Hepatic infarction					1			1			1		2			2									7
Splenic thrombosis							1	2		1	1			1											6

Table 137 Embolic and thrombotic events in thrombosis with thrombocytopenia case reports age group and gender

PT/Gender	Age - 18-29 Yrs			Age - 30-39 Yrs			Age - 40-49 Yrs			Age - 50-59 Yrs			Age - 60-69 Yrs			Age - 70-79 Yrs			Age - 80+ Yrs			Age Unknown			Grand Total
	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Antiphospholipid syndrome	1						1				1		1			1						1			6
Spontaneous heparin-induced thrombocytopenia syndrome				1						1			2										1		5
Atrial thrombosis													2	1			1						1		5
Vascular stent thrombosis				1										1			1			2					5
Renal vascular thrombosis					1		1	1		1															4
Quadriparesis				1				1					1	1											4
Monoplegia				1				1						1									1		4
Thrombectomy								1		1													1		3
Cerebellar infarction				1							1		1												3
Diplegia				1										1									1		3
Quadriplegia										1	2														3
Injection site thrombosis																						2			2
Adrenal thrombosis	1						1																		2
Paresis		1												1											2
Brain stem stroke																1							1		2
Brain stem infarction					1								1												2

Table 137 Embolic and thrombotic events in thrombosis with thrombocytopenia case reports age group and gender

PT/Gender	Age - 18-29 Yrs			Age - 30-39 Yrs			Age - 40-49 Yrs			Age - 50-59 Yrs			Age - 60-69 Yrs			Age - 70-79 Yrs			Age - 80+ Yrs			Age Unknown			Grand Total
	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Embolic stroke													1						1						2
Foetal vascular malperfusion				2																					2
Embolic cerebral infarction													1	1											2
Prosthetic cardiac valve thrombosis		1															1								2
Pancreatic infarction														1											1
Vascular operation																							1		1
Haemorrhoids thrombosed							1																		1
Post procedural stroke											1														1
Eye infarction				1																					1
Cerebrovascular disorder																	1								1
Cerebral congestion										1															1
Thalamic infarction										1															1
Vascular graft thrombosis														1											1
Mesenteric vascular occlusion				1																					1
Paraparesis														1											1

Table 137 Embolic and thrombotic events in thrombosis with thrombocytopenia case reports age group and gender

PT/Gender	Age - 18-29 Yrs			Age - 30-39 Yrs			Age - 40-49 Yrs			Age - 50-59 Yrs			Age - 60-69 Yrs			Age - 70-79 Yrs			Age - 80+ Yrs			Age Unknown			Grand Total
	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Autoimmune heparin-induced thrombocytopenia				1																					1
Thrombosis in device														1											1
Mixed Total	**101**	**64**	**1**	**160**	**89**	**0**	**156**	**126**	**0**	**155**	**133**	**1**	**175**	**133**	**2**	**81**	**80**	**0**	**32**	**34**	**0**	**78**	**52**	**110**	**1763**
Venous																									
Pulmonary embolism	31	12		33	17		52	44	2	66	53	1	86	112	1	51	84		29	30		19	22	2	747
Cerebral venous sinus thrombosis	28	36		50	31		84	25		56	35		50	18		10	4		1	3		20	8	4	463
Deep vein thrombosis	11	6		10	11		18	22		28	36	1	53	83		30	55	1	20	20		8	14	1	428
Portal vein thrombosis	12	7		20	15		24	12	1	29	22		13	12		7	3		3	1		3	2	1	187
Cerebral venous thrombosis	14	10		17	7		23	10		12	7		14	8		3	1					2	4	2	134
Superior sagittal sinus thrombosis	11	7	1	9	3		11	6		6	4		2	5		2			1			1	1		70
Venous thrombosis	2	1		6	6		4	8		9	3		7	1		4			1			2	2		56
Mesenteric vein thrombosis	1	1		7	6		6	4		8	5		2	4		5	1		1	1		2	1	1	56
Jugular vein thrombosis	3	2		2	1		13	7		7	4		8	1		1	1			1		2			53
Splenic vein thrombosis	3	1		10	5		4	1		6	4		4	3		2									43

Table 137 Embolic and thrombotic events in thrombosis with thrombocytopenia case reports age group and gender

PT/Gender	Age - 18-29 Yrs			Age - 30-39 Yrs			Age - 40-49 Yrs			Age - 50-59 Yrs			Age - 60-69 Yrs			Age - 70-79 Yrs			Age - 80+ Yrs			Age Unknown			Grand Total
	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Visceral venous thrombosis	2			4			5	4		8	6		4	2		1	1							1	38
Hepatic vein thrombosis	5	1		2	1		4	3		5			7	3		2	1					1	1		36
Superficial vein thrombosis				1	1		4	2		5	4		3	4		2	2		1	2					31
Transverse sinus thrombosis		2		6	1		5	3		3	3		3	1		4									31
Pulmonary thrombosis	2			3	1		3	1		3	2		2	5		1	1			2			1	1	28
Pelvic venous thrombosis	2			5	1		2	1		2	5		6	1			1					1			27
Venous thrombosis limb					1		4			4	2	1	4	1		1	2					2	1		23
Thrombophlebitis					1		2			3	5	1	3	2						1		1	1		20
Renal vein thrombosis	1	1		4			5			2			3	1		2									19
Pulmonary infarction							1	2		8	2		1			1	2		1				1		19
Embolism venous	1			1	1		2			1	2		1	2									1		12
Portosplenomesenteric venous thrombosis		1		1	1			1		2	2		2	1										1	12
Vena cava thrombosis							1			3	2			2			1								9
Ophthalmic vein thrombosis	1			2						4				1						1					9
Retinal vein occlusion		2		1									3	1			1								8

Table 137 Embolic and thrombotic events in thrombosis with thrombocytopenia case reports age group and gender

PT/Gender	Age - 18-29 Yrs			Age - 30-39 Yrs			Age - 40-49 Yrs			Age - 50-59 Yrs			Age - 60-69 Yrs			Age - 70-79 Yrs			Age - 80+ Yrs			Age Unknown			Grand Total
	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Sigmoid sinus thrombosis					2			1		2	1											1			7
Cavernous sinus thrombosis	2			1			1							1								1			6
Ovarian vein thrombosis				1			1			1						1									4
Portal vein occlusion							2	1																	3
Pulmonary venous thrombosis										1			2												3
Venous occlusion											1											2			3
Retinal vein thrombosis													2									1			3
Axillary vein thrombosis											1			1											2
Subclavian vein thrombosis											1								1						2
Budd-Chiari syndrome							2																		2
Peripheral vein thrombosis																						1	1		2
Portal vein embolism					1			1																	2
Jugular vein occlusion							1							1											2

Table 137 Embolic and thrombotic events in thrombosis with thrombocytopenia case reports age group and gender

PT/Gender	Age - 18-29 Yrs			Age - 30-39 Yrs			Age - 40-49 Yrs			Age - 50-59 Yrs			Age - 60-69 Yrs			Age - 70-79 Yrs			Age - 80+ Yrs			Age Unknown			Grand Total
	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Portal vein cavernous transformation																	1								1
Peripheral vein occlusion											1														1
Venoocclusive liver disease							1																		1
Hepatic vein occlusion					1																				1
Hepatic vein embolism										1															1
Vena cava filter insertion											1														1
Renal vein embolism		1																							1
Splenic vein occlusion								1																	1
Post thrombotic syndrome																1									1
Venous Total	**132**	**91**	**1**	**196**	**115**	**0**	**285**	**160**	**3**	**285**	**214**	**4**	**285**	**277**	**1**	**131**	**162**	**1**	**59**	**62**	**0**	**70**	**61**	**14**	**2609**

F Female; M Male; PT Preferred Term; U Unknown; Yrs Years

Reporting Rate

Reporting rate for thrombosis in combination with thrombocytopenia across all age groups based on the data from both UK and EEA by risk window of 21 days and 42 days is provided in Table 138 and Table 139 respectively. Reporting rate is also stratified by Dose 1 and Dose 2 and Dose 3.

The overall TTS reporting rate from the UK was 11.12/million (544 identified reports with time to onset ≤ 21 days; estimated exposure 48.91 million administered doses) when compared to 5.6 (event rates per 1M Person Years (PY) per 21 days Truven Market Scan-2019, aligned with the Observational Health Data Science and Informatics (OHDSI) TTS algorithm) and 10.7 (event rates per 1M PY per 21days Truven Market Scan-2019). The reporting rate for the cases where the MHRA case classification criteria was met (confirmed, probable, and possible) cases was 9.73 /million administered doses.

The reporting rate for Dose 1, Dose 2 and Dose 3 was 18.97, 3.02 and 95.78 /million doses administered doses respectively. For all administered doses and Dose 1, the reporting rate in the 18 to 39 and 40 to 49 age groups was higher when compared to background rate however reporting rate in 50 to 64 age group was less compared to the background rate. Reporting rate for Dose 2 was less when compared to the background rate for overall and all age stratifications.

The overall TTS reporting rate from the EEA was 13.19 /million (635 identified reports with time to onset ≤ 21 days; estimated exposure 48.15 million administered doses) when compared to 5.6 (event rates per 1M PY per 21 days Truven Market Scan-2019, aligned with the OHDSI TTS algorithm) and 10.7 (event rates per 1M PY per 21days Truven Market Scan- 2019). The reporting rate for the cases where the MHRA case classification criteria was met (confirmed, probable and possible) was 7.29/million administered doses. Reporting rate for Dose 1 Dose 2 and Dose 3 was 24.24, 0.96, and 53.25 /million doses administered doses. EEA Reporting rate in 18-49 age group and 50-59 years age group with all doses and Dose 1 was higher when compared to background rate; reporting rate for Dose 2 was within the background rate for overall and all age stratifications.

The reporting rate for cases occurring within 42 days from UK and EEA are provided in Table 139. About 94% of the cases have occurred within 42 days after vaccination.

Table 138 Reporting rate for thrombosis in combination with thrombocytopenia by risk window of 21 days

UK 21 Days RW								
Age Group	Total Exposed	Cases within Risk Window of 21 days	Confirmed, probable and possible cases within Risk Window of 21 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
All Dose (UK)								
Age - 18-39 Yrs	5227125	100	88	19.13	16.84	2.1-3.2	17.03 to 15.93	14.74 to 13.64
Age - 40-49 Yrs	8954709	139	121	15.52	13.51	3.4-6.3	12.12 to 9.22	10.11 to 7.21
Age - 50-64 Yrs	17999174	169	151	9.39	8.39	7.3-14.9	2.09 to -5.51	1.09 to -6.51
Age - > 65 Yrs	13443624	103	87	7.66	6.47	23.4-44.4	-15.74 to -36.74	-16.93 to -37.93
Age Unknown	3294137	33	28	10.02	8.5			
Grand Total	48918769	544	475	11.12	9.71	5.6-10.7	5.52 to 0.42	4.11 to -0.98
Dose 1 (UK)								
Age - 18-39 Yrs	2663686	96	84	36.04	31.54	2.1-3.2	33.94 to 32.84	29.44 to 28.34
Age - 40-49 Yrs	4535864	132	116	29.1	25.57	3.4-6.3	25.7 to 22.8	22.17 to 19.27
Age - 50-64 Yrs	9060897	152	138	16.78	15.23	7.3-14.9	9.48 to 1.88	7.93 to 0.33
Age - > 65 Yrs	6737698	63	54	9.35	8.01	23.4-44.4	-14.05 to -35.05	-15.39 to -36.39

Table 138 Reporting rate for thrombosis in combination with thrombocytopenia by risk window of 21 days

UK 21 Days RW								
Age Group	Total Exposed	Cases within Risk Window of 21 days	Confirmed, probable and possible cases within Risk Window of 21 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
Age Unknown	1723525	26	21	15.09	12.18			
Grand Total	24721670	469	413	18.97	16.71	5.6-10.7	13.37 to 8.27	11.11 to 6.01
Dose 2 (UK)								
Age - 18-39 Yrs	2558509	4	4	1.56	1.56	2.1-3.2	-0.54 to -1.64	-0.54 to -1.64
Age - 40-49 Yrs	4412378	7	5	1.59	1.13	3.4-6.3	-1.81 to -4.71	-2.27 to -5.17
Age - 50-64 Yrs	8921359	16	12	1.79	1.35	7.3-14.9	-5.51 to -13.11	-5.95 to -13.55
Age - > 65 Yrs	6679268	39	33	5.84	4.94	23.4-44.4	-17.56 to -38.56	-18.46 to -39.46
Age Unknown	1566438	7	7	4.47	4.47			
Grand Total	24137952	73	61	3.02	2.53	5.6-10.7	-2.58 to -7.68	-3.07 to -8.17
All Dose (EEA)								
18-49	11827734	239	140	20.21	11.84	2.61-4.34	15.87 to 17.6	7.5 to 9.23
50-59	6495374	107	69	16.47	10.62	5.98-12.3	4.17 to 10.49	-1.68 to 4.64
60-69	20461213	189	102	9.24	4.99	11-22.5	-13.26 to -1.76	-17.51 to -6.01
70-79	8193743	70	27	8.54	3.3	22.3-45.2	-36.66 to -13.76	-41.9 to -19

Table 138 Reporting rate for thrombosis in combination with thrombocytopenia by risk window of 21 days

UK 21 Days RW								
Age Group	Total Exposed	Cases within Risk Window of 21 days	Confirmed, probable and possible cases within Risk Window of 21 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
80+	1165347	14	7	12.01	6.01	34.2-55.9	-43.89 to -22.19	-49.89 to -28.19
Age Unknown	8441	16	6	1895.51	710.82	-		
Grand Total	48151852	635	351	13.19	7.29	5.62-10.7	2.49 to 7.57	-3.41 to 1.67
Dose 1 (EEA)								
18-49	6434510	234	136	36.37	21.14	2.61-4.34	32.03 to 33.76	16.8 to 18.53
50-59	3518799	105	69	29.84	19.61	5.98-12.3	17.54 to 23.86	7.31 to 13.63
60-69	10521781	180	99	17.11	9.41	11-22.5	-5.39 to 6.11	-13.09 to -1.59
70-79	4176155	64	25	15.33	5.99	22.3-45.2	-29.87 to -6.97	-39.21 to -16.31
80+	596132	14	7	23.48	11.74	34.2-55.9	-32.42 to -10.72	-44.16 to -22.46
Age Unknown	4187	15	6	3582.52	1433.01	-		
Grand Total	25251564	612	342	24.24	13.54	5.62-10.7	13.54 to 18.62	2.84 to 7.92
Dose 2 (EEA)								
18-49	5385769	5	4	0.93	0.74	2.61-4.34	-3.41 to -1.68	-3.6 to -1.87
50-59	2972927	2	0	0.67	0	5.98-12.3	-11.63 to -5.31	-12.3 to -5.98
60-69	9934975	9	3	0.91	0.3	11-22.5	-21.59 to -10.09	-22.2 to -10.7
70-79	4014635	6	2	1.49	0.5	22.3-45.2	-43.71 to -20.81	-44.7 to -21.8
80+	567777	0	0	0	0	34.2-55.9	-55.9 to -34.2	-55.9 to -34.2

Table 138 Reporting rate for thrombosis in combination with thrombocytopenia by risk window of 21 days

UK 21 Days RW								
Age Group	Total Exposed	Cases within Risk Window of 21 days	Confirmed, probable and possible cases within Risk Window of 21 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
Age Unknown	3931	0	0	0	0	-		
Grand Total	22880014	22	9	0.96	0.39	5.62-10.7	-9.74 to -4.66	-10.31 to -5.23

Background event rates per 1M PY per 21 days from Truven Market Scan-2019
EEA European Economic Area; UK United Kingdom.

Table 139 Reporting rate for thrombosis in combination with thrombocytopenia by risk window of 42 days

UK 42 Days RW								
Age Group	Total Exposed	Cases within Risk Window of 42 days	Confirmed, probable and possible cases within Risk Window of 42 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
All Dose (UK)								
Age - 18-39 Yrs	5227125	113	98	21.62	18.75	4.2-6.4	17.42 to 15.22	14.55 to 12.35
Age - 40-49 Yrs	8954709	155	134	17.31	14.96	6.8-12.6	10.51 to 4.71	8.16 to 2.36
Age - 50-64 Yrs	17999174	204	184	11.33	10.22	14.6-29.8	-3.27 to -18.47	-4.38 to -19.58

Table 139 Reporting rate for thrombosis in combination with thrombocytopenia by risk window of 42 days

UK 42 Days RW								
Age Group	Total Exposed	Cases within Risk Window of 42 days	Confirmed, probable and possible cases within Risk Window of 42 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
Age - > 65 Yrs	13443624	134	114	9.97	8.48	46.8-88.8	-36.83 to -78.83	-38.32 to -80.32
Age Unknown	3294137	43	35	13.05	10.62	-		
Grand Total	48918769	649	565	13.27	11.55	11.2-21.4	2.07 to -8.13	0.35 to -9.85
Dose 1 (UK)								
Age - 18-39 Yrs	2663686	107	93	40.17	34.91	4.2-6.4	35.97 to 33.77	30.71 to 28.51
Age - 40-49 Yrs	4535864	147	128	32.41	28.22	6.8-12.6	25.61 to 19.81	21.42 to 15.62
Age - 50-64 Yrs	9060897	182	166	20.09	18.32	14.6-29.8	5.49 to -9.71	3.72 to -11.48
Age - > 65 Yrs	6737698	86	73	12.76	10.83	46.8-88.8	-34.04 to -76.04	-35.97 to -77.97
Age Unknown	1723525	32	25	18.57	14.51	-		
Grand Total	24721670	554	485	22.41	19.62	11.2-21.4	11.21 to 1.01	8.42 to -1.78
Dose 2 (UK)								
Age - 18-39 Yrs	2558509	6	5	2.35	1.95	4.2-6.4	-1.85 to -4.05	-2.25 to -4.45

Table 139 Reporting rate for thrombosis in combination with thrombocytopenia by risk window of 42 days

UK 42 Days RW								
Age Group	Total Exposed	Cases within Risk Window of 42 days	Confirmed, probable and possible cases within Risk Window of 42 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
Age - 40-49 Yrs	4412378	8	6	1.81	1.36	6.8-12.6	-4.99 to -10.79	-5.44 to -11.24
Age - 50-64 Yrs	8921359	21	17	2.35	1.91	14.6-29.8	-12.25 to -27.45	-12.69 to -27.89
Age - > 65 Yrs	6679268	47	41	7.04	6.14	46.8-88.8	-39.76 to -81.76	-40.66 to -82.66
Age Unknown	1566438	11	10	7.02	6.38	-		
Grand Total	24137952	93	79	3.85	3.27	11.2-21.4	-7.35 to -17.55	-7.93 to -18.13
All Dose (EEA)								
18-49	11827734	259	146	21.9	12.34	5.22-8.68	13.22 to 16.68	3.66 to 7.12
50-59	6495374	118	74	18.17	11.39	11.96-24.6	-6.43 to 6.21	-13.21 to -0.57
60-69	20461213	218	115	10.65	5.62	22-45	-34.35 to -11.35	-39.38 to -16.38
70-79	8193743	81	30	9.89	3.66	44.6-90.4	-80.51 to -34.71	-86.74 to -40.94
80+	1165347	18	10	15.45	8.58	68.4-111.8	-96.35 to -52.95	-103.22 to -59.82
Age Unknown	8441	17	6	2013.98	710.82	-		
Grand Total	48151852	711	381	14.77	7.91	11.24-21.4	-6.63 to 3.53	-13.49 to -3.33
Dose 1 (EEA)								
18-49	6434510	253	142	39.32	22.07	5.22-8.68	30.64 to 34.1	13.39 to 16.85

Table 139 Reporting rate for thrombosis in combination with thrombocytopenia by risk window of 42 days

UK 42 Days RW								
Age Group	Total Exposed	Cases within Risk Window of 42 days	Confirmed, probable and possible cases within Risk Window of 42 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
50-59	3518799	116	74	32.97	21.03	11.96-24.6	8.37 to 21.01	-3.57 to 9.07
60-69	10521781	201	110	19.1	10.45	22-45	-25.9 to -2.9	-34.55 to -11.55
70-79	4176155	74	27	17.72	6.47	44.6-90.4	-72.68 to -26.88	-83.93 to -38.13
80+	596132	18	10	30.19	16.77	68.4-111.8	-81.61 to -38.21	-95.03 to -51.63
Age Unknown	4187	16	6	3821.35	1433.01	0-0		
Grand Total	25251564	678	369	26.85	14.61	11.24-21.4	5.45 to 15.61	-6.79 to 3.37
Dose 2 (EEA)								
18-49	5385769	6	4	1.11	0.74	5.22-8.68	-7.57 to -4.11	-7.94 to -4.48
50-59	2972927	2	0	0.67	0	11.96-24.6	-23.93 to -11.29	-24.6 to -11.96
60-69	9934975	17	5	1.71	0.5	22-45	-43.29 to -20.29	-44.5 to -21.5
70-79	4014635	7	3	1.74	0.75	44.6-90.4	-88.66 to -42.86	-89.65 to -43.85
80+	567777	0	0	0	0	68.4-111.8	-111.8 to -68.4	-111.8 to -68.4
Age Unknown	3931	0	0	0	0	-		
Grand Total	22880014	32	12	1.4	0.52	11.24-21.4	-20 to -9.84	-20.88 to -10.72

Background event rates per 1M PY per 42 days from Truven Market Scan-2019

EEA European Economic Area; UK United Kingdom.

Observed versus Expected Analysis

Observed versus expected analyses for TTS (including CVST) and CVST with thrombocytopenia are presented below (Table 140, Table 141 and Table 142. Background rates for TTS were derived from MarketScan (US claims) data, using OHDSI-aligned code lists and definitions for TTS. Algorithm 2 for TTS uses updated OHDSI-aligned code lists and washout periods (previously patients with thrombosis in the 2 years prior to 2019 were excluded).

The background rate (incidence rate) of TTS is 9.77 /100,000 person year and 11.14/100,000 person year. The observed number of cases, for all risk windows of 14, 21 and 42 days (with unknown time to onset not included) is less than expected post vaccination by VAXZEVRIA.

The observed number of cases are significantly more than expected, for risk windows of 14 days (with unknown time to onset included) post vaccination by VAXZEVRIA with both background rates.

The observed number of cases for risk windows of 21 days (with unknown time to onset included) post vaccination by VAXZEVRIA of TTS is less than the expected with background rate 9.77/100,000 person year and 11.14/100,000 person year.

The observed number of cases for risk windows of 42 days (with unknown time to onset included) post vaccination by VAXZEVRIA of TTS is less than expected with both background rates.

Table 140 Observed Versus Expected analysis for Thrombosis with thrombocytopenia (Overall)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS Overall	14	9.77	466115644	1292	1745.56	0.74 (0.7 - 0.78)	Observed significantly < expected
TTS Overall	21	9.77	466115644	1603	2618.34	0.61 (0.58 - 0.64)	Observed significantly < expected
TTS Overall	42	9.77	466115644	1866	5236.68	0.36 (0.34 - 0.37)	Observed significantly < expected
TTS Overall (RW14+Unk TTO)	14	9.77	466115644	1942	1745.56	1.11 (1.06 - 1.16)	Observed significantly > expected
TTS Overall (RW21+Unk TTO)	21	9.77	466115644	2253	2618.34	0.86 (0.83 - 0.9)	Observed significantly < expected
TTS Overall (RW42+Unk TTO)	42	9.77	466115644	2516	5236.68	0.48 (0.46 - 0.5)	Observed significantly < expected
TTS Overall	14	11.14	466115644	1292	1990.33	0.65 (0.61 - 0.69)	Observed significantly < expected
TTS Overall	21	11.14	466115644	1603	2985.5	0.54 (0.51 - 0.56)	Observed significantly < expected
TTS Overall	42	11.14	466115644	1866	5971	0.31 (0.3 - 0.33)	Observed significantly < expected

Table 140 Observed Versus Expected analysis for Thrombosis with thrombocytopenia (Overall)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS Overall (RW14+Unk TTO)	14	11.14	466115644	1942	1990.33	0.98 (0.93 - 1.02)	Observed < expected
TTS Overall (RW21+Unk TTO)	21	11.14	466115644	2253	2985.5	0.75 (0.72 - 0.79)	Observed significantly < expected
TTS Overall (RW42+Unk TTO)	42	11.14	466115644	2516	5971	0.42 (0.41 - 0.44)	Observed significantly < expected

Incidence Rate 9.77/100,000 PY from Truven Market Scan (2019) aligned with the OHDSI TTS algorithm.
TTS Thrombosis with Thrombocytopenia Syndrome

Table 141 Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group (EU+UK+Brazil+Australia)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Incidence Rate from Truven Market Scan (2019) aligned with the OHDSI TTS algorithm							
TTS - 18-49 EU+UK+Brazil+Australia	14	4.53	110094983	488	191.17	2.55 (2.33 - 2.79)	Observed significantly > expected
TTS - 50-59 EU+UK+Brazil+Australia	14	10.4	58336094	220	232.55	0.95 (0.83 - 1.08)	Observed < expected
TTS - 60-69 EU+UK+Brazil+Australia	14	19.19	57960860	244	426.34	0.57 (0.5 - 0.65)	Observed significantly < expected

Table 141 Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group (EU+UK+Brazil+Australia)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Over 70 EU+UK+Brazil+Australia	14	46.31	32376365	190	574.71	0.33 (0.29 - 0.38)	Observed significantly < expected
TTS - 18-49 EU+UK+Brazil+Australia	21	4.53	110094983	567	286.75	1.98 (1.82 - 2.15)	Observed significantly > expected
TTS - 50-59 EU+UK+Brazil+Australia	21	10.4	58336094	292	348.83	0.84 (0.74 - 0.94)	Observed significantly < expected
TTS - 60-69 EU+UK+Brazil+Australia	21	19.19	57960860	315	639.51	0.49 (0.44 - 0.55)	Observed significantly < expected
Over 70 EU+UK+Brazil+Australia	21	46.31	32376365	249	862.07	0.29 (0.25 - 0.33)	Observed significantly < expected
TTS - 18-49 EU+UK+Brazil+Australia	42	4.53	110094983	624	573.5	1.09 (1 - 1.18)	Observed significantly > expected
TTS - 50-59 EU+UK+Brazil+Australia	42	10.4	58336094	337	697.65	0.48 (0.43 - 0.54)	Observed significantly < expected
TTS - 60-69 EU+UK+Brazil+Australia	42	19.19	57960860	379	1279.02	0.3 (0.27 - 0.33)	Observed significantly < expected
Over 70 EU+UK+Brazil+Australia	42	46.31	32376365	322	1724.13	0.19 (0.17 - 0.21)	Observed significantly < expected

Table 141 Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group (EU+UK+Brazil+Australia)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Incidence Rate from Truven Market Scan database (2019) aligned with the OHDSI TTS algorithm, updated OHDSI-aligned codelists and washout periods							
TTS - 18-49 EU+UK+Brazil+Australia	14	4.99	110094983	488	210.58	2.32 (2.12 - 2.53)	Observed significantly > expected
TTS - 50-59 EU+UK+Brazil+Australia	14	12.6	58336094	220	281.74	0.78 (0.68 - 0.89)	Observed significantly < expected
TTS - 60-69 EU+UK+Brazil+Australia	14	22.33	57960860	244	496.1	0.49 (0.43 - 0.56)	Observed significantly < expected
Over 70 EU+UK+Brazil+Australia	14	49.5	32376365	190	614.3	0.31 (0.27 - 0.36)	Observed significantly < expected
TTS - 18-49 EU+UK+Brazil+Australia	21	4.99	110094983	567	315.87	1.8 (1.65 - 1.95)	Observed significantly > expected
TTS - 50-59 EU+UK+Brazil+Australia	21	12.6	58336094	292	422.62	0.69 (0.61 - 0.77)	Observed significantly < expected
TTS - 60-69 EU+UK+Brazil+Australia	21	22.33	57960860	315	744.15	0.42 (0.38 - 0.47)	Observed significantly < expected

Table 141 Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group (EU+UK+Brazil+Australia)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Over 70 EU+UK+Brazil+Australia	21	49.5	32376365	249	921.45	0.27 (0.24 - 0.31)	Observed significantly < expected
TTS - 18-49 EU+UK+Brazil+Australia	42	4.99	110094983	624	631.74	0.99 (0.91 - 1.07)	Observed < expected
TTS - 50-59 EU+UK+Brazil+Australia	42	12.6	58336094	337	845.23	0.4 (0.36 - 0.44)	Observed significantly < expected
TTS - 60-69 EU+UK+Brazil+Australia	42	22.33	57960860	379	1488.3	0.25 (0.23 - 0.28)	Observed significantly < expected
Over 70 EU+UK+Brazil+Australia	42	49.5	32376365	322	1842.9	0.17 (0.16 - 0.19)	Observed significantly < expected

Incidence Rate from Truven Market Scan database (2019) aligned with the OHDSI TTS algorithm, updated OHDSI-aligned codelists and washout periods
CI Confidence Interval; E Expected; EU European Union; O Observed; TTS Thrombosis with Thrombocytopenia Syndrome; UK United Kingdom

Table 142 Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group/sex (UK)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
Incidence Rate from Truven Market Scan (2019) aligned with the OHDSI TTS algorithm							
TTS - Female UK	14	8.2	23252503	216	73.09	2.96 (2.57 - 3.38)	Observed significantly > expected
TTS - Male UK	14	11.49	22377923	199	98.56	2.02 (1.75 - 2.32)	Observed significantly > expected
TTS - Female 18-49 UK	14	4.53	7414701	109	12.87	8.47 (6.95 - 10.22)	Observed significantly > expected
TTS - Female 50-59 UK	14	9.07	5944683	42	20.67	2.03 (1.46 - 2.75)	Observed significantly > expected
TTS - Female 60-69 UK	14	12.88	4783416	29	23.62	1.23 (0.82 - 1.76)	Observed > expected
TTS - Female 70-79 UK	14	31.05	3475875	16	41.37	0.39 (0.22 - 0.63)	Observed significantly < expected
TTS - Female over 80 UK	14	40.77	1630324	8	25.48	0.31 (0.14 - 0.62)	Observed significantly < expected
TTS - Male 18-49 UK	14	4.54	6766098	85	11.77	7.22 (5.77 - 8.93)	Observed significantly > expected

Table 142 Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group/sex (UK)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS - Male 50-59 UK	14	11.87	6510960	53	29.62	1.79 (1.34 - 2.34)	Observed significantly > expected
TTS - Male 60-69 UK	14	26.19	4934728	22	49.54	0.44 (0.28 - 0.67)	Observed significantly < expected
TTS - Male 70-79 UK	14	48.22	3137304	22	57.99	0.38 (0.24 - 0.57)	Observed significantly < expected
TTS - Male over 80 UK	14	86.28	1025046	7	33.9	0.21 (0.08 - 0.43)	Observed significantly < expected
TTS - Female UK	21	8.2	23252503	282	109.63	2.57 (2.28 - 2.89)	Observed significantly > expected
TTS - Male UK	21	11.49	22377923	257	147.84	1.74 (1.53 - 1.96)	Observed significantly > expected
TTS - Female 18-49 UK	21	4.53	7414701	133	19.31	6.89 (5.77 - 8.16)	Observed significantly > expected
TTS - Female 50-59 UK	21	9.07	5944683	59	31	1.9 (1.45 - 2.46)	Observed significantly > expected
TTS - Female 60-69 UK	21	12.88	4783416	38	35.42	1.07 (0.76 - 1.47)	Observed > expected

Table 142 Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group/sex (UK)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS - Female 70-79 UK	21	31.05	3475875	27	62.05	0.44 (0.29 - 0.63)	Observed significantly < expected
TTS - Female over 80 UK	21	40.77	1630324	8	38.22	0.21 (0.09 - 0.41)	Observed significantly < expected
TTS - Male 18-49 UK	21	4.54	6766098	103	17.66	5.83 (4.76 - 7.07)	Observed significantly > expected
TTS - Male 50-59 UK	21	11.87	6510960	70	44.44	1.58 (1.23 - 1.99)	Observed significantly > expected
TTS - Male 60-69 UK	21	26.19	4934728	34	74.31	0.46 (0.32 - 0.64)	Observed significantly < expected
TTS - Male 70-79 UK	21	48.22	3137304	27	86.98	0.31 (0.2 - 0.45)	Observed significantly < expected
TTS - Male over 80 UK	21	86.28	1025046	8	50.85	0.16 (0.07 - 0.31)	Observed significantly < expected
TTS - Female UK	42	8.2	23252503	330	219.26	1.51 (1.35 - 1.68)	Observed significantly > expected
TTS - Male UK	42	11.49	22377923	313	295.67	1.06 (0.94 - 1.18)	Observed > expected

Table 142 Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group/sex (UK)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS - Female 18-49 UK	42	4.53	7414701	153	38.62	3.96 (3.36 - 4.64)	Observed significantly > expected
TTS - Female 50-59 UK	42	9.07	5944683	68	62	1.1 (0.85 - 1.39)	Observed > expected
TTS - Female 60-69 UK	42	12.88	4783416	44	70.85	0.62 (0.45 - 0.83)	Observed significantly < expected
TTS - Female 70-79 UK	42	31.05	3475875	33	124.11	0.27 (0.18 - 0.37)	Observed significantly < expected
TTS - Female over 80 UK	42	40.77	1630324	11	76.43	0.14 (0.07 - 0.26)	Observed significantly < expected
TTS - Male 18-49 UK	42	4.54	6766098	112	35.32	3.17 (2.61 - 3.82)	Observed significantly > expected
TTS - Male 50-59 UK	42	11.87	6510960	87	88.87	0.98 (0.78 - 1.21)	Observed < expected
TTS - Male 60-69 UK	42	26.19	4934728	47	148.62	0.32 (0.23 - 0.42)	Observed significantly < expected
TTS - Male 70-79 UK	42	48.22	3137304	36	173.96	0.21 (0.14 - 0.29)	Observed significantly < expected

Table 142 Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group/sex (UK)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS - Male over 80 UK	42	86.28	1025046	11	101.7	0.11 (0.05 - 0.19)	Observed significantly < expected
Incidence Rate from Truven Market Scan database (2019) aligned with the OHDSI TTS algorithm, updated OHDSI-aligned codelists and washout periods							
TTS - Female UK	14	9.22	23252503	216	82.18	2.63 (2.29 - 3)	Observed significantly > expected
TTS - Male UK	14	13.24	22377923	199	113.57	1.75 (1.52 - 2.01)	Observed significantly > expected
TTS - Female 18-49 UK	14	4.64	7414701	109	13.19	8.26 (6.79 - 9.97)	Observed significantly > expected
TTS - Female 50-59 UK	14	10.71	5944683	42	24.4	1.72 (1.24 - 2.33)	Observed significantly > expected
TTS - Female 60-69 UK	14	15.87	4783416	29	29.1	1 (0.67 - 1.43)	Observed < expected
TTS - Female 70-79 UK	14	36.7	3475875	16	48.9	0.33 (0.19 - 0.53)	Observed significantly < expected
TTS - Female over 80 UK	14	39.61	1630324	8	24.75	0.32 (0.14 - 0.64)	Observed significantly < expected

Table 142 Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group/sex (UK)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS - Male 18-49 UK	14	5.36	6766098	85	13.9	6.12 (4.88 - 7.56)	Observed significantly > expected
TTS - Male 50-59 UK	14	14.7	6510960	53	36.69	1.44 (1.08 - 1.89)	Observed significantly > expected
TTS - Male 60-69 UK	14	29.51	4934728	22	55.82	0.39 (0.25 - 0.6)	Observed significantly < expected
TTS - Male 70-79 UK	14	54.04	3137304	22	64.99	0.34 (0.21 - 0.51)	Observed significantly < expected
TTS - Male over 80 UK	14	84.62	1025046	7	33.25	0.21 (0.08 - 0.43)	Observed significantly < expected
TTS - Female UK	21	9.22	23252503	282	123.26	2.29 (2.03 - 2.57)	Observed significantly > expected
TTS - Male UK	21	13.24	22377923	257	170.35	1.51 (1.33 - 1.7)	Observed significantly > expected
TTS - Female 18-49 UK	21	4.64	7414701	133	19.78	6.72 (5.63 - 7.97)	Observed significantly > expected
TTS - Female 50-59 UK	21	10.71	5944683	59	36.61	1.61 (1.23 - 2.08)	Observed significantly > expected

Table 142 Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group/sex (UK)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS - Female 60-69 UK	21	15.87	4783416	38	43.65	0.87 (0.62 - 1.19)	Observed < expected
TTS - Female 70-79 UK	21	36.7	3475875	27	73.34	0.37 (0.24 - 0.54)	Observed significantly < expected
TTS - Female over 80 UK	21	39.61	1630324	8	37.13	0.22 (0.09 - 0.42)	Observed significantly < expected
TTS - Male 18-49 UK	21	5.36	6766098	103	20.85	4.94 (4.03 - 5.99)	Observed significantly > expected
TTS - Male 50-59 UK	21	14.7	6510960	70	55.03	1.27 (0.99 - 1.61)	Observed > expected
TTS - Male 60-69 UK	21	29.51	4934728	34	83.73	0.41 (0.28 - 0.57)	Observed significantly < expected
TTS - Male 70-79 UK	21	54.04	3137304	27	97.48	0.28 (0.18 - 0.4)	Observed significantly < expected
TTS - Male over 80 UK	21	84.62	1025046	8	49.87	0.16 (0.07 - 0.32)	Observed significantly < expected
TTS - Female UK	42	9.22	23252503	330	246.53	1.34 (1.2 - 1.49)	Observed significantly > expected
TTS - Male UK	42	13.24	22377923	313	340.7	0.92 (0.82 - 1.03)	Observed < expected

Table 142 Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group/sex (UK)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS - Female 18-49 UK	42	4.64	7414701	153	39.56	3.87 (3.28 - 4.53)	Observed significantly > expected
TTS - Female 50-59 UK	42	10.71	5944683	68	73.21	0.93 (0.72 - 1.18)	Observed < expected
TTS - Female 60-69 UK	42	15.87	4783416	44	87.29	0.5 (0.37 - 0.68)	Observed significantly < expected
TTS - Female 70-79 UK	42	36.7	3475875	33	146.69	0.22 (0.15 - 0.32)	Observed significantly < expected
TTS - Female over 80 UK	42	39.61	1630324	11	74.26	0.15 (0.07 - 0.27)	Observed significantly < expected
TTS - Male 18-49 UK	42	5.36	6766098	112	41.7	2.69 (2.21 - 3.23)	Observed significantly > expected
TTS - Male 50-59 UK	42	14.7	6510960	87	110.06	0.79 (0.63 - 0.98)	Observed significantly < expected
TTS - Male 60-69 UK	42	29.51	4934728	47	167.46	0.28 (0.21 - 0.37)	Observed significantly < expected
TTS - Male 70-79 UK	42	54.04	3137304	36	194.96	0.18 (0.13 - 0.26)	Observed significantly < expected

Table 142 Observed Versus Expected analysis for Thrombosis with thrombocytopenia by age group/sex (UK)

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
TTS - Male over 80 UK	42	84.62	1025046	11	99.74	0.11 (0.06 - 0.2)	Observed significantly < expected

Only cases observed within 0-14, 0-21, and 0-42 days were included; Risk Window: 14, 21, and 42 days

CI Confidence interval, E Expected; O Observed; OHDSI Observational Health Data Science and Informatics, TTS Thrombosis with thrombocytopeniasyndrome

MHRA Case Definition

Anti-PF-4, D-Dimer, and platelet levels for Dose 1, Dose 2, Dose 3 and Fatal Reports

All 2644 case reports were reviewed to classify the cases based on the PTs and laboratory data, as per the Medicines and Healthcare products Regulatory Agency (MHRA) case definition for thrombosis in combination with thrombocytopenia (Figure 1).

Figure 1 Medicines and Healthcare products Regulatory Agency (MHRA) case definition for thrombosis in combination with thrombocytopenia

Confirmed	Any venous/arterial thrombosis +	Platelet count <150 x 10^9/L +	D-dimer >4000ng/mL +	Anti-PF4 Abs
Probable	Any venous/arterial thrombosis +	Platelet count <150 x 10^9/L +	D-dimer >4000ng/mL	
Possible	Any venous/arterial thrombosis +	Platelet count <150 x 10^9/L OR wording compatible with platelet count decreased		
Unlikely	Criteria met for any of the above BUT alternative diagnosis more likely to explain the event			
Criteria Not met	One or none of the criteria are met			

Information in case reports was limited, with missing laboratory data on platelet count, D-dimer level, and PF-4 antibodies and also in many case reports there were incomplete entries (units, date of test, and type of test) for platelet levels, D-dimer, and PF-4.

Information on platelet count was available in 1784 (67.5%) of 2644 case reports; platelet count was <150 x 109/L in 1715 of the 1784 reports and in 69 case reports platelet count was >150 x 109/L.

Among these 1717 vaccinees with reported platelet count <150 x 109/L, 758 (44%) had a platelet count of <50 x 109/L; in 447 (26%) had a platelet count was between 50 to <100 x 109/L; and 493 (29%) had a platelet count between 100 to 150 x 109/L.79, 17 had a platelet count was reported as <150 x 109/L, however exact value was not provided. In remaining 860 (33%) of the 2644 case reports information on platelet count was not available.

In 26 of the 2644 case reports there was no venous/arterial thrombosis reported. Of the 2644 case reports, PF-4 antibodies were positive in 695 (26%) reports, negative in 565 (21%) reports, unknown or pending in 1384 (52%) case reports. D-dimer levels were reported in 1040 (39%) of the 2644 case reports, however, in many reports the units were not specified. In 230 (8.7%) D- dimer levels were < 4000 ng/mL and in 810 (30%) case reports D-dimer levels were > 4000 ng/mL In 1604 (60%) case reports D-dimer levels were not provided/reported.

Of the 2644 case reports reviewed, based on the above case classification criteria, there were 1726 cases which met the MHRA criteria of TTS (Confirmed, probable or possible). The total number of confirmed cases were 383 (14%), probable cases were 394 (15%), possible cases were 949 (35%), unlikely 1 (0.03%) and criteria not met cases were 917 (35%). Out of all cases (1726) which met the criteria, the confirmed cases (383) comprised 22% of the total cases.

In cases (1726) where the MHRA case classification criteria were met, 571 (33%) cases had confounding factors. Many of the cases had more than one confounding factor. The confounding factors were reported as follows:

- Autoimmune disease (ITP, autoimmune thyroiditis, psoriasis, antiphospholipid syndrome (APLS), Crohn's disease, myasthenia gravis, inflammatory bowel disease, ulcerative colitis, ankylosing spondylitis, rheumatoid arthritis, guillain-barre syndrome, sarcoidosis, systemic lupus erythematous (SLE), autoimmune hepatitis (AIH), vasculitis, multiple sclerosis, hemolytic anaemia, polymyalgia rheumatica, thalassemia minor and connective tissue disorder);
- Malignancies (breast cancer, prostate cancer, malignant melanoma, brain cancer, thyroid cancer, non-hodgkin's lymphoma, polycythemia vera, bladder cancer, pituitary tumor, lung cancer, metastatic cancer, tonsil cancer, ovarian cancer, pancreatic cancer, testicular cancer, carcinoma endometrium uterus, vulvar cancer, cervix carcinoma, renal cell carcinoma, chronic lymphocytic leukemia, glioblastoma, gliomas, leukemia, lymphoma, lymphoproliferative disease, metastatic neoplasm, myelodysplastic neoplasm, neoplasm, sarcoma);
- Past history of heparin administration (information specially on the dates of heparin administration was not available), obesity, past and current history of contraceptives, past history of thrombosis, HIT, past history of frequent abortion, HIV infection, chronic hepatitis B, liver disease, covid-19 illness, cardiomyopathy resulting from fredrich's ataxia, chronic kidney disease, chronic glomerulonephritis, DRESS syndrome, liver transplant, past history of stroke, polycystic ovary syndrome, protein c deficiency, sickle cell disease, tcp chronic.
- Concomitant medications; venaflaxine, and combination of citalopram and clopidogrel.

Out of 383 confirmed reports, there were 158 (41%) cases with confounding factors. The confounding factor associated were past history of heparin, malignancies (neoplasm, abdominal neoplasm, thyroid cancer, prostate cancer, vulvar cancer, metastatic cancer, skin cancer, pancreatic cancer, carcinoma endometrium uterus, non-Hodgkin's disease, breast cancer, malignant melanoma), obesity, contraceptives, ITP, autoimmune disease (sarcoidosis, Guillain-Barre syndrome, myasthenia gravis, ankylosing spondylitis, autoimmune thyroiditis, antiphospholipid syndrome, ulcerative colitis, rheumatoid arthritis, Crohn's disease), hit, past history of thrombosis, chronic kidney disease. The dates of heparin administration were not reported in all cases.

Demographics (age, gender, and country) and clinical characteristics of thrombosis in combination of thrombocytopenia is provided in Table 143 and Table 144. Comparison of

Platelet count, thrombosis event, PF-4 antibodies and D-dimer levels is provided in Table 145.

Table 143 MHRA case classification criteria of thrombosis in combination with thrombocytopenia case reports by age and country

Characteristic	Confirmed reports (n=383)	Probable Reports (n=394)	Possible Reports (n=949)	Unlikely Reports (n=1)	Criteria not met Reports (n=917)	All case reports (n=2644)
Median age in years (range)	47 (18-88)	55 (18-94)	58 (18-104)	65 (00-00)	56 (18-95)	55 (18-104)
Sex						
Female n (%)	220 (8.32)	210 (7.94)	489 (18.49)	(0)	451 (17.06)	1370 (51.82)
Male n (%)	162 (6.13)	178 (6.73)	442 (16.72)	1 (0.04)	369 (13.96)	1152 (43.57)
Unknown n (%)	1 (0.04)	6 (0.23)	18 (0.68)	(0)	97 (3.67)	122 (4.61)
Region						
EEA						
Austria	4 (0.15)	4 (0.15)	10 (0.38)	0 (0)	9 (0.34)	27 (1.02)
Belgium	11 (0.42)	3 (0.11)	13 (0.49)	0 (0)	16 (0.61)	43 (1.63)
Bulgaria	(0)	1 (0.04)	1 (0.04)	0 (0)	3 (0.11)	5 (0.19)
Croatia	1 (0.04)	1 (0.04)	1 (0.04)	0 (0)	(0)	3 (0.11)
Cyprus	(0)	2 (0.08)	1 (0.04)	0 (0)	1 (0.04)	4 (0.15)
Czech Republic	1 (0.04)	5 (0.19)	7 (0.26)	0 (0)	(0)	13 (0.49)
Denmark	1 (0.04)	(0)	(0)	0 (0)	4 (0.15)	5 (0.19)
Estonia	(0)	(0)	1 (0.04)	0 (0)	1 (0.04)	2 (0.08)
Finland	5 (0.19)	1 (0.04)	1 (0.04)	0 (0)	11 (0.42)	18 (0.68)
France	1 (0.04)	2 (0.08)	19 (0.72)	0 (0)	47 (1.78)	69 (2.61)
Germany	35 (1.32)	22 (0.83)	101 (3.82)	0 (0)	175 (6.62)	333 (12.59)
Greece	2 (0.08)	2 (0.08)	4 (0.15)	0 (0)	6 (0.23)	14 (0.53)
Hungary	1 (0.04)	(0)	2 (0.08)	0 (0)	2 (0.08)	5 (0.19)
Iceland	(0)	(0)	1 (0.04)	0 (0)	3 (0.11)	4 (0.15)
Ireland	4 (0.15)	1 (0.04)	6 (0.23)	0 (0)	(0)	11 (0.42)
Italy	13 (0.49)	21 (0.79)	30 (1.13)	0 (0)	70 (2.65)	134 (5.07)
Latvia	(0)	(0)	2 (0.08)	0 (0)	1 (0.04)	3 (0.11)
Lithuania	1 (0.04)	(0)	2 (0.08)	0 (0)	(0)	3 (0.11)
Luxembourg	2 (0.08)	(0)	2 (0.08)	0 (0)	(0)	4 (0.15)
Malta	(0)	(0)	2 (0.08)	0 (0)	1 (0.04)	3 (0.11)
Netherlands	7 (0.26)	11 (0.42)	31 (1.17)	0 (0)	11 (0.42)	60 (2.27)
Norway	9 (0.34)	3 (0.11)	3 (0.11)	0 (0)	7 (0.26)	22 (0.83)
Poland	(0)	3 (0.11)	9 (0.34)	0 (0)	12 (0.45)	24 (0.91)

Table 143 MHRA case classification criteria of thrombosis in combination with thrombocytopenia case reports by age and country

Characteristic	Confirmed reports (n=383)	Probable Reports (n=394)	Possible Reports (n=949)	Unlikely Reports (n=1)	Criteria not met Reports (n=917)	All case reports (n=2644)
Portugal	1 (0.04)	2 (0.08)	2 (0.08)	0 (0)	4 (0.15)	9 (0.34)
Slovakia	(0)	(0)	1 (0.04)	0 (0)	1 (0.04)	2 (0.08)
Slovenia	3 (0.11)	2 (0.08)	2 (0.08)	0 (0)	1 (0.04)	8 (0.3)
Spain	8 (0.3)	8 (0.3)	20 (0.76)	0 (0)	25 (0.95)	61 (2.31)
Sweden	(0)	(0)	5 (0.19)	0 (0)	20 (0.76)	25 (0.95)
UK						
United Kingdom	186 (7.03)	205 (7.75)	287 (10.85)	153 (5.79)	1 (0.04)	832 (31.47)
Rest of the world (ROW)						
Argentina	0 (0)	0 (0)	1 (0.04)	0 (0)	2 (0.08)	3 (0.11)
Australia	27 (1.02)	42 (1.59)	214 (8.09)	0 (0)	159 (6.01)	442 (16.72)
Brazil	20 (0.76)	28 (1.06)	96 (3.63)	0 (0)	31 (1.17)	175 (6.62)
Canada	16 (0.61)	3 (0.11)	17 (0.64)	0 (0)	49 (1.85)	85 (3.21)
Chile	0 (0)	1 (0.04)	0 (0)	0 (0)	4 (0.15)	5 (0.19)
Colombia	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.04)	1 (0.04)
Costa Rica	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.04)	1 (0.04)
Ecuador	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.04)	1 (0.04)
Egypt	0 (0)	0 (0)	1 (0.04)	0 (0)	2 (0.08)	3 (0.11)
Georgia	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.04)	1 (0.04)
India	3 (0.11)	6 (0.23)	23 (0.87)	0 (0)	30 (1.13)	62 (2.34)
Iran	2 (0.08)	3 (0.11)	2 (0.08)	0 (0)	2 (0.08)	9 (0.34)
Japan	1 (0.04)	1 (0.04)	1 (0.04)	0 (0)	0 (0)	3 (0.11)
Jordan	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.04)	1 (0.04)
Korea, Republic of	2 (0.08)	(0)	1 (0.04)	0 (0)	8 (0.3)	11 (0.42)
Kuwait	0 (0)	0 (0)	1 (0.04)	0 (0)	0 (0)	1 (0.04)
Macedonia	0 (0)	2 (0.08)	(0)	0 (0)	1 (0.04)	3 (0.11)
Malaysia	(0)	1 (0.04)	1 (0.04)	0 (0)	5 (0.19)	7 (0.26)
Mexico	0 (0)	0 (0)	5 (0.19)	0 (0)	8 (0.3)	13 (0.49)
New Zealand	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.04)	1 (0.04)
Northern Ireland	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.08)	2 (0.08)
Oman	1 (0.04)	1 (0.04)	0 (0)	0 (0)	1 (0.04)	3 (0.11)
Philippines	0 (0)	0 (0)	0 (0)	0 (0)	4 (0.15)	4 (0.15)
Saudi Arabia	0 (0)	2 (0.08)	5 (0.19)	0 (0)	1 (0.04)	8 (0.3)
Sri Lanka	0 (0)	0 (0)	6 (0.23)	0 (0)	0 (0)	6 (0.23)
Sudan	0 (0)	0 (0)	3 (0.11)	0 (0)	0 (0)	3 (0.11)

Table 143 MHRA case classification criteria of thrombosis in combination with thrombocytopenia case reports by age and country

Characteristic	Confirmed reports (n=383)	Probable Reports (n=394)	Possible Reports (n=949)	Unlikely Reports (n=1)	Criteria not met Reports (n=917)	All case reports (n=2644)
Syria	0 (0)	0 (0)	1 (0.04)	0 (0)	0 (0)	1 (0.04)
Taiwan	12 (0.45)	1 (0.04)	3 (0.11)	0 (0)	4 (0.15)	20 (0.76)
Thailand	3 (0.11)	3 (0.11)	1 (0.04)	0 (0)	2 (0.08)	9 (0.34)
Ukraine	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.04)	1 (0.04)
United States	0 (0)	0 (0)	1 (0.04)	0 (0)	8 (0.3)	9 (0.34)
Uruguay	0 (0)	1 (0.04)	0 (0)	0 (0)	0 (0)	1 (0.04)
Venezuela	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.04)	1 (0.04)
Vietnam	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.08)	2 (0.08)
Seriousness						
Serious	383 (14.49)	394 (14.9)	945 (35.74)	909 (34.38)	1 (0.04)	2632 (99.55)
Non-serious	0 (0)	0 (0)	4 (0.15)	8 (0.3)	0 (0)	12 (0.45)
Medical confirmation						
Medically confirmed	349 (13.2)	335 (12.67)	706 (26.7)	527 (19.93)	1 (0.04)	1918 (72.54)
Consumer reports	34 (1.29)	59 (2.23)	243 (9.19)	390 (14.75)	0 (0)	726 (27.46)

EEA European Economic Area; MHRA Medicines and Healthcare Products Regulatory Agency; ROW Rest of World; UK United Kingdom

Table 144 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All Reports
Dose						
Dose 1	365	341	812	1	818	2337
Dose 2	15	50	129		93	287
Dose 3	3	3	7		6	19
Dose 4			1			1
Median Time to onset in days: AZD1222 Dose 1	11	13	12	9	11	12
Median Time to onset in days: AZD1222 Dose 2	9.5	13	15	NA	10	14
Median Time to onset in days: AZD1222 Dose 3	NA	12	9	NA	14	10

Table 144 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All Reports
Median Time to onset in days: AZD1222 Dose 4	NA	NA	Unk TTO	NA	NA	Unk TTO
Embolic and thrombotic events						
Embolic and thrombotic events, Arterial	73	58	133	1	124	389
Embolic and thrombotic events, Venous	298	317	669		479	1763
Embolic and thrombotic events, Mixed	228	176	435	1	519	1359
Embolic and thrombotic events, Unspecified	325	357	825	1	790	2298
Embolic and thrombotic events, Arterial						
Acute coronary syndrome	1		1		3	5
Acute myocardial infarction	8	7	10		6	31
Amaurosis fugax					4	4
Aortic embolus	1	3	3		2	9
Aortic thrombosis	15	4	14	1	7	41
Arterial occlusive disease			2		1	3
Arterial thrombosis	10	7	8		7	32
Basilar artery thrombosis					1	1
Blindness transient					1	1
Carotid artery occlusion	2	1	2		3	8
Carotid artery thrombosis	8	8	11		4	31
Cerebral artery embolism			1		1	2

Table 144 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All Reports
Cerebral artery occlusion	5	1	5			11
Cerebral artery thrombosis	6	4	9		2	21
Cerebrovascular insufficiency	1					1
Coronary artery bypass					1	1
Coronary artery occlusion	1					1
Coronary artery thrombosis	5	1	5		1	12
Embolism arterial	2	3	1		1	7
Femoral artery embolism		1				1
Hepatic artery occlusion		1				1
Hepatic artery thrombosis		3			1	4
Iliac artery occlusion				1	1	2
Internal capsule infarction			1			1
Ischaemic cerebral infarction	3		3		1	7
Ischaemic stroke	8	7	16		21	52
Lacunar infarction	1	1	1		2	5
Leriche syndrome			1			1
Mesenteric arterial occlusion			1			1
Mesenteric artery stenosis					2	2
Mesenteric artery thrombosis		3	2		2	7
Myocardial infarction	8	3	12		7	30
Peripheral arterial occlusive disease		1	3		1	5
Peripheral artery occlusion	4		10		1	15
Peripheral artery thrombosis	14	6	19		11	50

Table 144 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All Reports
Peripheral embolism	1	1	3		3	8
Pulmonary artery occlusion	1		2			3
Pulmonary artery thrombosis	4	1	1		3	9
Renal artery occlusion				1		1
Renal artery thrombosis		1	2		2	5
Renal embolism		1				1
Retinal artery occlusion		1			2	3
Retinal artery thrombosis					1	1
Splenic artery thrombosis		2	4		2	8
Stress cardiomyopathy	1					1
Subclavian artery thrombosis	1				1	2
Thromboembolectomy		1				1
Thrombotic microangiopathy	1	1			5	7
Thrombotic thrombocytopenic purpura	3	5	16		25	49
Transient ischaemic attack	1	1	3		12	17
Truncus coeliacus thrombosis					1	1
Vertebral artery occlusion			1			1
Vertebral artery thrombosis	1				2	3
Embolic and thrombotic events, Mixed						
Adrenal thrombosis	1	1				2
Antiphospholipid syndrome	1	1	4			6
Atrial thrombosis	1	1	2		1	5

Table 144 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All Reports
Autoimmune heparin-induced thrombocytopenia	1					1
Brain stem infarction			1		1	2
Brain stem stroke					2	2
Cardiac ventricular thrombosis	3	2	2		4	11
Cerebellar infarction	1		2			3
Cerebral congestion	1					1
Cerebral infarction	12	11	26		22	71
Cerebral ischaemia	2	1	2		2	7
Cerebral thrombosis	7	14	20		17	58
Cerebrovascular accident	10	8	30		45	93
Cerebrovascular disorder	1					1
Diplegia	1		1		1	3
Disseminated intravascular coagulation	15	14	11		20	60
Embolic cerebral infarction	1		1			2
Embolic stroke			1		1	2
Embolism	8	18	34		14	74
Eye infarction					1	1
Foetal vascular malperfusion	1		1			2
Haemorrhagic adrenal infarction	4	1	2		1	8
Haemorrhagic cerebral infarction	3	4	2		1	10
Haemorrhagic infarction	1	1	7		3	12
Haemorrhagic stroke	2	3	14		7	26
Haemorrhagic transformation stroke	7	1	4		3	15
Haemorrhoids thrombosed					1	1
Hemiparesis	26	17	29		16	88

Table 144 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All Reports
Hemiplegia	5	4	9		14	32
Heparin-induced thrombocytopenia	9	4	12		16	41
Hepatic infarction	1	2	2		2	7
Hepatic vascular thrombosis			2		5	7
Infarction	2		4		3	9
Injection site thrombosis					2	2
Intestinal infarction		2	4		2	8
Intracardiac thrombus	2	3	4		2	11
Mesenteric vascular occlusion					1	1
Monoparesis	2	1	5		1	9
Monoplegia			2		2	4
Pancreatic infarction					1	1
Paraparesis		1				1
Paresis		1	1			2
Post procedural stroke					1	1
Prosthetic cardiac valve thrombosis	1	1				2
Quadriparesis		2	1		1	4
Quadriplegia	1	2				3
Renal infarct	4	4	6	1	5	20
Renal vascular thrombosis	2		2			4
Splenic infarction	2	6	9		5	22
Splenic thrombosis	3		2		1	6
Spontaneous heparin-induced thrombocytopenia syndrome			2		3	5
Thalamic infarction			1			1
Thrombectomy			1		2	3
Thrombosis	52	55	128		200	435
Thrombosis in device				1		1

Table 144 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All Reports
Thrombosis mesenteric vessel	4	2	2			8
Thrombosis with thrombocytopenia syndrome	116	52	167		196	531
Thrombotic stroke	2	1	2		3	8
Vascular graft thrombosis			1			1
Vascular operation			1			1
Vascular stent thrombosis		1	2		2	5
Embolic and thrombotic events, Venous						
Axillary vein thrombosis					2	2
Budd-Chiari syndrome	1		1			2
Cavernous sinus thrombosis	1	2	1		2	6
Cerebral venous sinus thrombosis	119	79	143		121	462
Cerebral venous thrombosis	37	15	56		26	134
Deep vein thrombosis	49	74	185		120	428
Embolism venous	5	2	2		3	12
Hepatic vein embolism			1			1
Hepatic vein occlusion	1					1
Hepatic vein thrombosis	7	10	10		9	36
Jugular vein occlusion	2					2
Jugular vein thrombosis	15	10	14		14	53
Mesenteric vein thrombosis	13	11	21		11	56
Ophthalmic vein thrombosis	1	4	3		1	9

Table 144 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All Reports
Ovarian vein thrombosis		1	2		1	4
Pelvic venous thrombosis	4	8	9		6	27
Peripheral vein occlusion	1					1
Peripheral vein thrombosis					2	2
Portal vein cavernous transformation			1			1
Portal vein embolism		1	1			2
Portal vein occlusion	1		2			3
Portal vein thrombosis	40	35	66		46	187
Portosplenomesenteric venous thrombosis	2	2	2		6	12
Post thrombotic syndrome	1					1
Pulmonary embolism	108	170	274		195	747
Pulmonary infarction	5	2	7		5	19
Pulmonary thrombosis	6	3	11		8	28
Pulmonary venous thrombosis			2		1	3
Renal vein embolism	1					1
Renal vein thrombosis	3	7	6		3	19
Retinal vein occlusion	1		2		5	8
Retinal vein thrombosis			1		2	3
Sigmoid sinus thrombosis	4		1		2	7
Splenic vein occlusion			1			1
Splenic vein thrombosis	11	9	13		10	43
Subclavian vein thrombosis			1		1	2

Table 144 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All Reports
Superficial vein thrombosis	8	6	10		7	31
Superior sagittal sinus thrombosis	22	6	28		14	70
Thrombophlebitis	1	3	8		8	20
Transverse sinus thrombosis	16	2	8		5	31
Vena cava filter insertion					1	1
Vena cava thrombosis	1	5	2		1	9
Venoocclusive liver disease			1			1
Venous occlusion	1		1		1	3
Venous thrombosis	9	8	21		18	56
Venous thrombosis limb	5	2	4		12	23
Visceral venous thrombosis	16	7	10		5	38
Platelet Level						
<150 x 109/L	380	393	924	1	17	1715
Reported as < 150 x 109/L, however value not provided	6	4	7			17
100-150 x 109/L	36	113	341		3	493
50-100 x 109/L	117	98	225		7	447
<50 x 109/L	221	178	351	1	7	758
>150 x 109/L or 'normal'		1	5		63	69
Unk	3		20		837	860
Co-Reported Events						
Coagulopathy	24	24	27		34	109
Co-reported bleeding event from Haemorrhage terms (excl laboratory terms) (SMQ)-Narrow* (≥10 events)	200	149	280		276	905

Table 144 Clinical characteristics of thrombosis in combination with thrombocytopenia case reports

Characteristic	Confirmed	Probable	Possible	Unlikely	Criteria not met	All Reports
Immune thrombocytopenia	63	20	63		87	233
Cerebral haemorrhage	54	37	73		58	222
Haemorrhage	21	15	31		11	78
Haemorrhage intracranial	19	14	25		12	70
Subarachnoid haemorrhage	20	16	20		10	66
Disseminated intravascular coagulation	15	14	11		20	60
Contusion	10	9	24		15	58
Petechiae	9	10	21		13	53
Thrombotic thrombocytopenic purpura	3	5	16		25	49
Haemoptysis	8	9	9		1	27
Haemorrhagic stroke	2	3	14		7	26
Haematoma	4	5	7		8	24
Cerebral haematoma	5	7	5		6	23
Adrenal haemorrhage	10	4	4		2	20
Epistaxis		2	8		6	16
Haemorrhagic transformation stroke	7	1	4		3	15
Rectal haemorrhage	5	3	4		2	14
Subdural haematoma	3		4		5	12
Ecchymosis	3	2	2		5	12
Haemorrhagic infarction	1	1	7		3	12
Haematuria	6	2	2		1	11
Purpura	1	2	3		4	10
Haemorrhagic cerebral infarction	3	4	2		1	10

NA Not Applicable; SMQ Standardised MedDRA Query; TTO Time To Onset UNK Unknown

Table 145 Comparison of platelet levels, thrombosis event, PF-4 antibodies and D-dimer levels in Thrombosis in combination with thrombocytopenia case reports (N=2644)

	Venous or arterial thrombosis				PF4 Antibodies				D dimer level			
Platelet Labels	Yes	No	Unk	Grand Total	Yes	No	pending/Unk	Grand Total	Yes (>4000ng/mL)	Yes (<4000ng/mL)	Unk	Grand Total
<150	1701	11	3	1715	119	47	144	310	780	205	730	1715
>150	69			69		2	6	8	18	20	31	69
Unk	843	15	2	860	15	37	112	164	12	5	843	860
Grand Total	2613	26	5	2644	134	86	262	482	810	230	1604	2644
Dose 1												
<150	1497	11	2	1510	114	42	132	288	707	172	631	1510
>150	57			57		1	6	7	14	15	28	57
Unk	754	14	2	770	14	34	104	152	7	5	758	770
Grand Total	2308	25	4	2337	128	77	242	447	728	192	1417	2337
Dose 2												
<150	192		1	193	3	5	9	17	67	32	94	193
>150	11			11		1		1	4	5	2	11
Unk	82	1		83	1	2	7	10	4		79	83
Grand Total	285		1	287	4	8	16	28	75	37	175	287
Dose 3												
<150	11			11	2		2	4	6	1	4	11
>150	1			1							1	1
Unk	7			7		1	1	2	1		6	7
Grand Total	19			19	2	1	3	6	7	1	11	19
Fatal reports												

Table 145 Comparison of platelet levels, thrombosis event, PF-4 antibodies and D-dimer levels in Thrombosis in combination with thrombocytopenia case reports (N=2644)

	Venous or arterial thrombosis				PF4 Antibodies				D dimer level			
Platelet Labels	Yes	No	Unk	Grand Total	Yes	No	pending/Unk	Grand Total	Yes (>4000ng/mL)	Yes (<4000ng/mL)	Unk	Grand Total
<150	308	2		310	119	47	144	310	162	9	139	310
>150	8			8		2	6	8	3		5	8
Unk	162	1	1	164	15	37	112	164	2		162	164
Grand Total	478	2	1	482	134	86	262	482	167	9	306	482

Unk Unknown

Table 146 Thrombosis with Thrombocytopenia Syndrome Case Reports by age/gender, Dose, Case Classification and fatality

	Confirmed			Probable			Possible			Unlikely			Criteria not met			Grand Total
Row Labels	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Age - 18-29 Yrs	22 (4)	19 (4)	0 (0)	20 (7)	12 (4)	1 (1)	42 (9)	36 (6)	0 (0)	0 (0)	0 (0)	0 (0)	49 (11)	29 (7)	1 (0)	231 (53)
Age - 30-39 Yrs	34 (11)	28 (7)	0 (0)	19 (7)	12 (4)	0 (0)	72 (20)	37 (8)	0 (0)	0 (0)	0 (0)	0 (0)	55 (11)	33 (7)	0 (0)	290 (75)
Age - 40-49 Yrs	62 (15)	39 (5)	1 (0)	49 (10)	26 (2)	0 (0)	54 (12)	61 (5)	0 (0)	0 (0)	0 (0)	0 (0)	75 (15)	37 (8)	1 (0)	405 (72)
Age - 50-59 Yrs	48 (9)	39 (7)	0 (0)	43 (13)	42 (4)	2 (0)	100 (15)	75 (12)	2 (1)	0 (0)	0 (0)	0 (0)	63 (16)	51 (12)	0 (0)	465 (89)
Age - 60-69 Yrs	24 (4)	27 (6)	0 (0)	35 (5)	44 (7)	1 (0)	119 (24)	94 (9)	0 (0)	0 (0)	1 (1)	0 (0)	87 (11)	97 (14)	1 (1)	530 (82)
Age - 70-79 Yrs	14 (4)	6 (3)	0 (0)	22 (2)	23 (3)	0 (0)	57 (11)	84 (4)	1 (0)	0 (0)	0 (0)	0 (0)	49 (5)	65 (8)	1 (0)	322 (40)

Table 146 Thrombosis with Thrombocytopenia Syndrome Case Reports by age/gender, Dose, Case Classification and fatality

	Confirmed			Probable			Possible			Unlikely			Criteria not met			Grand Total
Age - 80+ Yrs	4 (1)	2 (1)	0 (0)	8 (3)	11 (2)	0 (0)	27 (3)	29 (2)	0 (0)	0 (0)	0 (0)	0 (0)	23 (3)	22 (5)	0 (0)	126 (20)
Age Unknown	12 (1)	2 ()	0 (0)	14 (4)	8 (1)	2 (0)	18 (7)	26 (2)	15 (5)	0 (0)	0 (0)	0 (0)	50 (13)	35 (4)	93 (14)	275 (51)
Grand Total	220 (49)	162 (33)	1 (0)	210 (51)	178 (27)	6 (1)	489 (101)	442 (48)	18 (6)	0 (0)	1 (1)	0 (0)	451 (85)	369 (65)	97 (15)	2644 (482)
Dose 1																
Row Labels	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Age - 18-29 Yrs	21 (4)	19 (4)	0 (0)	18 (6)	11 (4)	1 (1)	39 (9)	32 (5)	0 (0)	0 (0)	0 (0)	0 (0)	48 (11)	27 (7)	1 (0)	217 (51)
Age - 30-39 Yrs	33 (11)	27 (7)	0 (0)	19 (7)	12 (4)	0 (0)	67 (18)	36 (8)	0 (0)	0 (0)	0 (0)	0 (0)	53 (11)	32 (7)	0 (0)	279 (73)
Age - 40-49 Yrs	61 (14)	38 (5)	1 (0)	47 (10)	24 (2)	0 (0)	50 (12)	53 (5)	0 (0)	0 (0)	0 (0)	0 (0)	70 (12)	34 (8)	1 (0)	379 (68)
Age - 50-59 Yrs	47 (9)	36 (7)	0 (0)	41 (13)	39 (4)	2 (0)	96 (15)	61 (9)	2 (1)	0 (0)	0 (0)	0 (0)	58 (15)	46 (11)	0 (0)	428 (84)
Age - 60-69 Yrs	24 (4)	25 (6)	0 (0)	32 (5)	33 (7)	1 (0)	102 (24)	78 (9)	0 (0)	0 (0)	1 (1)	0 (0)	80 (9)	80 (11)	1 (1)	457 (77)
Age - 70-79 Yrs	13 (4)	3 (1)	0 (0)	18 (2)	12 (0)	0 (0)	48 (8)	61 (3)	1 (0)	0 (0)	0 (0)	0 (0)	41 (5)	56 (7)	1 (0)	254 (30)
Age - 80+ Yrs	3 (1)	0 (0)	0 (0)	5 (2)	8 (1)	0 (0)	17 (2)	21 (1)	0 (0)	0 (0)	0 (0)	0 (0)	17 (3)	20 (5)	0 (0)	91 (15)
Age Unknown	12 (1)	2 (0)	0 (0)	10 (3)	6 (1)	2 (0)	17 (7)	18 (2)	13 (5)	0 (0)	0 (0)	0 (0)	49 (13)	30 (3)	73 (14)	232 (49)
Grand Total	214 (48)	150 (30)	1 (0)	190 (48)	145 (23)	6 (1)	436 (95)	360 (42)	16 (6)	0 (0)	1 (1)	0 (0)	416 (79)	325 (59)	77 (15)	2337 (447)

Table 146 Thrombosis with Thrombocytopenia Syndrome Case Reports by age/gender, Dose, Case Classification and fatality

	Confirmed			Probable			Possible			Unlikely			Criteria not met			Grand Total
Dose 2																
Row Labels	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Age - 18-29 Yrs	1 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	3 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0)	0 (0)	8 (0)
Age - 30-39 Yrs	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0)	0 (0)	0 (0)	7 (0)
Age - 40-49 Yrs	0 (0)	0 (0)	0 (0)	2 (0)	2 (0)	0 (0)	3 (0)	8 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5 (3)	3 (0)	0 (0)	23 (3)
Age - 50-59 Yrs	1 (0)	3 (0)	0 (0)	2 (0)	2 (0)	0 (0)	4 (0)	13 (2)	0 (0)	0 (0)	0 (0)	0 (0)	5 (1)	5 (1)	0 (0)	35 (4)
Age - 60-69 Yrs	0 (0)	2 (0)	0 (0)	3 (0)	11 (0)	0 (0)	17 (0)	15 (0)	0 (0)	0 (0)	0 (0)	0 (0)	7 (2)	17 (3)	0 (0)	72 (5)
Age - 70-79 Yrs	1 (0)	3 (2)	0 (0)	4 (0)	11 (3)	0 (0)	9 (3)	23 (1)	0 (0)	0 (0)	0 (0)	0 (0)	7 (0)	8 (1)	0 (0)	66 (10)
Age - 80+ Yrs	1 (0)	2 (1)	0 (0)	3 (1)	3 (1)	0 (0)	10 (1)	8 (1)	0 (0)	0 (0)	0 (0)	0 (0)	6 (0)	2 (0)	0 (0)	35 (5)
Age Unknown	0 (0)	0 (0)	0 (0)	4 (1)	2 (0)	0 (0)	1 (0)	8 (0)	2 (0)	0 (0)	0 (0)	0 (0)	1 (0)	4 (0)	19 (0)	41 (1)
Grand Total	5 (0)	10 (3)	0 (0)	19 (2)	31 (4)	0 (0)	50 (4)	77 (4)	2 (0)	0 (0)	0 (0)	0 (0)	33 (6)	41 (5)	19 (0)	287 (28)
Dose 3																
Row Labels	F	M	U	F	M	U	F	M	U	F	M	U	F	M	U	
Age - 18-29 Yrs	0 (0)	0 (0)	0 (0)	1 (1)	1 (0)	0 (0)	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	6 (2)
Age - 30-39 Yrs	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	4 (2)

Table 146 Thrombosis with Thrombocytopenia Syndrome Case Reports by age/gender, Dose, Case Classification and fatality

	Confirmed			Probable			Possible			Unlikely			Criteria not met			Grand Total
Age - 40-49 Yrs	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0)
Age - 70-79 Yrs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	0 (0)	0 (0)	1 (0)
Age Unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (0)	2 (1)
Grand Total	0 (0)	2 (0)	0 (0)	1 (1)	1 (0)	0 (0)	3 (2)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0)	2 (1)	1 ()	15 (5)

Yrs Years

Events with fatal outcome

Of the 2644 total events reported, 482 (18%) events in 2644 cases were reported with a fatal outcome, of which 376 (78%) events were medically confirmed and 106 (22%) events were non-medically confirmed.

Age and gender stratification for fatal reports is presented in Table 147

Table 147 Thrombosis with Thrombocytopenia Syndrome Case Reports by age/gender and fatality

Age group	Female N (fatal cases)	Male N (fatal cases)	Unknown Gender N (Fatal cases)	Grand Total
Age - 18-29 Yrs	133 (31)	96 (21)	2 (1)	231 (53)
Age - 30-39 Yrs	180 (49)	110 (26)	()	290 (75)
Age - 40-49 Yrs	240 (52)	163 (20)	2 ()	405 (72)
Age - 50-59 Yrs	254 (53)	207 (35)	4 (1)	465 (89)
Age - 60-69 Yrs	265 (44)	263 (37)	2 (1)	530 (82)
Age - 70-79 Yrs	142 (22)	178 (18)	2 ()	322 (40)
Age - 80+ Yrs	62 (10)	64 (10)	()	126 (20)
Age Unknown	94 (25)	71 (7)	110 (19)	275 (51)
Grand Total	**1370 (286)**	**1152 (174)**	**122 (22)**	**2644 (482)**

N Number, Yrs Years.

TTO was available in 350/482 (73%) of the 482 fatal reports and ranged from 0 to 121 days with a median TTO of 11 days. Of the 482 fatal events, 447 fatal reports occurred after Dose 1, 28 fatal case reports occurred after Dose 2, 05 fatal cases after Dose 3 and there were one fatal case reports after Dose 4. TTO was available in 23 reports after Dose 2 with a range of 0 to 88 days and a median of 13 days.

The most frequently reported events of thrombosis in the fatal reports were: Thrombosis with thrombocytopenia syndrome (147), followed by (> 10), Cerebral venous sinus thrombosis (137), Pulmonary embolism (82), Thrombosis (68), Cerebral venous thrombosis (47), Portal vein thrombosis (37), Hemiparesis (33), Cerebral thrombosis (27), Cerebrovascular accident (26), Disseminated intravascular coagulation (26), Cerebral infarction (21), Deep vein thrombosis (20), Haemorrhagic stroke (18), Superior sagittal sinus thrombosis (18), Transverse sinus thrombosis (14), Mesenteric vein thrombosis (14), Ischaemic stroke (13), Acute myocardial infarction (12), Peripheral artery thrombosis (11).

The highest number of the fatal cases were due to HLT: Cerebrovascular and venous sinus thrombosis (199/482, 41%).

In 284 out of 482 fatal reports (59%), there was a co-reported bleeding event from the narrow SMQ: Haemorrhage terms (excl. laboratory terms). Most common (>10) bleeding events

included Cerebral haemorrhage (128), Immune thrombocytopenia (40), Haemorrhage intracranial (38), Subarachnoid haemorrhage (34), Disseminated intravascular coagulation (26), Haemorrhagic stroke (18), Haemorrhage (17), Contusion (12), Petechiae (12), Cerebral haematoma (11). Thirty-seven (37) case reports had the co-reported events from the HLT: Coagulopathies, including 26 cases with DIC.

Fatality/survival rate over time

Fatality/survival rate over time was calculated based on the case onset date. The onset date was not reported in 741 of the 2644 case reports, and for 159 case reports with fatal outcome. In cases where the onset date was not reported, date initially received by AstraZeneca was used to calculate the reporting fatality/survival rate over time. Fatality/survival rate cumulatively for each month up to 28 December 2022 is presented in Table 148 and Figure 2.

The total number and percent of fatal reports since September 2022 are decreasing compared to June 2022-August 2022. There is an increased fatality rate in November 2022 (10 reported fatal events out of 29 reports) compared to the earlier months. These cases onset date was not reported, date initially received by AstraZeneca was used to calculate the reporting fatality/survival rate over time. The total number and percent of fatal report was decreased in December 2022 (one reported fatal event out of 6 report). This literature case ([redacted]) was reported from France with date of vaccination was unknown.

The total number and percent of fatal reports has decreased, which suggests the effectiveness of the diagnostic and treatment guidelines implemented.

Table 148 TTS fatality/survival rate over time

Case onset month[a]	Number of non-fatal reports	Number of Fatal reports	Grand Total	% of fatal reports
January 2021	15	10	25	40
February 2021	79	27	106	26
March 2021	325	94	419	22
April 2021	447	71	518	14
May 2021	355	68	423	16
June 2021	223	45	268	17
July 2021	116	25	141	18
August 2021	122	22	144	15
September 2021	85	13	98	13
October 2021	64	11	75	15
November 2021	24	4	28	14
December 2021	18	7	25	28
January 2022	26	7	33	21
February 2022	15	7	22	32

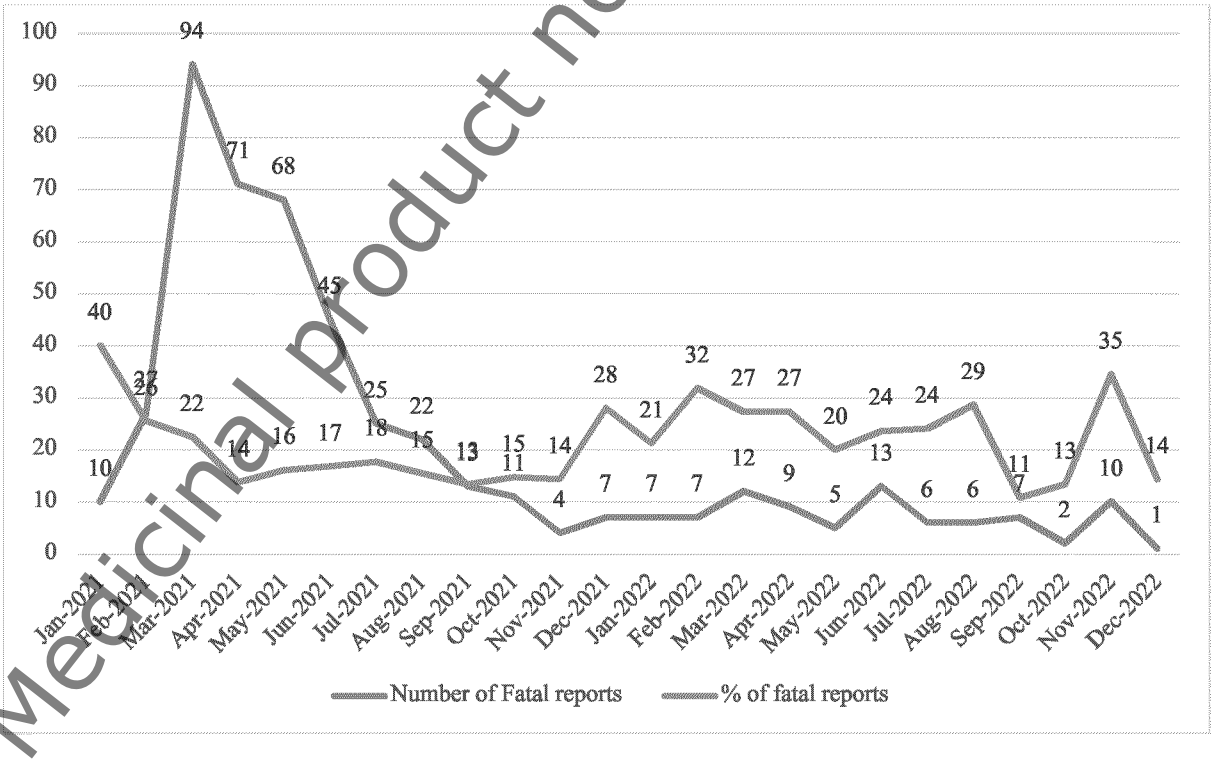
Table 148 TTS fatality/survival rate over time

Case onset month[a]	Number of non-fatal reports	Number of Fatal reports	Grand Total	% of fatal reports
March 2022	32	12	44	27
April 2022	24	9	33	27
May 2022	20	5	25	20
June 2022	42	13	55	24
July 2022	19	6	25	24
August 2022	15	6	21	29
September 2022	58	7	65	11
October 2022	13	2	15	13
November 2022	19	10	29	35
December 2022	6	1	7	14
Grand Total	**2162**	**482**	**2644**	**18**

[a] In cases where case onset date was not available, date initially received by AstraZeneca was used to calculate the reporting fatality/survival rate over time.

TTS Thrombosis with thrombocytopenia syndrome.

Figure 2 TTS fatality/survival rate over time



Fatality rate over time by age group/gender for all cases is presented in Table 149 and fatality rate over time by age group/gender and doses (separately for all doses, Dose 1, and Dose 2) for confirmed/probable/possible cases is presented in Table 150

Fatality rate in female vaccinees is higher (60%) compared to male (37%) for all cases and fatality rate in confirmed/probable/possible cases, is higher in female compared to male for all doses (63% vs 34%) and Dose 1 (65% vs 32%) but for Dose 2, fatality rate in female is less than male (35% vs 54%); the reason for this difference might be cases received with Dose 2 are very little and this would increase the percentage markedly.

For all cases, highest fatality rate in female vaccinees was 18% in 40 to 49 years and 19% in 50 to 59 years age group, whereas in male vaccinees the highest fatality rate was 20% in 50 to 59 years and 21% in 60 to 69 years age group.

In confirmed/probable/possible cases, highest fatality rate in female vaccinees was 18% in 40-49 years, 50-59 years and 16% 60 to 69 years age groups (all doses) and 18 % in 40-49 years, 19% 50-59 years and 17% 60 to 69 years age groups (dose 1) and 50% in 70-79 years age group (dose 2), while in male vaccinees highest fatality rate in male vaccinees was 21% in 50-59 years and 20% 60-69 years (all doses) and 23% in 60 to 69 years age group (dose 1) and 54% in 70-79 years age group (dose 2). Fatality rate for some age groups/gender/months is increased compared to the previous period; however, reports received for these age groups/gender/months did not have onset dates of events and case received date was considered for analysis. This may be the reason for increased fatality rate, also cases received for these months are very little and this would increase the percentages markedly.

TTS fatality/survival rate over time by age group/gender for all cases and confirmed/probable and possible cases provided in Table 149 and Table 150.

Table 149 TTS fatality/survival rate over time by age group/gender for all cases

Case onset month/ Age group	FEMALE			MALE			UNKNOWN			Grand Total			
	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total reports	% of fatal reports
Age - 18-29 Yrs													
February 2021	4	1	20	2	1	33.3				6	2	8	25
March 2021	25	2	7.4	6	4	40				31	6	37	16.2
April 2021	15		0	17	3	15				32	3	35	8.6
May 2021	3		0	7	2	22.2				10	2	12	16.7
June 2021	6	5	45.5	11	2	15.4	1	1	50	18	8	26	30.8
July 2021	4	2	33.3	3		0				7	2	9	22.2
August 2021	11	4	26.7	3	2	40				14	6	20	30
September 2021	2	2	50	2	1	33.3				4	3	7	42.9
October 2021	6		0	2	1	33.3				8	1	9	11.1
November 2021	3	1	25		1	100				3	2	5	40
December 2021	1	2	66.7							1	2	3	66.7
January 2022	3	2	40	3		0				6	2	8	25
February 2022				1		0				1	0	1	0
March 2022	3	3	50	4		0				7	3	10	30
April 2022	3	1	25	1		0				4	1	5	20
May 2022		2	100	2		0				2	2	4	50
June 2022	6	2	25	2	3	60				8	5	13	38.5
July 2022	2	1	33.3	1		0				3	1	4	25

Table 149 TTS fatality/survival rate over time by age group/gender for all cases

Case onset month/ Age group	FEMALE			MALE			UNKNOWN			Grand Total			
	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total reports	% of fatal reports
August 2022				2		0				2	0	2	0
September 2022	1	1	50	4		0				5	1	6	16.7
October 2022					1	100				0	1	1	100
November 2022	4		0	2		0				6	0	6	0
Age - 30-39 Yrs										0	0		
January 2021	2	1	33.3	1	2	66.7				3	3	6	50
February 2021	5	2	28.6	3	1	25				8	3	11	27.3
March 2021	33	9	21.4	11	6	35.3				44	15	59	25.4
April 2021	25	6	19.4	8	5	38.5				33	11	44	25
May 2021	14	6	30	10	1	9.1				24	7	31	22.6
June 2021	12	6	33.3	11	3	21.4				23	9	32	28.1
July 2021	6	5	45.5	6	4	40				12	9	21	42.9
August 2021	9	3	25	5	1	16.7				14	4	18	22.2
September 2021	2	1	33.3	5	1	16.7				7	2	9	22.2
October 2021	1	2	66.7	1		0				2	2	4	50
November 2021	2		0	2		0				4	0	4	0
December 2021	1		0	1	1	50				2	1	3	33.3
January 2022	3		0							3	0	3	0
February 2022	1	1	50	2		0				3	1	4	25

Table 149 TTS fatality/survival rate over time by age group/gender for all cases

Case onset month/ Age group	FEMALE			MALE			UNKNOWN			Grand Total			
	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total reports	% of fatal reports
March 2022	4	2	33.3	5		0				9	2	11	18.2
April 2022	1		0							1	0	1	0
May 2022	3		0	1		0				4	0	4	0
June 2022	3	1	25	4		0				7	1	8	12.5
July 2022		2	100	3		0				3	2	5	40
August 2022	1	1	50	2		0				3	1	4	25
September 2022	2	1	33.3	1		0				3	1	4	25
October 2022				1		0				1	0	1	0
November 2022	1		0	1	1	50				2	1	3	33.3
Age - 40-49 Yrs										0	0		
February 2021	7	4	36.4	2		0				9	4	13	30.8
March 2021	33	17	34	17	2	10.5				50	19	69	27.5
April 2021	38	7	15.6	23	3	11.5	1		0	62	10	72	13.9
May 2021	41	7	14.6	43	5	10.4	1		0	85	12	97	12.4
June 2021	18	7	28	16	1	5.9				34	8	42	19
July 2021	4	2	33.3	4	2	33.3				8	4	12	33.3
August 2021	3	2	40	6	1	14.3				9	3	12	25
September 2021	6	1	14.3	7		0				13	1	14	7.1
October 2021	8		0	4	1	20				12	1	13	7.7

Table 149 TTS fatality/survival rate over time by age group/gender for all cases

Case onset month/ Age group	FEMALE			MALE			UNKNOWN			Grand Total			
	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total reports	% of fatal reports
November 2021	5	1	16.7	1		0				6	1	7	14.3
December 2021	1		0	1	1	50				2	1	3	33.3
January 2022	1	1	50	2		0				3	1	4	25
February 2022	2		0	3		0				5	0	5	0
March 2022	4	1	20	1		0				5	1	6	16.7
April 2022	5		0	1	1	50				6	1	7	14.3
May 2022	1		0	4		0				5	0	5	0
June 2022		1	100	2	1	33.3				2	2	4	50
July 2022	3		0	2		0				5	0	5	0
August 2022	1		0	1	1	50				2	1	3	33.3
September 2022	3		0		1	100				3	1	4	25
October 2022	3		0	1		0				4	0	4	0
November 2022	1	1	50	1		0				2	1	3	33.3
December 2022				1		0				1	0	1	0
Age - 50-59 Yrs										0	0		
January 2021	2	2	50							2	2	4	50
February 2021	8	1	11.1	5		0				13	1	14	7.1
March 2021	53	17	24.3	25	8	24.2				78	25	103	24.3
April 2021	47	6	11.3	47	6	11.3	3		0	97	12	109	11

Table 149 TTS fatality/survival rate over time by age group/gender for all cases

Case onset month/ Age group	FEMALE			MALE			UNKNOWN			Grand Total			
	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total reports	% of fatal reports
May 2021	26	1	3.7	23	7	23.3		1	100	49	9	58	15.5
June 2021	16	5	23.8	24	3	11.1				40	8	48	16.7
July 2021	10	1	9.1	9	2	18.2				19	3	22	13.6
August 2021	7	3	30	9	1	10				16	4	20	20
September 2021	4	3	42.9	9		0				13	3	16	18.8
October 2021	3	1	25	4	2	33.3				7	3	10	30
November 2021	2	1	33.3	1		0				3	1	4	25
December 2021	2		0	1	1	50				3	1	4	25
January 2022	4	2	33.3		1	100				4	3	7	42.9
February 2022	1	1	50	1		0				2	1	3	33.3
March 2022	1	3	75	3	1	25				4	4	8	50
April 2022	2	2	50	2		0				4	2	6	33.3
May 2022	1		0	1		0				2	0	2	0
June 2022	4		0							4	0	4	0
July 2022		1	100	2	1	33.3				2	2	4	50
August 2022	2	1	33.3	1	2	66.7				3	3	6	50
September 2022	2	2	50	2		0				4	2	6	33.3
October 2022	2		0	3		0				5	0	5	0
November 2022	1		0							1	0	1	0

Table 149 TTS fatality/survival rate over time by age group/gender for all cases

Case onset month/ Age group	FEMALE			MALE			UNKNOWN			Grand Total			
	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total reports	% of fatal reports
December 2022	1		0							1	0	1	0
Age - 60-69 Yrs										0	0		
January 2021		1	100	3	3	50				3	4	7	57.1
February 2021	8	9	52.9	6	1	14.3				14	10	24	41.7
March 2021	36	7	16.3	33	6	15.4				69	13	82	15.9
April 2021	55	10	15.4	43	7	14	1		0	99	17	116	14.7
May 2021	47	11	19	47	12	20.3		1	100	94	24	118	20.3
June 2021	27	2	6.9	19	2	9.5				46	4	50	8
July 2021	8		0	13	1	7.1				21	1	22	4.5
August 2021	13		0	16	1	5.9				29	1	30	3.3
September 2021	3	1	25	14		0				17	1	18	5.6
October 2021	2		0	12	1	7.7				14	1	15	6.7
November 2021	1		0	1		0				2	0	2	0
December 2021	3		0	3		0				6	0	6	0
January 2022	6		0	1	1	50				7	1	8	12.5
February 2022				1	1	50				1	1	2	50
March 2022	2		0	2		0				4	0	4	0
April 2022	1	1	50	2	1	33.3				3	2	5	40
May 2022	2	1	33.3	2		0				4	1	5	20

Table 149 TTS fatality/survival rate over time by age group/gender for all cases

Case onset month/ Age group	FEMALE			MALE			UNKNOWN			Grand Total			
	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total reports	% of fatal reports
June 2022	3		0	1		0				4	0	4	0
July 2022	1		0							1	0	1	0
August 2022				2		0				2	0	2	0
September 2022	3	1	25	3		0				6	1	7	14.3
October 2022				1		0				1	0	1	0
December 2022				1		0				1	0	1	0
Age - 70-79 Yrs										0	0		
January 2021	2		0	3		0				5	0	5	0
February 2021	14	1	6.7	8	2	20				22	3	25	12
March 2021	11	3	21.4	7	2	22.2				18	5	23	21.7
April 2021	32	7	17.9	40	2	4.8	2		0	74	9	83	10.8
May 2021	15	3	16.7	28	6	17.6				43	9	52	17.3
June 2021	13	1	7.1	15	1	6.3				28	2	30	6.7
July 2021	10	1	9.1	15	2	11.8				25	3	28	10.7
August 2021	6	1	14.3	13		0				19	1	20	5
September 2021	4		0	11	1	8.3				15	1	16	6.3
October 2021	2		0	7		0				9	0	9	0
November 2021	1		0	2		0				3	0	3	0
December 2021				1		0				1	0	1	0

Table 149 TTS fatality/survival rate over time by age group/gender for all cases

Case onset month/ Age group	FEMALE			MALE			UNKNOWN			Grand Total			
	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total reports	% of fatal reports
February 2022				1		0				1	0	1	0
March 2022	2	1	33.3							2	1	3	33.3
April 2022	1		0	4		0				5	0	5	0
May 2022	1		0	1		0				2	0	2	0
June 2022		2	100							0	2	2	100
July 2022	2		0	1		0				3	0	3	0
August 2022	1		0	1		0				2	0	2	0
September 2022	3		0	2		0				5	0	5	0
November 2022		1	100		2	100				0	3	3	100
December 2022		1	100							0	1	1	100
Age - 80+ Yrs										0	0		
January 2021	2		0		1	100				2	1	3	33.3
February 2021	2	2	50		2	100				2	4	6	66.7
March 2021	2	2	50	6	4	40				8	6	14	42.9
April 2021	13	3	18.8	12	1	7.7				25	4	29	13.8
May 2021	6	1	14.3	6		0				12	1	13	7.7
June 2021	7	2	22.2	7	2	22.2				14	4	18	22.2
July 2021	10		0	2		0				12	0	12	0
August 2021	4		0	9		0				13	0	13	0

Table 149 TTS fatality/survival rate over time by age group/gender for all cases

Case onset month/ Age group	FEMALE			MALE			UNKNOWN			Grand Total			
	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total reports	% of fatal reports
September 2021	5		0	3		0				8	0	8	0
October 2021				3		0				3	0	3	0
November 2021				2		0				2	0	2	0
December 2021				1		0				1	0	1	0
June 2022				1		0				1	0	1	0
July 2022				2		0				2	0	2	0
October 2022	1		0							1	0	1	0
Age Unknown										0	0		
February 2021	4		0	1		0				5	0	5	0
March 2021	14	2	12.5	6	3	33.3	7		0	27	5	32	15.6
April 2021	11	4	26.7	11	1	8.3	3		0	25	5	30	16.7
May 2021	13	1	7.1	10	1	9.1	15	2	11.8	38	4	42	9.5
June 2021	4	2	33.3	9		0	7		0	20	2	22	9.1
July 2021	4	3	42.9	8		0				12	3	15	20
August 2021	3	1	25	5		0		2	100	8	3	11	27.3
September 2021	3	1	25	2		0	3	1	25	8	2	10	20
October 2021	2	1	33.3	1		0	6	2	25	9	3	12	25
November 2021				1		0				1	0	1	0
December 2021	1	1	50				1	1	50	2	2	4	50

Table 149 TTS fatality/survival rate over time by age group/gender for all cases

Case onset month/ Age group	FEMALE			MALE			UNKNOWN			Grand Total			
	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total reports	% of fatal reports
January 2022	1		0				2		0	3	0	3	0
February 2022		2	100	2	2	50				2	4	6	66.7
March 2022		1	100	1		0				1	1	2	50
April 2022	1	1	50					2	100	1	3	4	75
May 2022		1	100				1	1	50	1	2	3	66.7
June 2022	4		0	7		0	5	3	37.5	16	3	19	15.8
July 2022		1	100							0	1	1	100
August 2022	1	1	50							1	1	2	50
September 2022		1	100				32		0	32	1	33	3
October 2022	1		0					1	100	1	1	2	50
November 2022	1	1	50				7	4	36.4	8	5	13	38.5
December 2022	1		0				2		0	3	0	3	0
Grand Total	**1084**	**286**	**20.9**	**978**	**174**	**15.1**	**100**	**22**	**18**	**2162**	**482**	**2644**	**18.2**

TTS Thrombosis with thrombocytopenia syndrome; Yrs Years

Table 150 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

Case onset month/ Age group	FEMALE			MALE			UNKNOWN			Grand Total			
	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total	% of fatal reports
Age - 18-29 Yrs													
February 2021	3	1	25	1	1	50				4	2	6	33.3
March 2021	17	2	10.5	5	3	37.5				22	5	27	18.5
April 2021	11		0	14	1	6.7				25	1	26	3.8
May 2021	3		0	4	1	20				7	1	8	12.5
June 2021	5	3	37.5	6	2	25		1	100	11	6	17	35.3
July 2021	4	1	20	2		0				6	1	7	14.3
August 2021	7	3	30	2	2	50				9	5	14	35.7
September 2021	2	2	50	2	1	33.3				4	3	7	42.9
October 2021	2		0	1		0				3	0	3	0
November 2021	2	1	33.3							2	1	3	33.3
January 2022	1		0	2		0				3	0	3	0
February 2022				1		0				1	0	1	0
March 2022	2	2	50	3		0				5	2	7	28.6
April 2022	1	1	50	1		0				2	1	3	33.3
May 2022		1	100	1		0				1	1	2	50
June 2022	1	2	66.7		2	100				1	4	5	80

Table 150 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

Case onset month/ Age group	FEMALE			MALE			UNKNOWN			Grand Total			
	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total	% of fatal reports
July 2022	1		0	1		0				2	0	2	0
August 2022				2		0				2	0	2	0
September 2022	1	1	50	4		0				5	1	6	16.7
October 2022					1	100				0	1	1	100
November 2022	1		0	1		0				2	0	2	0
Age - 30-39 Yrs										**0**	**0**		
January 2021	1	1	50	1	2	66.7				2	3	5	60
February 2021	4	2	33.3	1	1	50				5	3	8	37.5
March 2021	22	7	24.1	7	3	30				29	10	39	25.6
April 2021	19	4	17.4	6	5	45.5				25	9	34	26.5
May 2021	11	6	35.3	8	1	11.1				19	7	26	26.9
June 2021	3	3	50	4	1	20				7	4	11	36.4
July 2021	6	3	33.3	5	4	44.4				11	7	18	38.9
August 2021	4	3	42.9	4	1	20				8	4	12	33.3
September 2021	1	1	50	3		0				4	1	5	20
October 2021	1	1	50	1		0				2	1	3	33.3

Table 150 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

Case onset month/ Age group	FEMALE			MALE			UNKNOWN			Grand Total			
	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total	% of fatal reports
November 2021	2		0	2		0				4	0	4	0
December 2021	1		0	1	1	50				2	1	3	33.3
January 2022	2		0							2	0	2	0
February 2022	1		0	1		0				2	0	2	0
March 2022	2	2	50	5		0				7	2	9	22.2
May 2022	3		0	1		0				4	0	4	0
June 2022	1	1	50	4		0				5	1	6	16.7
July 2022		2	100	2		0				2	2	4	50
August 2022	1	1	50							1	1	2	50
September 2022	2	1	33.3	1		0				3	1	4	25
October 2022				1		0				1	0	1	0
Age - 40-49 Yrs										**0**	**0**		
February 2021	4	4	50	2		0				6	4	10	40
March 2021	22	13	37.1	12		0				34	13	47	27.7
April 2021	27	4	12.9	18	1	5.3				45	5	50	10
May 2021	30	6	16.7	37	4	9.8	1		0	68	10	78	12.8

Table 150 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

Case onset month/ Age group	FEMALE			MALE			UNKNOWN			Grand Total			
	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total	% of fatal reports
June 2021	7	4	36.4	9		0				16	4	20	20
July 2021	4	1	20	3	1	25				7	2	9	22.2
August 2021	2		0	4	1	20				6	1	7	14.3
September 2021	5	1	16.7	7		0				12	1	13	7.7
October 2021	5		0	3	1	25				8	1	9	11.1
November 2021	5	1	16.7	1		0				6	1	7	14.3
December 2021	1		0		1	100				1	1	2	50
January 2022	1	1	50	2		0				3	1	4	25
February 2022	1		0	3		0				4	0	4	0
March 2022	2	1	33.3	1		0				3	1	4	25
April 2022	2		0	1	1	50				3	1	4	25
May 2022	1		0	4		0				5	0	5	0
June 2022				2		0				2	0	2	0
July 2022	3		0	2		0				5	0	5	0
August 2022				1	1	50				1	1	2	50
September 2022	3		0		1	100				3	1	4	25

Table 150 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

Case onset month/ Age group	FEMALE			MALE			UNKNOWN			Grand Total			
	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total	% of fatal reports
October 2022	3		0	1		0				4	0	4	0
November 2022		1	100							0	1	1	100
December 2022				1		0				1	0	1	0
Age - 50-59 Yrs										**0**	**0**		
January-2021	1	1	50							1	1	2	50
February 2021	6	1	14.3	4		0				10	1	11	9.1
March 2021	39	13	25	21	3	12.5				60	16	76	21.1
April 2021	36	3	7.7	41	6	12.8	3		0	80	9	89	10.1
May 2021	18		0	19	4	17.4		1	100	37	5	42	11.9
June 2021	14	4	22.2	15	2	11.8				29	6	35	17.1
July 2021	8	1	11.1	6	1	14.3				14	2	16	12.5
August 2021	4	3	42.9	7	1	12.5				11	4	15	26.7
September 2021	4	1	20	6		0				10	1	11	9.1
October 2021	2		0	2	2	50				4	2	6	33.3
November 2021	2	1	33.3	1		0				3	1	4	25

Table 150 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

Case onset month/ Age group	FEMALE			MALE			UNKNOWN			Grand Total			
	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total	% of fatal reports
December 2021	2		0	1	1	50				3	1	4	25
January 2022	3	2	40		1	100				3	3	6	50
February 2022	1	1	50	1		0				2	1	3	33.3
March 2022	1	2	66.7	3	1	25				4	3	7	42.9
April 2022	1	1	50	1		0				2	1	3	33.3
May 2022	1		0							1	0	1	0
June 2022	3		0							3	0	3	0
July 2022				1	1	50				1	1	2	50
August 2022	2	1	33.3							2	1	3	33.3
September 2022	2	2	50	1		0				3	2	5	40
October 2022	2		0	3		0				5	0	5	0
November 2022	1		0							1	0	1	0
December 2022	1		0							1	0	1	0
Age - 60-69 Yrs										**0**	**0**		
January-2021		1	100	2	2	50				2	3	5	60
February 2021	7	7	50	4	1	20				11	8	19	42.1

Table 150 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

Case onset month/ Age group	FEMALE			MALE			UNKNOWN			Grand Total			
	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total	% of fatal reports
March 2021	27	6	18.2	22	3	12				49	9	58	15.5
April 2021	27	8	22.9	27	5	15.6	1		0	55	13	68	19.1
May 2021	31	9	22.5	31	8	20.5				62	17	79	21.5
June 2021	17		0	10	1	9.1				27	1	28	3.6
July 2021	5		0	6		0				11	0	11	0
August 2021	11		0	6		0				17	0	17	0
September 2021	2	1	33.3	11		0				13	1	14	7.1
October 2021	1		0	11	1	8.3				12	1	13	7.7
December 2021	1		0	1		0				2	0	2	0
January 2022	4		0	1		0				5	0	5	0
March 2022	2		0	2		0				4	0	4	0
April 2022	1	1	50	1	1	50				2	2	4	50
May 2022	2		0	1		0				3	0	3	0
June 2022	3		0	1		0				4	0	4	0
July 2022	1		0							1	0	1	0
August 2022				1		0				1	0	1	0
September 2022	3		0	3		0				6	0	6	0

Table 150 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

Case onset month/ Age group	FEMALE			MALE			UNKNOWN			Grand Total			
	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total	% of fatal reports
October 2022				1		0				1	0	1	0
December 2022				1		0				1	0	1	0
Age - 70-79 Yrs										**0**	**0**		
January 2021	2		0	2		0				4	0	4	0
February 2021	11	1	8.3	7	1	12.5				18	2	20	10
March 2021	5	1	16.7	6	1	14.3				11	2	13	15.4
April 2021	15	6	28.6	24	1	4	1		0	40	7	47	14.9
May 2021	9	1	10	16	3	15.8				25	4	29	13.8
June 2021	10	1	9.1	7	1	12.5				17	2	19	10.5
July 2021	9	1	10	10	1	9.1				19	2	21	9.5
August 2021	4	1	20	10		0				14	1	15	6.7
September 2021	3		0	6	1	14.3				9	1	10	10
October 2021	2		0	7		0				9	0	9	0
November 2021				2		0				2	0	2	0
February 2022				1		0				1	0	1	0
March 2022	2	1	33.3							2	1	3	33.3

Table 150 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

Case onset month/ Age group	FEMALE			MALE			UNKNOWN			Grand Total			
	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total	% of fatal reports
April 2022				1		0				1	0	1	0
May 2022				1		0				1	0	1	0
June 2022		2	100							0	2	2	100
July 2022	1		0	1		0				2	0	2	0
September 2022	3		0	2		0				5	0	5	0
November 2022		1	100		1	100				0	2	2	100
December 2022		1	100							0	1	1	100
Age - 80+ Yrs										**0**	**0**		
January 2021	1		0							1	0	1	0
February 2021	1	1	50		1	100				1	2	3	66.7
March 2021	1	2	66.7	3	1	25				4	3	7	42.9
April 2021	8	2	20	8	1	11.1				16	3	19	15.8
May 2021	5	1	16.7	2		0				7	1	8	12.5
June 2021	1	1	50	6	2	25				7	3	10	30
July 2021	6		0	2		0				8	0	8	0
August 2021	3		0	6		0				9	0	9	0

Table 150 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

Case onset month/ Age group	FEMALE			MALE			UNKNOWN			Grand Total			
	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total	% of fatal reports
September 2021	5		0	3		0				8	0	8	0
October 2021				3		0				3	0	3	0
November 2021				2		0				2	0	2	0
June 2022				1		0				1	0	1	0
July 2022				1		0				1	0	1	0
October 2022	1		0							1	0	1	0
Age Unknown										**0**	**0**		
February 2021	2		0							2	0	2	0
March 2021	8	1	11.1	4	1	20	2		0	14	2	16	12.5
April 2021	7	2	22.2	6	1	14.3				13	3	16	18.8
May 2021	7	1	12.5	8	1	11.1	2		0	17	2	19	10.5
June 2021	3	1	25	7		0	1		0	11	1	12	8.3
July 2021	1	2	66.7	2		0				3	2	5	40
August 2021	2	1	33.3	4		0				6	1	7	14.3
September 2021		1	100	1		0				1	1	2	50
October 2021	1		0							1	0	1	0

Table 150 TTS fatality/survival rate over time by age group/gender and doses for confirmed/probable and possible cases

Case onset month/ Age group	FEMALE			MALE			UNKNOWN			Grand Total			
	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	% of fatal reports	Number of non-fatal reports	Number of Fatal reports	Total	% of fatal reports
November 2021				1		0				1	0	1	0
February 2022		1	100							0	1	1	100
April 2022								1	100	0	1	1	100
June 2022							1		0	1	0	1	0
August 2022	1	1	50							1	1	2	50
October 2022								1	100	0	1	1	100
November 2022		1	100				5	3	37.5	5	4	9	44.4
December 2022							1		0	1	0	1	0
Grand Total	**718**	**201**	**21.9**	**674**	**108**	**13.8**	**18**	**7**	**28**	**1410**	**316**	**1726**	**18.3**

TTS Thrombosis with thrombocytopenia syndrome.

TTS reports after Dose 2 of VAXZEVRIA

A search of the AstraZeneca global safety database was undertaken to retrieve adverse event reports of thrombosis in combination with thrombocytopenia reported following administration of the Dose 2 of the VAXZEVRIA. The search encompassed all cases retrieved up to 28 December 2022. The search criteria mentioned above was used to identify TTS cases post Dose 2.

The cases of TTS following the Dose 2 were confirmed based on the dose number/information provided in the narrative, if the reports did not contain information on Dose 2, they were not included in the below analysis. The search identified 287 cumulative cases of TTS following the second dose of VAXZEVRIA. Time to onset was available in 231 of the 287 cases and ranged from 0 to 174 days with a median TTO of 13 days after 2nd dose. Time to onset by 14 days, 21 days, and 42 days is presented in Table 136.

The majority of the 287 case reports of TTS following second dose occurred in male vaccinees (159, 55%). Of the 287 case reports of TTS following second dose, 107 were female (38%), and gender was unknown in 21 report.

The age range of vaccinees was from 22 to 95 years, age was not provided in 21 of the 287 reports. Median age was 66 years and 205 (71%) of the reports were in vaccinees > 50 years. Outcome in 87 cases were reported as Not recovered, 21 Recovered, 76 Recovering, 10 Recovered with sequalae and Unknown in 65 report.

These events included the following sites of thrombosis (≥ 5): Pulmonary embolism (122), Deep vein thrombosis (70), Thrombosis with thrombocytopenia syndrome (45), Thrombosis (36), Cerebrovascular accident (16), Cerebral venous sinus thrombosis (15), Embolism (10), Portal vein thrombosis (9), Peripheral artery thrombosis (6), Superior sagittal sinus thrombosis (5), Thrombotic thrombocytopenic purpura (5), Mesenteric vein thrombosis (5), Ischaemic stroke (5).

In 61 out of 287 reports (21%) with Dose 2, there was a co-reported bleeding event from the narrow SMQ: Haemorrhage terms (excl laboratory terms). The reported events (≥ 2) included: Haemorrhage (10), Contusion (8), Cerebral haemorrhage (7), Haemoptysis (6), Thrombotic thrombocytopenic purpura (5), Petechiae (4), Melaena (2), Haemorrhagic adrenal infarction (2), Haematuria (2), Subarachnoid haemorrhage (2), Haemorrhage intracranial (2), Haemorrhagic stroke (2). There were two case report with the co-reported events from the HLT: Coagulopathies following Dose 2 with the event Coagulopathy (1) and Antiphospholipid syndrome (1).

Using the estimated exposure of 158.59 million administered 2nd vaccinations with VAXZEVRIA in EEA, UK, Brazil, Australia, Canada, Taiwan and Thailand and the reporting rate of thrombotic events in combination with thrombocytopenia (with time to onset ≤ 21 days; 146 reports) following the Dose 2 of VAXZEVRIA was estimated to be 0.92 per million doses. The majority of the vaccines who experienced TTS post Dose 2 were male

(60%) and were older in age with a median age of 68 years. The rate of TTS following 2nd of VAXZEVRIA is less compared to the background rate for all age groups (see Table 138 and Table 139) of 5.62 (event rates per 1M PY per 21 days Truven Market Scan-2019, aligned with the OHDSI TTS algorithm) and 10.75 (event rates per 1M PY per 21 days Truven Market Scan-2019, aligned with the OHDSI TTS algorithm [with updated OHDSI aligned codelists and washout periods]).

This rate of thrombotic events in combination with thrombocytopenia following 1st dose of VAXZEVRIA is below the estimated reporting rate of 8.96 per million doses for first dose of VAXZEVRIA (1458 identified reports with time to onset ≤ 21 days; estimated exposure 162.71 million administered doses). TTS events following the second dose had a different demographic pattern as well, being older and more likely male compared to Dose 1.

TTS reports after Dose 3 of VAXZEVRIA

A search of the AstraZeneca global safety database was undertaken to retrieve adverse event reports of thrombosis in combination with thrombocytopenia reported following administration of the Dose 3 of the VAXZEVRIA. The search encompassed all cases retrieved up to 28 December 2022. The cases of TTS following the Dose 3 were confirmed based on the dose number/information provided in the narrative. There were 19 cases occurred after administration of a Dose 3/booster (either of AZD1222 or an mRNA vaccine): 15 after an AZD1222 booster, and 4 after an mRNA booster. The 4 cases after an mRNA booster are not further discussed here as they do not concern the use of AZD1222 as a booster. Time to onset was available in 10 of the 15 cases and ranged from 1 to 60 days with a median TTO of 12 days after 3rd dose. Time to onset by 14 days, 21 days, and 42 days is presented in Table 136.

Of the 15 case reports of TTS following Dose 3/booster, 6 were female (40%), and 8 were male. The age range of vaccinees was from 20 to 74 years. Median age was 28 years. Outcome in 3 cases were reported as Not recovered, 3 Recovering, 5 Fatal report. 3, recovered 2, Unknown 3.

No confirmed cases of TTS following a heterologous AZD1222 booster have been identified. The rate of TTS following a homologous booster dose could not be estimated as the only potential homologous booster TTS case was in Mexico and exposure data are not available for Mexico.

No new or emerging concern regarding TTS has been identified with booster doses of VAXZEVRIA. Based on the review of available safety data, there is no indication suggesting that the safety profile of an AZD1222 booster after a primary series with another vaccine would be different with respect to TTS from that of a first vaccine dose of AZD1222.

Table 151 Post-Marketing Cases of Thrombosis with Thrombocytopenia Syndrome Related to AZD1222 and COVID-19 Vaccine Booster Use

Case ID Country	Events (PT)	Age/Sex	Primary / Booster vaccine	Time to onset	MHRA case classification	Comment
[redacted]	Cerebral venous sinus thrombosis; Immune thrombocytopenia; Cerebral venous thrombosis; Haemorrhage intracranial; Incorrect route of product administration; Seizure; Interchange of vaccine products	26/F	CoronaVac /AZD1222 (19 January 2022)	16 days	Criteria not met	This is a consumer report. Past drug therapy included COVID-19 vaccine (first 2 doses of the vaccine corresponded to the CoronaVac brand, without any problem) for prevention. On 19 January 2022, patient received Dose 3 of VAXZEVRIA. There is no radiological confirmation for thrombosis event.
[redacted]	Pulmonary embolism; Sepsis; Pulmonary sepsis; Lung neoplasm malignant; Thrombocytopenia; Pyrexia; Respiratory rate increased	74/F	AZD1222 /AZD1222	Same day	Criteria not met	No evidence of thrombocytopenia; considered to be a coding error and case was received from regulatory authority. Pulmonary embolism event was reported on same day of booster and in the context of pulmonary sepsis and malignant lung neoplasm. The patient outcome at the time of the report was not recovered.
[redacted]	Paralysis; Thrombosis; Speech disorder; Coordination abnormal; Muscular weakness; Diplopia; Petechiae; Contusion; Pallor; Heavy menstrual bleeding; Vision blurred; Thrombocytopenia; Dizziness; Nausea; Expired product administered; Incorrect route of product administration; Fatigue; Headache; Decreased appetite; Pain in extremity	46/F	AZD1222 /AZD1222	5 days	Possible	This is a consumer report. VAXZEVRIA Dose 1: 09 June 2021 VAXZEVRIA Dose 2: 03 August 2021 VAXZEVRIA Dose 3: 06 September 2021 There are events of medication error (subcutaneous route administration and expired product administered). The lot ID for reported Dose 2 and Dose 3 are same; hence, it cannot be confirmed as booster dose. There is no radiological confirmation for thrombosis event (site of thrombosis not reported), and the patient was treated with prednisolone for thrombocytopenia. No information on D-dimer and anti-PF4.

Table 151 Post-Marketing Cases of Thrombosis with Thrombocytopenia Syndrome Related to AZD1222 and COVID-19 Vaccine Booster Use

Case ID Country	Events (PT)	Age/Sex	Primary / Booster vaccine	Time to onset	MHRA case classification	Comment
[redacted] Italy	Thrombosis; Platelet count decreased; Off label use	NA/M	Unknown/Unidentified AstraZeneca Product	Unknown	Criteria not met	Report was based on a social media post. There is very little information in this case. Not clear if this was VAXZEVRIA, as VAXZEVRIA is not used in Italy for booster dose. The patient died from the event of thrombosis during December 2021.
[redacted]	Venous thrombois; Pulmonary embolism; Thrombocytopenia	28/M	COMIRNATY / AZD1222 (03 March 2022)	2 days	Possible	This is a consumer report. Pfizer Dose 1: 11 August 2021 Pfizer Dose 2: 25 October 2021 AstraZeneca Dose 3: 03 March 2022Venous thrombosis occurred 2 days after the VAXZEVRIA and pulmonary embolism occurred, 14 days after last dose. Events were confirmed by CT angiography of chest and abdominal aorta on 18 March 2022. Patient had history of DVT 14 months back, was put-on long-term anticoagulation with oral Rivaroxaban, which was stopped prior to the events. Normal D-dimer and negative PF4. Patient recovered from all events
[redacted]	Splenic infarction; Renal infarct; Thrombosis; Thrombosis with thrombocytopenia syndrome; Influenza; Haematuria; Dysuria; Back pain; Headache; Facial pain; Pyrexia; Abdominal pain lower	M/21	COMIRNATY /VAXZEVRIA	10 days	Probable	Spontaneous report. The vaccinee received First and second dose of Comirnaty (dates unknown). VAXZEVRIA (Dose 3) received on 06 May 2022. CT scan abdomen revealed splenic infarction, renal infarct. Patient received Fondaparinux, Rivaroxaban and IVIg as treatment and was recovering

Table 151 Post-Marketing Cases of Thrombosis with Thrombocytopenia Syndrome Related to AZD1222 and COVID-19 Vaccine Booster Use

Case ID Country	Events (PT)	Age/Sex	Primary / Booster vaccine	Time to onset	MHRA case classification	Comment
[redacted] Brazil	Pulmonary embolism; Haemorrhagic stroke; Thrombocytopenia	38 years /F	VAXZEVRIA booster	10 days	Possible	Spontaneous report. VAXZEVRIA received as Dose 3 on 22 June 2022. 10 days later developed pulmonary embolism, haemorrhagic stroke diagnosed by skull and chest CT. High D-dimer and anti PF-4 positive. Outcome was fatal.
[redacted]	Thrombosis with thrombocytopenia syndrome	32 years /M	VAXZEVRIA booster	N/A	Criteria not met	Spontaneous report. VAXZEVRIA received as Dose 4 on 25 June 2022. Previous doses were Coronavac/Coronavac/Pfizer. Symptoms began 7 days later with headache. Rapid neurological deterioration with seizures. CT skull revealed intracranial bleed. No radiological conformation of any cerebral venous sinus thrombosis or thrombosis at any other site. High D-dimer, PF 4 positive. Treated with IVIg. The patient outcome at the time of the report was not recovered.
[redacted] Brazil	Thrombosis with thrombocytopenia syndrome	37 years /F	VAXZEVRIA booster	8 days	Possible	Spontaneous report. VAXZEVRIA received as Dose 4 on 22 June 2022. 8 days later developed thrombosis at multiple sites with complications. Outcome was fatal.
[redacted]	Thrombosis with thrombocytopenia syndrome; Haemorrhoids; Headache; Pyrexia	41 years/M	VAXZEVRIA booster	N/A	Confirmed	This is a consumer report. VAXZEVRIA received as Dose 4 on 26 July 2022. Previous doses were with the Pfizer vaccine. Symptomatic 13 days later starting with headache. CT skull revealed CVST. High D-dimer, PF 4 positive. Treated with Rivaroxaban. Had intercurrent COVID-19 illness. Outcome was recovered.

Table 151 Post-Marketing Cases of Thrombosis with Thrombocytopenia Syndrome Related to AZD1222 and COVID-19 Vaccine Booster Use

Case ID Country	Events (PT)	Age/Sex	Primary / Booster vaccine	Time to onset	MHRA case classification	Comment
[redacted]	Seizure; Cerebral thrombosis; Acute respiratory distress syndrome; Thrombocytopenia; Vision blurred; Paraesthesia	20 years/M	VAXZEVRIA booster	13 days	Criteria not met	This is a consumer report. VAXZEVRIA received as Dose 1 on 16 June 2021. 2nd and 3rd doses were with Coronavac vaccine (dates unknown). 5 days after receiving VAXZEVRIA became symptomatic with blurred vision and paraesthesia. Later on, progressed to Cerebral venous thrombosis with intracranial bleed. During hospitalization, he had a lowered level of consciousness and required orotracheal intubation, which led to pulmonary complications. Anti PF4 positive. Treated with IVIg. Outcome unknown
[redacted]	Cerebral venous sinus thrombosis; Seizure; Thrombosis with thrombocytopenia syndrome; Interchange of vaccine products; Off label use	Unknown	AZD1222	14 days	Criteria not met	Spontaneous report. VAXZEVRIA received as Dose 3 on 19 January 2022. The 1st and 2nd vaccine shots were Sinovac. Insufficient information on complete demographics, outcome of the event, concomitant conditions and detailed diagnostic and etiologic workup
[redacted]	Cerebral venous sinus thrombosis; Cystitis; Transverse sinus thrombosis; Fibrin D dimer increased; Thrombocytopenia; Dysuria; Perineal pain; Testicular oedema; Urethritis; Chills; Abdominal pain lower; Headache; Pyrexia	M	AZD1222	Unknown	Confirmed	Spontaneous report. VAXZEVRIA received as Dose 3 on 14 February 2022. The vaccinee received primary vaccination series with Comirnaty. Concurrent conditions, relevant medical and family history, risk factors (hypercoagulability, ongoing infection), complete etiological work up not reported. Had radiologically confirmed CVST with high D-dimer and positive PF4. Outcome was recovered.

Table 151 Post-Marketing Cases of Thrombosis with Thrombocytopenia Syndrome Related to AZD1222 and COVID-19 Vaccine Booster Use

Case ID Country	Events (PT)	Age/Sex	Primary / Booster vaccine	Time to onset	MHRA case classification	Comment
[redacted] Brazil	Loss of consciousness; Hypotension; Platelet disorder; Thrombosis	22/F	AZD1222	Unknown	Probable	. Spontaneous report. First two doses of Pfizer vaccine. VAXZEVRIA received as Dose 3 on 04 April 2022. After 10 days developed the events. No radiological confirmation of site of thrombosis. High D-dimer and positive PF4. Outcome was fatal.
[redacted] Brazil	Thrombosis with thrombocytopenia syndrome	28/M	AZD1222	7 days	Possible	This is a spontaneous report. On 03 June 2022 patient took the 3rd dose of the AstraZeneca vaccine. Thrombosis at multiple sites was radiologically confirmed. Thrombocytopenia, Anti PF4 antibodies positive. D-dimer levels not reported, fibrinogen normal. Event had fatal outcome

CT computed tomography; MHRA Medicines and Healthcare products Regulatory Agency; NA not available; PT Preferred term

Literature

A periodic literature search of the databases in Embase, Insight Meme and PubMed was conducted for relevant articles on topic in association with VAXZEVRIA.

Significant safety articles summary TTS (MOA):

On 27 June 2022, the European Medicines Agency (EMA) hosted a virtual workshop to review the current understanding of the pathophysiology of TTS post-vaccination, to foster the discussion on potential disease mechanisms and to identify the most important next steps in the research (Buoninfante et al 2022).

An overview of the clinical and diagnostic features of VITT in the UK was presented. VITT was described as a cause of TTS but not synonymous with it. As cases were collected from daily clinical meetings during the vaccination campaign, a pattern consisting of five equally weighted clinical features emerged, and by using those the likelihood of the case being VITT could be categorized into definite, probable, possible, and unlikely (Pavord et al 2022). The initial female over-representation of TTS cases appeared to reflect the demographics during the early rollout of the adenovirus-vector vaccine in the UK. Of note, the administration of second doses of COVID- 19 vaccine in 40 UK patients who had either definite (26), probable (2) and possible (12) VITT after a first dose of VAXZEVRIA did not lead to recurrent VITT (Lacy et al 2022), including in the few subjects (n = 5) who had received a second dose of VAXZEVRIA. This was corroborated by the work conducted in an independent research group in Germany. The latter demonstrated that anti-PF4-antibodies in TTS vaccinees are transient (Schonborn et al 2022 (a). The detection of anti-PF4 antibodies is a crucial marker for VITT but available assays have different sensitivities, and Enzyme-Linked Immunosorbent Assay (ELISA) based approaches can be combined with specific functional assays (Reilly-Stitt et al 2021). It has been previously shown that anti-PF4 antibodies associated with VITT do not cross react with the spike protein, indicating that VITT is specifically induced post adenovirus vector vaccination (Greinacher et al 2021 (a). The human in vivo evidence that the anti- PF4 response in VITT is neither related to the spike protein nor to SARS-CoV2 came from data collected in a cohort of 11 patients with a history of VITT and subsequent COVID-19. In these patients no significant increase in anti-PF4 antibody levels was observed after recovery from COVID-19 (Schonborn et al 2022 (b) As VITT occurs starting from 5 days post-vaccine administration, the anti-PF4 B cell response does not align with the notions of the conventional immunological response post primary antigen exposure and appears to be a secondary immune response.

Recently, the molecular signature of clonotypic anti-PF4 antibodies was identified in five patients, defined as a single IgG heavy (H)-chain species paired with a single lambda light (L)-chain species, and all L-chains were encoded by the identical IGLV3- 21*02 gene subfamily (Wang et al 2022 [C]) analysed Serum specimens obtained from 5 patients with AstraZeneca-associated VITT, and their serological findings. Anti-PF4 IgGs were immunopurified by PF4-coupled magnetic beads from VITT patient serum. Prior to sequencing, monospecificity of anti-PF4 IgGs was verified by ELISAs, and no cross-

reactivity was found between eluted anti-PF4 IgGs and SARS-CoV-2 S1 and S2 proteins. Purifiedanti-PF4 IgGs were then separated by sodium dodecyl–sulfate polyacrylamide gel electrophoresis; heavy- and light-chain bands excised for in-gel digestion; and analysis of peptides performed in a Thermo Orbitrap Fusion Lumos Tribrid mass spectrometer with de novo sequencing and International Immunogenetics Database (IMGT) database matching. Mass spectrometric sequencing of anti-PF4 immunoglobulins revealed a single IgG H-chain species paired with a single λ L-chain species in all 5 unrelated patients. Remarkably, all L chains were encoded by the identical IGLV3-21*02 gene subfamily and showed identical LCDR3 peptide lengths consistent with a high degree of L-chain stereotypy. Notably, the shared IGLV3-21*02 allele expresses an acidic (negatively charged) DDxD motif in the CDR2 region, which suggest may be of potential importance in antibody binding to the positively charged PF4 epitope. The frequencies of different alleles of the IGLV3-21 gene vary among ethnicities, with the highest prevalence of IGLV3-21*02 in Europeans and lowest in East Asians. The IGLV3-21*02 represents ~4% of IGLV transcripts from peripheral blood mononuclear cells in healthy donors and has been observed as a minor component of the total serum antibody proteome, such as human anti–double-stranded Deoxyribonucleic Acid (DNA) and anti-Ro60 autoantibodies. As per the authors the dominant stereotyped expression of IGLV3-21*02 has not been observed in any other serum antibody responses to date and can be regarded as a unique fingerprint of anti-PF4 IgGs in VITT. The finding of a stereotyped clonotypic anti-PF4 antibody in this preliminary study of a small number of subjects represents a significant advance in elucidating the molecular pathways of pathologic antibody production in VITT and offers a rare example in human disease of a dangerous small B-cell clone that undergoes rapid clonal expansion and secretion of a harmful monoclonal antibody.

These results may reveal a shared pathway of antibody production in VITT patients and could point to a possible genetic predisposition at the basis of the syndrome. According to one working hypothesis, complexes formed by PF4 and adenovirus vector vaccines together with vaccination induced strong immune activation could lead to the formation of anti-PF4 pathogenic autoantibodies triggering platelet activation and the downstream prothrombotic cascade (Greinacher et al 2021 (b).

Adenovirus vaccine constituents binding to PF4 may induce conformational changes in PF4 and create potential neoantigen(s), responsible for marginal zone B cells activation. This latter immunobiological process still requires further investigation. However, data generated with super-resolution microscopy show that vaccine components form complexes with PF4 to which anti-PF4 antibodies obtained from VITT patients bind in vitro.

An overview of the clinical cases of vaccine associated TTS post VAXZEVRIA in Australia was also provided. These cases in Australia are classified according to the International Network of Special Immunization Services approach to characterize risk factors and mechanisms underlying adverse events of special interests following vaccination (Top et al 2022). Of relevance, the mortality cases post second dose of VAXZEVRIA in Australia appeared to be associated with a shorter dosing interval than the current national

recommendations. Furthermore, ongoing research plans to study genetic risk factors and the characterization of B-cell clones producing autoantibodies in VITT via multi-omics were discussed among the participants.

Interestingly, data generated by mass-spectrometry showed that anti-PF4 antibodies obtained from VITT patients are monoclonal or oligoclonal, in contrast to anti-PF4 antibodies in conventional HIT, which are always polyclonal (Kanack et al 2022). It was commented that beside the dichotomous distinction of monoclonal versus polyclonal humoral response between VITT and HIT, it will be crucial to understand the exact binding epitopes to PF4 shared or not between the two antibody responses. Recent data suggests that antibody binding to un-complexed PF4 seems to be the key differentiating feature of VITT from HIT and spontaneous HIT cases, however the degree of specificity of this assay needs to be evaluated in larger studies. VITT antibodies only occasionally activate platelets in the presence of heparin as in the serotonin release assay, but consistently activate PF4-treated platelets, in line with previous findings. Thus, it is important to only use PF4-treated platelets in functional testing for VITT.

Two academic research groups studied the interactions between the adenovirus capsid and PF4 and demonstrated that the capsids of the adenoviruses Ad5, ChAdOx1 and Ad26 can form a complex with PF4 (Baker et al 2021). It was shown in ChAdOx1 that this complex is sufficiently stable to support tertiary complex formation with anti-PF4 IgG. Computational modelling and Brownian dynamic simulations, utilizing the experimentally determined capsid structure indicated that the interactions are not randomly distributed over the virion surface but mainly occur at the interfaces between hexons. Data was described in which purified hexons, with no DNA component, were also able to interact with PF4 in surface plasmon resonance studies. Also, research focused on the molecular mapping of the PF4–ChAdOx1 adenovector interaction and on the biochemical characterization of VITT antibodies confirmed the binding data from Baker et al 2021. It was demonstrated that PF4 binds to ChAdOx1 by biolayer interferometry using both streptavidin and amine-coupling sensors. A mutagenesis study allowed the identification of the PF4 amino acid residues involved in ChAdOx1 binding. It appeared that the ChAdOx1 binding site on PF4 overlaps with the heparin binding site but not all amino acids are shared between the two binding sites (Huynh et al 2021). In addition, the binding of anti-PF4 antibodies from VITT patients were restricted to eight surface amino acids on PF4, all of which located within the heparin-binding site. It was also reported that some VITT patients had anti-PF4 antibodies binding only to one site on PF4 (the heparin binding site), while other VITT patients were able to bind to two distinct sites on PF4 (a characteristic shared with antibodies from some HIT patients). Taken together, the induction of disease specific anti-PF4 antibodies in VITT and HIT result in similar but yet distinct molecular interactions that are reflected by the apparent phenotypical similarity of the two diseases.

(Marietta et al 2022) discussed the potential mechanisms of vaccine-induced thrombosis and thrombocytopenia. In VITT, they hypothesized that following microvascular damage during vaccine administration, trace amounts of 50 billion virus particles in each dose come into

contact with blood, bringing AdV DNA and polyadenylated hexone proteins the AdV vectors in contact with PF4. Either component of AdV could replace heparin as a scaffold of negative charges leading to the conformational changes of PF4 molecule already described in HIT and to the formation of anti-PF4/polyanion antibodies. These VITT antibodies bind to PF4 epitopes which overlap with the binding site of heparin but differ from those recognized by anti-PF4 antibodies seen in HIT. Following the binding of anti-PF4 antibodies, PF4 tetramers cluster and form immune complexes, which in turn cause Fcγ receptor IIa dependent platelet activation, monocytic activation, release of procoagulant platelet microparticles (MPs) and production of neutrophil extracellular traps (NETs). The resulting immunothrombosis drives the clinical features of VITT. Of note, the Ad26 and Ad5 AdV vectors used in the Ad26.COV2.S and Sputnik V COVID-19 vaccines have lower negative surface charges compared to ChAdOx1. This finding is consistent with the lower incidence of VITT observed in recipients of these vaccines.

The induction of the anti-PF4 immune response requires a proinflammatory milieu, which can be elicited by several vaccine components, such as human cell line proteins, free virus proteins, Ethylenediaminetetraacetic Acid (EDTA) and AdV genetic material. Relevant to this, a higher proportion of host-cell proteins, active proteases and unassembled hexon proteins has been found in the ChAdOx1 nCoV-19 vaccine as compared to the Ad26.COV2.S. This finding suggests that a different intensity of the inflammatory response elicited by different AdV vaccines can play a role in the production of the functionally active PF4 antibodies involved in the development of VITT.

Another postulated mechanism for the development of VITT takes into account the availability of soluble spike protein variants resulting from alternative splice events following administration of the ChAdOx1 vaccine. Soluble spike protein variants can bind to ACE2-expressing endothelial cells, thus triggering the immune-mediated endothelial cell damage and subsequent thrombosis. Moreover, the spike protein can act as superantigen, thus eliciting a polyclonal activation. This, together with the high immunogenicity of PF4-adenovirus complexes, may facilitate the induction of PF4-specific antibodies. Moreover, besides their potential to elicit anti-PFA antibodies, AdV vaccines induce a more pronounced increase in thrombin generation, inflammatory (ie, TNF-a, IL-1b and IL-8) and platelet activation (ie, TGF-b and CD40L) markers compared to the mRNA ones.

It has been proposed that HIT may occur in susceptible individuals immunologically primed to produce PF4 antibodies, possibly as the result of exposures to other environmental factors (for example, bacterial infection) that produce the same antigen as that produced by the heparin/platelet 4 complexes. A similar individual predisposition could be involved also in the development of VITT, and the hypothesis of a previous priming by bacterial infections fits well with the peculiar sites of thrombosis in VITT, ie, cerebral venous sinuses and splanchnic veins. These venous territories share the common feature of draining the nasal sinus and intestines, thus allowing access of microbiotal and viral products.

It was originally hypothesized that VAXZEVRIA and JCOVDEN associated impurities may drive the immune thrombotic activation cascade. However, given the remarkable differences

between the two vaccines in terms of impurities due to the differences in manufacturing of the vaccines, this is rather unlikely (Krutzke et al 2022)

AstraZeneca comment on MOA articles

Despite the tremendous amount of scientific research done so far, several gaps remain in our understanding of how PF4 binding occurs in vivo across different adenoviral vaccine platforms, and further in-depth characterization of the immune responses mounted by VITT subjects.

The recent evidence on the interaction between PF4 and the adenovector from VAXZEVRIA and JCOVDEN point towards a model in which binding of the capsid protein of both adenovectors, ChAdOx1 and Ad26, to PF4 results in complex formation and subsequent downstream activation of PF4-specific B-cells. The produced anti-PF4 antibodies then cause prothrombotic activation of several cells in the blood. However, there are some key missing information and yet unanswered questions, regarding to what extent the shape complementarity and electrostatic mechanism contribute to this interaction. It appears that ChAdOx1-PF4 complexes are recognized by pre-existing B-cell clones encoding "pathogenic" anti-PF4 IgG. The boosted production of TTS inducing anti-PF4 antibodies (IgG) subsequently triggers thrombosis via activation of platelets and neutrophils. The nature of the individual host response probably determines whether TTS is induced upon exposure to the ChAdOx1-PF4 complex. The anti-PF4 IgG then leads to the downstream activation cascade as it has been shown that IgG from TTS patients is capable of activating platelets and neutrophils and inducing thrombosis via Fc receptor. Hence, VITT may develop in patients with a defined genetic background; the ethnicity component is a key element to be further explored. More research is needed to discover potential genetic risk factors involved in the aetiology of VITT.

Presence of antibodies to platelet factor 4 is the key feature and driver of VITT with an adenovirus vector COVID-19 vaccine. Additional research is needed to discern the various forms of TTS, and to understand to what extent these are related to vaccination. The spike protein present in the COVID-19 vaccines does not appear to be the main driver of the immune response at the start of the prothrombotic cascade as VITT patients experiencing COVID-19 after vaccination do not show a boosted anti-PF4 antibody response nor a relapse of VITT. However, these data do not exclude a potential role of the spike protein in the co-inflammatory response and, in this regard, characterization of (co-)factors contributing to or associated with the pro-inflammatory milieu potentially involved in triggering VITT remains one of the top priority areas requiring further research.

Significant safety articles summary TTS (Epidemiology)

Müllerová et al 2023 presented a prepandemic single background rate for thrombosis with thrombocytopaenia syndrome (TTS), as well as by type of thrombosis/thromboembolism and age group. Prepandemic background TTS rates were generated via secondary data analysis using a cohort design in the International Business Machines Corporation (IBM) Truven

MarketScan (now Merative MarketScan) US health insurance claims database, from 01 January 2019 to 31 December 2019. Two algorithms were applied: thrombocytopaenia occurring±7 days (algorithm 1) or occurring 1 day prior to ≤14 days after the thrombotic/thromboembolic event (algorithm 2). The study population derived from the MarketScan database analysis included approximately 9.8 million adults (aged ≥18 years; mean age 45 years, 52% females). Using this study population, prepandemic background TTS incidence was estimated as 9.8–11.1 per 100 000 person-years. Event rates stratified by sex and age show that the 2019 prepandemic TTS event rates were typically higher in males than in females and increased with age with both algorithms. When considering specific type of thrombotic/thromboembolic events, the most common prepandemic TTS subtypes were deep vein thrombosis (DVT) with thrombocytopaenia (2019 incident event rate (95% CI) using algorithm 1: 6.6 (6.1 to 7.2) per 100K PY) and PE with thrombocytopaenia (3.9 (3.5 to 4.4) per 100K PY). CVST with thrombocytopaenia was very rare (0.2 (0.2 to 0.4) per 100K PY). Published event rates for TTS by specific thrombotic/thromboembolic sites show substantial heterogeneity. Differences between reported event rates demonstrate that estimating background event rates for rare, unprecedented safety events is methodologically challenging. This study presents an estimate of aggregate prepandemic background TTS event rates including by type of thrombosis/thromboembolism and age group. The background event rates are dependent on the precision of capturing underlying TTS events in variable data sources, and the ability of electronic health records or insurance claims databases to reflect the TTS clinical definition.

AstraZeneca Comment on epidemiology article:

Strengths of this study include clearly specified algorithms for defining TTS used in the analysis of the large MarketScan database. This study presents a prepandemic single background rate for thrombosis with thrombocytopaenia syndrome (TTS), as well as by type of thrombosis/ thromboembolism and age group, setting the stage for pandemic background rates. Limitations include the inherent challenges in defining point estimates for a background event rate, such as the limited epidemiological/observational information about the event, the databases available and their types/nature, the observation periods (prepandemic vs contemporary) and event capture. Furthermore, the use of International Classification of Diseases (ICD) codes only and not recorded platelet count to define TTS may lead to decreased diagnostic specificity. In the case of TTS, there remains a need to align the clinical definitions that will permit a unified approach for studying geographical variations in event rates, especially considering the current lack of an agreed system to code the condition. Postmarketing surveillance is based on self-reported data, usually lacking clinical and laboratory details, limiting application of diagnostic algorithms such as those proposed for TTS.

CVST with thrombocytopenia

Of the 2644 thrombosis with thrombocytopenia case reports reviewed cumulatively, the reported venous thrombotic sites included CVST (HLT: Cerebrovascular venous and sinus

thrombosis) in 644 (24%) cases. Of these 644 cases, 414 (64%) were in females, 223 (35%) occurred in males, and in 1% gender was unknown.

In 200 of the 644 (30%) of the CVST with Thrombocytopenia cases were fatal. CVST with thrombocytopenia cases by age group/gender/dose and fatality are provided.

Table 152 Cerebral venous sinus thrombosis with Thrombocytopenia Case Reports by age/gender

Age group	Female N (fatal)	Male N (fatal)	Unknown N (fatal)	Grand Total
Age - 18-29 Yrs	51 (11)	51 (11)	1 (0)	103 (22)
Age - 30-39 Yrs	75 (31)	38 (15)	0 (0)	113 (46)
Age - 40-49 Yrs	108 (34)	40 (10)	0 (0)	148 (44)
Age - 50-59 Yrs	73 (21)	45 (17)	0 (0)	118 (38)
Age - 60-69 Yrs	67 (17)	29 (8)	0 (0)	96 (25)
Age - 70-79 Yrs	16 (9)	5 (2)	0 (0)	21 (11)
Age - 80+ Yrs	2(0)	3(0)	0(0)	5(0)
Age Unknown	22(9)	12(2)	6(3)	40(14)
Grand Total	**413(131)**	**223(65)**	**7(3)**	**644(200)**
Dose 1				
Age - 18-29 Yrs	50(11)	50(11)	1(0)	101(22)
Age - 30-39 Yrs	75(31)	37(15)	0(0)	112(46)
Age - 40-49 Yrs	103(31)	34(10)	0(0)	137(41)
Age - 50-59 Yrs	71(21)	42(15)	0(0)	113(36)
Age - 60-69 Yrs	66(17)	26(8)	0(0)	92(25)
Age - 70-79 Yrs	16(9)	4(1)	0(0)	20(10)
Age - 80+ Yrs	1(0)	3(0)	0(0)	4(0)
Age Unknown	21(9)	10(2)	5(3)	36(14)
Grand Total	**402(128)**	**206(62)**	**6(3)**	**614(193)**
Dose 2				
Age - 18-29 Yrs	0(0)	1(0)	0(0)	1(0)
Age - 30-39 Yrs	0(0)	0(0)	0(0)	0(0)
Age - 40-49 Yrs	4(2)	6(0)	0(0)	10(2)
Age - 50-59 Yrs	2(0)	3(2)	0(0)	5(1)
Age - 60-69 Yrs	1(0)	3(1)	0(0)	4(1)
Age - 70-79 Yrs	0(0)	1(0)	0(0)	1(0)
Age - 80+ Yrs	1(0)	0(0)	0(0)	1(0)
Age Unknown	1(0)	2(0)	0(0)	3(0)
Grand Total	**9(2)**	**16(3)**	**0(0)**	**25(5)**

N Number, Yrs Years.

Reporting rates for CVST with thrombocytopenia

Reporting rates for CVST in combination with thrombocytopenia across age groups based on the data from the UK and EEA by risk window of 21 days and 42 days are provided in Table 153 and Table 154 respectively; reporting rate is also stratified by Dose 1, Dose 2 and Dose 3.

The reporting rate of CVST in combination with thrombocytopenia in the UK was higher across the age groups when compared to the background rate except for reports in vaccinees aged > 65 years (risk window 21 days) and > 50 years (risk window 42 days) with Dose 2.

The reporting rate of CVST in combination with thrombocytopenia in the EEA was higher when compared to the background rate in vaccinees aged < 70 years with all doses. In the EEA the reporting rate of CVST in combination with thrombocytopenia with Dose 2 was higher than the background rate for vaccinees aged < 49 years, however reporting rate in age group > 50 years was less compared to the background rate.

The observed versus expected analyses for TTS (including CVST) and CVST with thrombocytopenia are presented in Table 155. Background rates for TTS were derived from MarketScan (US claims) data, using OHDSI-aligned code lists and definitions for TTS.

Algorithm 2 for TTS uses updated OHDSI-aligned code lists and washout periods (previously patients with thrombosis in the 2 years prior to 2019 were excluded). The results of the observed versus expected analyses suggests that observed cases of CVST with thrombocytopenia are more than expected for all age stratifications.

Table 153 Reporting rate for CVST and thrombocytopenia (UK and EEA data) by risk window of 21 days

UK 21 Days RW								
Age Group	Total Exposed	Cases within Risk Window of 21 days	Confirmed, probable and possible cases within Risk Window of 21 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
All Dose (UK)								
Age - 18-39 Yrs	5227125	45	41	8.61	7.84	0.1	8.51	7.74
Age - 40-49 Yrs	8954709	57	52	6.37	5.81	0.1	6.27	5.71
Age - 50-64 Yrs	17999174	56	52	3.11	2.89	0.2	2.91	2.69
Age - > 65 Yrs	13443624	7	7	0.52	0.52	0.2	0.32	0.32
Age Unknown	3294137	8	6	2.43	1.82		2.43	1.82
Grand Total	48918769	173	158	3.54	3.23	0.1	3.44	3.13
Dose 1 (UK)								
Age - 18-39 Yrs	2663686	45	41	16.89	15.39	0.1	16.79	15.29
Age - 40-49 Yrs	4535864	54	50	11.91	11.02	0.1	11.81	10.92
Age - 50-64 Yrs	9060897	54	51	5.96	5.63	0.2	5.76	5.43
Age - > 65 Yrs	6737698	6	6	0.89	0.89	0.2	0.69	0.69

Table 153 Reporting rate for CVST and thrombocytopenia (UK and EEA data) by risk window of 21 days

UK 21 Days RW								
Age Group	Total Exposed	Cases within Risk Window of 21 days	Confirmed, probable and possible cases within Risk Window of 21 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
Age Unknown	1723525	7	5	4.06	2.9		4.06	2.9
Grand Total	24721670	166	153	6.71	6.19	0.1	6.61	6.09
Dose 2 (UK)								
Age - 18-39 Yrs	2558509	0	0	0	0	0.1	-0.1	-0.1
Age - 40-49 Yrs	4412378	3	2	0.68	0.45	0.1	0.58	0.35
Age - 50-64 Yrs	8921359	2	1	0.22	0.11	0.2	0.02	-0.09
Age - > 65 Yrs	6679268	1	1	0.15	0.15	0.2	-0.05	-0.05
Age Unknown	1566438	1	1	0.64	0.64		0.64	0.64
Grand Total	24137952	7	5	0.29	0.21	0.1	0.19	0.11
All Dose (EEA)								
18-49	11827734	113	67	9.55	5.66	0.07	9.48	5.59
50-59	6495374	24	17	3.69	2.62	0.16	3.53	2.46
60-69	20461213	43	27	2.1	1.32	0.4	1.7	0.92
70-79	8193743	6	3	0.73	0.37	0.47	0.26	-0.1

Table 153 Reporting rate for CVST and thrombocytopenia (UK and EEA data) by risk window of 21 days

UK 21 Days RW								
Age Group	Total Exposed	Cases within Risk Window of 21 days	Confirmed, probable and possible cases within Risk Window of 21 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
80+	1165347	1	0	0.86	0	0	0.86	0
Age Unknown	8441	4	3	473.88	355.41	-	-	-
Grand Total	48151852	191	117	3.97	2.43	-	-	-
Dose 1 (EEA)								
18-49	6434510	110	65	17.1	10.1	0.07	17.03	10.03
50-59	3518799	24	17	6.82	4.83	0.16	6.66	4.67
60-69	10521781	41	27	3.9	2.57	0.4	3.5	2.17
70-79	4176155	6	3	1.44	0.72	0.47	0.97	0.25
80+	596132	1	0	1.68	0	0	1.68	0
Age Unknown	4187	3	3	716.5	716.5	-	-	-
Grand Total	25251564	185	115	7.33	4.55	-	-	-
Dose 2 (EEA)								
18-49	5385769	3	2	0.56	0.37	0.07	0.49	0.3
50-59	2972927	0	0	0	0	0.16	-0.16	-0.16
60-69	9934975	2	0	0.2	0	0.4	-0.2	-0.4
70-79	4014635	0	0	0	0	0.47	-0.47	-0.47
80+	567777	0	0	0	0	0	0	0

Table 153 Reporting rate for CVST and thrombocytopenia (UK and EEA data) by risk window of 21 days

UK 21 Days RW								
Age Group	Total Exposed	Cases within Risk Window of 21 days	Confirmed, probable and possible cases within Risk Window of 21 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
Age Unknown	3931	0	0	0	0	-	-	-
Grand Total	22880014	5	2	0.22	0.09	-	-	-

Background event rates per 1M PY per 21 days from Truven Market Scan-2019.

CVST Cerebral Venous Sinus Thrombosis, EEA European Economic Area, PY Person Years, UK United Kingdom, Yrs Years.

Table 154 Reporting rate for CVST and thrombocytopenia (UK and EEA data) by risk window of 42 days

UK 42 Days RW								
Age Group	Total Exposed	Cases within Risk Window of 42 days	Confirmed, probable and possible cases within Risk Window of 42 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
All Dose (UK)								
Age - 18-39 Yrs	5227125	47	42	8.99	8.04	0.2	8.79	7.84
Age - 40-49 Yrs	8954709	63	57	7.04	6.37	0.2	6.84	6.17
Age - 50-64 Yrs	17999174	62	58	3.44	3.22	0.4	3.04	2.82

Table 154 Reporting rate for CVST and thrombocytopenia (UK and EEA data) by risk window of 42 days

UK 42 Days RW								
Age Group	Total Exposed	Cases within Risk Window of 42 days	Confirmed, probable and possible cases within Risk Window of 42 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
Age - > 65 Yrs	13443624	10	9	0.74	0.67	0.4	0.34	0.27
Age Unknown	3294137	10	8	3.04	2.43	-	-	-
Grand Total	48918769	192	174	3.92	3.56	0.2	3.72	3.36
Dose 1 (UK)								
Age - 18-39 Yrs	2663686	47	42	17.64	15.77	0.2	17.44	15.57
Age - 40-49 Yrs	4535864	60	55	13.23	12.13	0.2	13.03	11.93
Age - 50-64 Yrs	9060897	59	56	6.51	6.18	0.4	6.11	5.78
Age - > 65 Yrs	6737698	9	8	1.34	1.19	0.4	0.94	0.79
Age Unknown	1723525	8	6	4.64	3.48	-	-	-
Grand Total	24721670	183	167	7.4	6.76	0.2	7.2	6.56
Dose 2 (UK)								
Age - 18-39 Yrs	2558509	0	0	0	0	0.2	-0.2	-0.2

Table 154 Reporting rate for CVST and thrombocytopenia (UK and EEA data) by risk window of 42 days

UK 42 Days RW								
Age Group	Total Exposed	Cases within Risk Window of 42 days	Confirmed, probable and possible cases within Risk Window of 42 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
Age - 40-49 Yrs	4412378	3	2	0.68	0.45	0.2	0.48	0.25
Age - 50-64 Yrs	8921359	3	2	0.34	0.22	0.4	-0.06	-0.18
Age - > 65 Yrs	6679268	1	1	0.15	0.15	0.4	-0.25	-0.25
Age Unknown	1566438	2	2	1.28	1.28	-		
Grand Total	24137952	9	7	0.37	0.29	0.2	0.17	0.09
All Dose (EEA)								
18-49	11827734	119	67	10.06	5.66	0.14	9.92	5.52
50-59	6495374	27	17	4.16	2.62	0.32	3.84	2.3
60-69	20461213	47	30	2.3	1.47	0.8	1.5	0.67
70-79	8193743	7	3	0.85	0.37	0.94	-0.09	-0.57
80+	1165347	1	0	0.86	2.57	0	0.86	2.57
Age Unknown	8441	4	3	473.88	0.04	-		
Grand Total	48151852	205	120	4.26	2.49	-		
Dose 1 (EEA)								
18-49	6434510	116	65	18.03	10.1	0.14	17.89	9.96

Table 154 Reporting rate for CVST and thrombocytopenia (UK and EEA data) by risk window of 42 days

UK 42 Days RW								
Age Group	Total Exposed	Cases within Risk Window of 42 days	Confirmed, probable and possible cases within Risk Window of 42 days	Reporting Rate (per million)	Reporting Rate (per million) for Confirmed, probable and possible cases	Background Rate (per million)[a]	Rate relative to Background (per million)	Rate relative to Background (per million) for Confirmed, probable and possible cases
50-59	3518799	27	17	7.67	4.83	0.32	7.35	4.51
60-69	10521781	45	30	4.28	2.85	0.8	3.48	2.05
70-79	4176155	7	3	1.68	0.72	0.94	0.74	-0.22
80+	596132	1	0	1.68	0	0	1.68	0
Age Unknown	4187	3	3	0	0	-	-	-
Grand Total	25251564	199	118	7.88	4.67	-	-	-
Dose 2 (EEA)								
18-49	5385769	3	2	0.56	0.37	0.14	0.42	0.23
50-59	2972927	0	0	0	0	0.32	-0.32	-0.32
60-69	9934975	2	0	0.2	0	0.8	-0.6	-0.8
70-79	4014635	0	0	0	0	0.94	-0.94	-0.94
80+	567777	0	0	0	0	0	0	0
Age Unknown	3931	0	0	0	0	-		
Grand Total	22880014	5	2	0.22	0.09	-		

Background event rates per 1M PY per 42 days from Truven Market Scan-2019.

CVST, Cerebral Venous Sinus Thrombosis; EEA, European Economic Area; PY, Person Years; UK, United Kingdom, Yrs Years.

Table 155 Observed versus Expected Analysis for CVST+TCP

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
CVST-TCP - Overall	14	0.25	466115644	396	44.67	8.87 (8.01 - 9.78)	Observed significantly > expected
CVST-TCP - Overall	21	0.25	466115644	467	67	6.97 (6.35 - 7.63)	Observed significantly > expected
CVST-TCP - Overall	42	0.25	466115644	502	134	3.75 (3.43 - 4.09)	Observed significantly > expected
CVST-TCP - Overall (RW14 + Unk TTO)	14	0.25	466115644	529	44.67	11.84 (10.85 - 12.9)	Observed significantly > expected
CVST-TCP - Overall (RW14 + Unk TTO)	21	0.25	466115644	600	67	8.96 (8.25 - 9.7)	Observed significantly > expected
CVST-TCP - Overall (RW42 + Unk TTO)	42	0.25	466115644	635	134	4.74 (4.38 - 5.12)	Observed significantly > expected
Observed Versus Expected analysis for CVST+TCP by age group (EU/UK/Brazil/Australia)							
CVST-TCP - 18-49	14	0.17	110094983	216	7.17	30.13 (26.24 - 34.42)	Observed significantly > expected
CVST-TCP - 50-59	14	0.39	58336094	62	8.72	7.11 (5.45 - 9.11)	Observed significantly > expected
CVST-TCP - 60-69	14	0.33	57960860	56	7.33	7.64 (5.77 - 9.92)	Observed significantly > expected
CVST+TCP:70+	14	0.24	32376365	12	2.98	4.03 (2.08 - 7.03)	Observed significantly > expected
CVST-TCP - 18-49	21	0.17	110094983	246	10.76	22.86 (20.09 - 25.91)	Observed significantly > expected
CVST-TCP - 50-59	21	0.39	58336094	81	13.08	6.19 (4.92 - 7.7)	Observed significantly > expected

Table 155 Observed versus Expected Analysis for CVST+TCP

Concept	Risk window (days)	Incidence rates (per 100,000)	Exposure	Observed cases	Expected number of cases	O over E ratio (95% CI)	Conclusion
CVST-TCP - 60-69	21	0.33	57960860	69	11	6.27 (4.88 - 7.94)	Observed significantly > expected
CVST+TCP:70+	21	0.24	32376365	17	4.47	3.8 (2.22 - 6.09)	Observed significantly > expected
CVST-TCP - 18-49	42	0.17	110094983	260	21.52	12.08 (10.66 - 13.64)	Observed significantly > expected
CVST-TCP - 50-59	42	0.39	58336094	88	26.16	3.36 (2.7 - 4.14)	Observed significantly > expected
CVST-TCP - 60-69	42	0.33	57960860	78	21.99	3.55 (2.8 - 4.43)	Observed significantly > expected
CVST+TCP:70+	42	0.24	32376365	19	8.94	2.13 (1.28 - 3.32)	Observed significantly > expected

Background event rates per 1M PY per 42 days from Truven Market Scan-2019.

CI, Confidence Interval; CVST, Cerebral Venous Sinus Thrombosis; E, Expected; O, Observed; TCP, Thrombocytopenia

Summary

The analysis of thrombosis in combination with thrombocytopenia following the second dose of VAXZEVRIA showed that the rate of events was extremely low and lower than after administration of the first dose. The majority of the vaccinees who experienced TTS events post Dose 2 were male (59% vs 42%) and were older (Median age was 65.5 years vs. 45 years) compared to first dose recipients. The median time to onset of second dose cases was 14 days compared to12 days for the cases with first dose. Of the 644 CVST cases, 64% were in females, 35% occurred in males, and in 1% gender was unknown.

Overall, the most common events were Cerebral venous sinus thrombosis, Deep vein thrombosis, Pulmonary embolism, and Thrombosis.

Overall, there were more fatal reports for TTO within 14 and 21 days. Seventy-four (74%) percent of the fatal reports occurred with 14 days compare to 64% for all cases and 88% of the fatal report occurred with 21 days compare to 80% for all cases. The highest number of fatal reports occurred due to HLT of Cerebrovascular venous and sinus thrombosis. Cerebral haemorrhage was the most common bleeding event associated with fatal event.

The arterial events were reported highest in the age group of 50-59 and 60-69. The distribution of events in male and female was roughly equal. The mixed or the combined arterial and venous was equally distributed in age group 30-39,40-49,50-59 and 60-69 and the distribution of cases in female and male was roughly equal. The venous events were reported highest in the age group of 40-49, 50-59 and 60 – 69 years. The occurrence in female was higher than in the male.

Overall, there were information on platelet count was available in (67.5%) of case reports, PF-4 antibodies were positive in 26% reports, negative in 21% reports, unknown or pending in 52% case reports, D-dimer levels were reported in 39% of the case reports, however, in many reports the units were not specified. The total number of confirmed cases were (14%), probable cases were (15%), possible cases were (35%), unlikely (0.03%) and criteria not met cases were (35%).

The highest number of cases were reported from EEA (34.5%) while it received 48.15 million doses of the total worldwide doses.

The most common confounding factors in descending order of frequency in all 2644 cases were autoimmune conditions, malignancy, past history of heparin therapy, obesity and concomitant use of contraceptives. The most common confounding factors in the confirmed reports were past history of heparin use and malignancy. The dates and the type of heparin administered were not reported in all cases.

Conclusion

Based on currently available data, no new safety information concerning TTS was identified. The current risk minimisation measures described in the product information are considered adequate.

From the data identified during the reporting period and also taking into account the cumulative experience, no updates to the VAXZEVRIA CDS or RMP are warranted at this time.

Thrombosis in combination with thrombocytopenia/TTS is contained in Section 4.4 (Special warnings and special precautions for use) and 4.8 in the VAXZEVRIA CDS. In addition, VAXZEVRIA is contraindicated (CDS Section 4.3) for use in any persons who have experienced thrombosis in combination with thrombocytopenia with any COVID-19 vaccine. Finally, thrombosis in combination with thrombocytopenia/ TTS is listed as an Important Identified Risk in the Core and EU RMPs for VAXZEVRIA. As such, the topic will continue to be kept under close safety surveillance by AstraZeneca and further actions will be taken as deemed appropriate.

More detailed information regarding this Important identified risk is provided in Section 16.4.1.1.

16.3.3 New information on other potential risks not categorised as important

The AESIs for VAXZEVRIA and associated PTs are listed in Appendix 7.

AESIs listed in Appendix 7 for VAXZEVRIA have been included for an O/E analyses for this PBRER and results are provided in Appendix 8 (O/E Analyses). Following an agreement with the MHRA, the frequency of the O/E analyses have been reduced from biweekly to 6-monthly aligned with PBRER.

16.3.4 New information on other identified risks not categorised as important

No new information relevant to any other identified risks not categorised as important has been identified during the reporting period.

16.3.5 Update on missing information

16.3.5.1 Use of VAXZEVRIA in pregnant and breastfeeding women

16.3.5.1.1 Use of VAXZEVRIA in pregnant women

Review of Cases

Reports of pregnancy were retrieved from the ASTRAZENECA Global Safety Database using VAXZEVRIA and ASTRAZENECA customized 'PSUR pregnancy' Business Objects Report which includes the following search criteria: The field Pregnant is marked as YES or Events

code to one of the Medical Dictionary for Regulatory Activities (MedDRA) (Version 25.1) System Organ Classes (SOCs): Congenital, familial and genetic disorders, Pregnancy, puerperium and perinatal conditions or Events code to the MedDRA High-level Group Term: Foetal and neonatal investigations or Events code to one of the MedDRA High-level Terms: Induced abortion complications, Induced abortions or Events code to one of the MedDRA Preferred Terms (PTs): Aborted pregnancy, Amastia, Amnioscopy, Amnioscopy abnormal, Amnioscopy normal, Ectopic pregnancy termination, External cephalic version, Pregnancy of partner, Pregnancy test positive, Pregnancy test urine positive, Hyperplasia adrenal and Macroorchidism. Cases describing Pregnancy with adverse neonatal outcomes are included below.

Interval Review (29 June 2022 – 28 December 2022)

During the reporting period, 792 case reports were retrieved using the above search strategy. However, 90 case reports were excluded as these cases were non-valid (i e, duplicate cases or invalid cases). The remaining 702 cases were considered for further analysis. Of the 702 case reports, 541 reports included pregnancy/breastfeeding reports with other co-reported AEs and 161 reports without other AEs. Of the 702 case reports of exposure to VAXZEVRIA during or before pregnancy/breastfeeding, 116 reports were from interventional clinical trials, 368 post-marketing studies and 218 were from spontaneous sources. Of the 702 reports, 278 reports were medically confirmed (79 serious and 199 non-serious). Regarding the outcome of the pregnancy cases, of the total 702 case reports, there were 41 cases of spontaneous abortion (SAB), 4 with abnormal maternal outcome, 2 still birth, 11 elective abortion and 3 premature births/infants. Pregnancy outcome was not available for the majority of the cases.

Cumulative Review (through 28 December 2022)

Cumulatively, 6173 case reports were retrieved using the above search criteria. However, 781 case reports were excluded as these cases were non-valid (ie, duplicate cases or invalid cases). The remaining 5392 cases were considered for further analysis. Of the 5392 case reports, 4490 reports included pregnancy/breastfeeding reports with other co-reported AEs and 902 reports without other AEs. Of the 5392 case reports of exposure to VAXZEVRIA during or before pregnancy/breastfeeding, 143 reports were from interventional clinical trials, 1218 post-marketing studies and 4031 spontaneous. Of these 5392 reports, 1198 reports were medically confirmed (342 serious and 856 non-serious respectively).

Spontaneous Abortion – Interval Review

A total of 41 pregnancy cases reported spontaneous abortion, of which 39% (16 out of 41) were consumer reports, 56% (23 out of 41) medically confirmed and with 46.3% of the reports being from the United Kingdom and 24.4% from Brazil. Age was reported in 28 of the 41 case reports; median age was 33 years (range: from 20 to 44 years, ie, 5 reports in women aged

< 25 years, 10 reports in women aged 26 to 35 years and 13 reports were in women aged > 36 years). Gestational age of exposure occurred in the 1st trimester in all cases.

Spontaneous Abortion – Cumulative Review

A total of 454 pregnancy cases reported spontaneous abortion. A total of 87% (395 out of 454) were reports from consumers and 24.2% (110 out of 454) medically confirmed with 62.8% of the reports being from the United Kingdom. Age was reported in 386 of the 454 case reports; median age was 34.5 years (range: from 19 to 46 years; ie, 40 reports in women aged < 25 years, 197 reports in women aged 26 to 35 years and 149 reports were in women aged > 36 years). In 219 of the 454 reports, gestational age of exposure was unknown; in the remaining 235 reports, 100.0% occurred in the 1st trimester. Gestational week at the time spontaneous abortion occurred was unknown.

Observed Vs. Expected Analysis – Spontaneous abortion

The incidence rates for spontaneous abortions were calculated based on the reported rates by Hemminki and Forssas 1999 data on conceptions among women in England and Wales, 2018 from the UK Office of National Statistics (Conceptions in England and Wales 2018) to estimate the rates of spontaneous abortions per 100,000 women years.

Vaccine administration data based on the age and gender is only available from UK and the below analysis was based on case reports from UK. The observed versus expected analysis of spontaneous abortions with DLP 28 December 2022 showed that observed cases occurred significantly less frequently than expected for overall and for different age stratifications from UK. A summary of spontaneous abortion observed versus expected analysis is presented in Table 156.

Conservatively, the exposure for global reports (448306152) is based on doses administered in 13 markets as explained in Appendix 8.

Table 156 Spontaneous Abortion Observed Versus Expected Analysis (UK cases only)

Age group (years)	IR/100,000 PY	Risk Window	Exposure from UK	Observed Cases	Expected Cases	Ratio	Interpretation
18 to 24	1780.8	60	498587	3	1458.57	0 (0 - 0.01)	Observed significantly < expected
25 to 29	1437.5	60	610901	19	1442.61	0.01 (0.01 - 0.02)	Observed significantly < expected

Table 156 Spontaneous Abortion Observed Versus Expected Analysis (UK cases only)

Age group (years)	IR/100,000 PY	Risk Window	Exposure from UK	Observed Cases	Expected Cases	Ratio	Interpretation
30 to 34	1447	60	842004	37	2001.49	0.02 (0.01 - 0.03)	Observed significantly < expected
35 to 39	864.6	60	1050964	45	1492.7	0.03 (0.02 - 0.04)	Observed significantly < expected
40 to 44	223.3	60	2041971	28	749.05	0.04 (0.02 - 0.05)	Observed significantly < expected
18 to 24 plus Unk TTO	1780.8	60	498587	9	1458.57	0.01 (0 - 0.01)	Observed significantly < expected
25 to 29 plus Unk TTO	1437.5	60	610901	25	1442.61	0.02 (0.01 - 0.03)	Observed significantly < expected
30 to 34 plus Unk TTO	1447	60	842004	62	2001.49	0.03 (0.02 - 0.04)	Observed significantly < expected
35 to 39 60 plus Unk TTO	864.6	60	1050964	72	1492.7	0.05 (0.04 - 0.06)	Observed significantly < expected
40 to 44 60 plus Unk TTO	223.3	60	2041971	39	749.05	0.05 (0.04 - 0.07)	Observed significantly < expected
All ages	995.3	60	7418105	150	12128.77	0.01 (0.01 - 0.01)	Observed significantly < expected
All ages plus Unk TTO	995.3	60	7418105	251	12128.77	0.02 (0.02 - 0.02)	Observed significantly < expected

IR, Incidence Rate; PY, Person Years; TTO, Time to onset; UK, United Kingdom; Unk, Unknown.

For the observed versus expected analysis of Gestational diabetes, please see Appendix 8.

Conclusion

From the data identified during the reporting period, and also taking into account the cumulative experience, no causal relationship could be established between **Abortion spontaneous and VAXZEVRIA.** Pregnancy and Abortion spontaneous will continue to be kept under close surveillance by AstraZeneca.

Adverse Maternal Outcomes – Interval and Cumulative Review

Maternal outcomes that are part of the AE of Special Interest concept of "Pregnancy outcome – maternal" (as presented in the Risk Management Plan) are shown in Table 157.

Table 157 Adverse Maternal Outcomes – Interval and Cumulative Period

PT	Event Count (Interval)	Event Count (Cumulative)
Gestational diabetes	**14**	**39**
Pre-eclampsia	8	21
Caesarean section	5	12
Premature labour	4	12
Placenta praevia	1	7
Eclampsia	0	5
Uterine rupture	0	3
Amniotic cavity infection	0	1
Grand Total	32	100

PT Preferred Term.

The most common relevant risk factors reported in the cases included: previous history of gestational diabetes, increased Body Mass Index (BMI), hypertension, tobacco use, substance and alcohol use, multigravida, diabetes, history of spontaneous abortion and stillbirth, Factor V Leiden mutation, previous "high risk pregnancy", history of kidney disease, Fabry's disease, suspected COVID-19, asthma and polycystic ovaries. No safety concern was identified from the review of these reported PTs.

Conclusion

From the data identified and analysed during the reporting period, and also taking into account the cumulative experience, no causal relationship could be established between adverse maternal outcomes and VAXZEVRIA**.** Pregnancy and adverse maternal outcomes will continue to be kept under close surveillance by ASTRAZENECA.

Co-reported Adverse Events in the Pregnancy Cases - Interval Review

Of the 702 pregnancy case reports, 541 cases had co-reported AEs in both mothers and infants. Most of the AEs reported in these cases were known reactogenicity events (i e, headache, pyrexia, fatigue, chills, myalgia, nausea, pain in extremity and arthralgia). There were 112 cases with 327 AEs that occurred in the paediatric population, the top 3 AEs being: foetal exposure during pregnancy (69), maternal exposure during pregnancy (30) and COVID-19 (10). There was no trend or signal observed from these AEs reported from the pregnancy cases.

Other co-reported Adverse Events in the Pregnancy Cases – Cumulative Review

Of the 5392 case reports, 4490 cases had reported AEs in both mothers and infants. Most of the AEs reported in these cases were known reactogenicity events (headache, pyrexia, fatigue, chills, myalgia, nausea, pain in extremity and arthralgia). There were 318 cases with 1002 AEs that occurred in the paediatric population, the top 3 AEs being: exposure via breast milk (138), foetal exposure during pregnancy (118) and pyrexia (6). There was no trend or signal seen from these AEs reported from the pregnancy cases.

Abnormal Neonatal Outcomes – Cumulative and Interval Review

In order to appropriately assess all cases reported to the company with any congenital anomaly or adverse neonatal outcome, a search cumulatively and during the reporting period of this PBRER was done with the following MedDRA (version 25.1) PTs: " Congenital musculoskeletal disorder of limbs; Congenital musculoskeletal disorder of skull; Congenital musculoskeletal disorder of spine; Congenital female genital tract fistula; Oculo-digito-oesophageal-duodenal syndrome; Congenital musculoskeletal disorder of head and neck; Macrophthalmos; Congenital female reproductive tract disorder; Congenital musculoskeletal disorder; Congenital laryngeal malformation; Athelia; Congenital vocal cord paralysis; Congenital subglottic stenosis; Congenital vena cava stenosis; Aphallia; Congenital connective tissue disorder; Congenital musculoskeletal disorder of trunk; Congenital anisocoria; Congenital lip pits; Pleural malformation; Arhinencephaly; Acrocephalosyndactyly; Amniotic band syndrome; Anencephaly; Annular pancreas; Anomalous pulmonary venous connection; Anophthalmos; Anorectal malformation; Anotia; Aorticopulmonary septal defect; Arnold-Chiari malformation; Arteriovenous malformation; Atrial septal defect; Atrioventricular septal defect; Auditory neuropathy spectrum disorder; Brain malformation; Breast malformation; Cardiac septal defect; Cataract congenital; Cerebral arteriovenous malformation haemorrhagic; Cerebral cavernous malformation; Cerebrovascular arteriovenous malformation; Choanal atresia; Cleft lip; Cleft lip and palate; Cleft palate; Cloacal exstrophy; Coarctation of the aorta; Congenital absence of bile ducts; Congenital aortic valve stenosis; Congenital arterial malformation; Congenital cerebral haemangioma; Congenital coronary artery malformation; Congenital cystic kidney disease; Congenital diaphragmatic hernia; Congenital ectopic bladder; Congenital eye disorder; Congenital eyelid malformation; Congenital foot malformation; Congenital genital malformation; Congenital genital malformation female; Congenital genital malformation male; Congenital hand malformation; Congenital hearing disorder; Congenital heart valve disorder; Congenital heart valve incompetence; Congenital hydrocephalus; Congenital hydronephrosis; Congenital intestinal malformation; Congenital jaw malformation; Congenital joint malformation; Congenital large intestinal atresia; Congenital lymphoedema; Congenital megacolon; Congenital mitral valve incompetence; Congenital mitral valve stenosis; Congenital nose malformation; Congenital oesophageal stenosis; Congenital oral

malformation; Congenital pulmonary artery anomaly; Congenital pulmonary valve atresia; Congenital rubella infection; Congenital rubella syndrome; Congenital skin disorder; Congenital small intestinal atresia; Congenital syphilis; Congenital tricuspid valve atresia; Congenital vesicoureteric reflux; Conjoined twins; Constricted ear deformity; Craniorachischisis; Craniosynostosis; Cryptorchism; Cystic lymphangioma; Deaf mutism; Deafness congenital; Death neonatal; Developmental glaucoma; Developmental hip dysplasia; Double outlet right ventricle; Duodenal atresia; Dysmorphism; Ear malformation; Ebstein's anomaly; Encephalocele; Epispadias; Exomphalos; Fallot's tetralogy; Foetal alcohol syndrome; Foetal anticonvulsant syndrome; Foetal distress syndrome; Foetal growth restriction; Foetal malformation; Gastrointestinal arteriovenous malformation; Gastrointestinal malformation; Gastroschisis; Genitalia external ambiguous; Haemangioma congenital; Haemangioma of retina; Haemorrhagic arteriovenous malformation; Hepatic arteriovenous malformation; Heterotaxia; Holoprosencephaly; Hydrops foetalis; Hypoplastic left heart syndrome; Hypoplastic right heart syndrome; Hypospadias; Iniencephaly; Interruption of aortic arch; Intestinal atresia; Kidney malformation; Limb reduction defect; Lissencephaly; Low birth weight baby; Malformation biliary; Malformation venous; Microcephaly; Microencephaly; Microphthalmos; Microtia; Mitral valve atresia; Mitral valve hypoplasia; Multiple gastrointestinal atresias; Neural tube defect; Oesophageal atresia; Parachute mitral valve; Patent ductus arteriosus; Polydactyly; Porencephaly; Premature baby; Pulmonary aplasia; Pulmonary artery atresia; Pulmonary artery stenosis congenital; Pulmonary malformation; Pulmonary valve stenosis congenital; Pyloric stenosis; Rectal atresia; Renal aplasia; Renal arteriovenous malformation; Renal dysplasia; Renal failure neonatal; Renal hypoplasia; Respiratory tract malformation; Retinal arteriovenous malformation; Schizencephaly; Skeletal dysplasia; Skin malformation; Spina bifida; Spina bifida cystica; Spina bifida occulta; Spleen malformation; Stillbirth; Syndactyly; Talipes; Thyroid malformation; Tracheo-oesophageal fistula; Transposition of the great vessels; Truncus arteriosus persistent; Umbilical malformation; Univentricular heart; Urethral valves; Urinary tract malformation; Vertebral Defects, Anal Atresia, Cardiac Defects, Tracheo-Esophageal Fistula, Renal Anomalies, And Limb Abnormalities (VACTERL) syndrome; Vascular malformation; Vein of Galen aneurysmal malformation; Venolymphatic malformation; Ventricular septal defect; Vallecular cyst; Foetal vascular malperfusion; Beaver tail liver; Congenital ectopic spleen; Congenital pulmonary airway malformation; Vertebral artery fenestration; Foetal cardiac function test abnormal".

Cumulatively, 161 cases reporting any PTs (outlined as above) from the concept of pregnancy outcomes - "Neonates" were reported since launch until the DLP of this PBRER. Upon further review, 80 of these cases were acquired conditions and/or presented in elderly age or adults and not congenital malformations and hence not included for further review.

During the reporting period of this PBRER until 28 December 2022, 46 cases were reported among this concept of pregnancy outcomes - "Neonates". Upon further review of 20 cases

(containing 24 neonatal outcome events) reported among neonatal age or case reports linked to a neonate or a pregnancy product, such cases were therefore included in this section. Among these, there were premature baby (11), Low Birth Weight baby (6), pyloric stenosis (1), gastroschisis (1), Developmental Hip Dysplasia (1), cryptorchism (1), congenital syphilis (1), congenital hydronephrosis (1), congenital cystic kidney disease (1).

The above twenty cases were described in use of VAXZEVRIA in pregnant women. Review of these 20 cases with adverse neonatal outcomes received during the reporting period did not highlight any new significant safety concerns. The majority of cases were either confounded or contained limited information to ascribe a causal relationship to VAXZEVRIA. (**Case IDs:** [redacted]

AstraZeneca Comment: Due to confounders for maternal history (including but not limited to the history of Diabetes Mellitus type I, II, obesity, Covid-19, syphilis, smoking cigarettes during pregnancy, recreational drug use, Polycystic Ovary Syndrome) and mother/patient receiving a different Covid-19 vaccine ie, Pfizer Biontech Covid-19 Vaccine (tozinameran) for covid-19 immunisation, and with, limited information for maternal history (including but not limited to the relevant medical, obstetric and family history, concomitant medications work-up and genetic/environmental factors exposure), complete demographics of vaccinee, baseline health condition before vaccination, particular details of the vaccines received, circumstances surrounding the event, outcome of the event, further risk factors (for eg, chromosomal abnormalities, cerebral anoxia, severe maternal malnutrition and chronic conditions, family history of undescended testicles or other problems of genital development and parents' exposure to pesticides) and detailed diagnostic and etiologic workup (for eg, physical examination, neurological, genetics testing, imaging studies such as Ultrasound and X-ray), the evaluation did not find evidence to suggest a causal relationship between all neonatal outcomes and VAXZEVRIA.

Conclusion

From the data identified during the reporting period, and also taking into account the cumulative experience, no causal relationship could be established between these **events reported in neonates and VAXZEVRIA**. **Pregnancy and neonatal outcomes** will continue to be kept under close surveillance by ASTRAZENECA.

Literature review – Pregnancy

A periodic literature search of the databases in Embase, InsightMeme and PubMed was conducted for relevant articles on topic in association with VAXZEVRIA.

The search did not yield any articles that were considered relevant for further evaluation and presentation.

Summary

In summary, the cumulative and periodic reviews up and until 28 December 2022 of all reports of exposure to **VAXZEVRIA during pregnancy** did not identify any new safety concerns for the **mother or baby**. The reported adverse events are similar between the pregnant and non-pregnant populations. The results of the O/E analyses for spontaneous abortion (UK reports) suggest that observed cases are less than would be expected in the unvaccinated pregnant women.

Conclusion

Based on these interval and cumulative reviews of the currently available data, it is ASTRAZENECA's opinion that no updates to product labelling or RMP are warranted. **Use of VAXZEVRIA during pregnancy** remains as **Missing information** for the product and is closely monitored.

16.3.5.1.2 Use of AZD1222 in Breastfeeding women

Breastfeeding cases were retrieved from the ASTRAZENECA customized 'PSUR pregnancy' Report by filtering for breastfeeding related PTs (Exposure via breast milk, Maternal exposure during breast feeding).

Interval Period (29 June 2022 – 28 December 2022)

During the interval period, there were 12 reports pertaining to infant exposure to VAXZEVRIA during breastfeeding. Overall, 4 cases were serious (of which only one was medically confirmed). Within these 12 reports, there were 24 events in infants following breastfeeding. Of these 24 events, 16 were serious adverse events. Events occurring with a frequency of 2 or more in paediatric cases are shown in Table 158. No safety concern was identified.

Table 158 Adverse Events in Infants Following Breastfeeding (with a Frequency of ≥ 2 in Paediatric Cases)

Preferred Term	Non-serious	Serious	Total
Diarrhoea	2	2	4
Fatigue	2	2	4
Decreased appetite	1	1	2

There were no fatal cases reported within the infant lactation cases. Outcomes of these 12 cases were: Recovered (6), Not recovered (3) and Unknown (3).

Of the interval review of reports of VAXZEVRIA exposure during breastfeeding retrieved from the ASTRAZENECA Global Safety Database, there was limited information to suggest any reasonable association between exposure to VAXZEVRIA via breastfeeding and adverse outcomes in the neonates. No safety relevant literature relating to VAXZEVRIA and breastfeeding was identified during the reporting period.

Cumulative Review (29 December 2020 – 28 December 2022)

Cumulatively, there were 193 reports pertaining to infant exposure to VAXZEVRIA during breastfeeding. Overall, 76 cases were serious (of which 4 were medically confirmed). Within these 193 reports, there were 685 events in infants following breastfeeding. Of these 685 events, 319 were serious adverse events. No safety concern was identified.

Adverse Events in Maternal Vaccinees

Interval Period (29 June 2022 – 28 December 2022)

During the interval period, there were 31 reports pertaining to exposure to VAXZEVRIA whist lactating. Overall, 10 cases were serious (of which only four were medically confirmed). Within these 10 reports, there were 75 events in maternal vaccinees. Of these 75 events, 45 were serious adverse events. Events occurring with a frequency of 3 or more are shown in Table 159. No safety concern was identified.

Table 159 Adverse Events in Maternal Vaccinees (with a Frequency of ≥ 3)

Preferred Term	Non-serious	Serious	Total
Fatigue	0	4	4
Pyrexia	1	2	3

There were no fatal cases reported. Outcomes of these 31 cases were: Recovered (8), Not recovered (11), Recovered with sequelae (1) and Unknown (11).

Of the interval review of reports of exposure of maternal vaccinees to VAXZEVRIA retrieved from the ASTRAZENECA Global Safety Database, there was limited information to suggest any reasonable association between exposure to VAXZEVRIA and adverse outcomes in the maternal vaccinees.

Section **4.6 of the** VAXZEVRIA **CDS** includes the following text on breastfeeding:

Anti-SARS-CoV-2 S antibodies are excreted in breast milk of mothers vaccinated with VAXZEVRIA. In animal studies, lactational transfer of anti-SARS-CoV-2 S antibodies from maternal female mice to pups was observed. It is unknown whether the vaccine itself is excreted in human milk.

In animal studies no quantifiable levels of the vaccine were detected in the mammary gland in female mice.

Available non-clinical, clinical and post-marketing data do not suggest a risk to breastfed newborns/infants.

Conclusion

From the data identified during the reporting period, and also taking into account the cumulative experience, there is no new safety information or a safety concern identified with the exposure to VAXZEVRIA during pregnancy or while breast feeding. Use of VAXZEVRIA in pregnant and breastfeeding women/ Use during pregnancy and while breastfeeding will continue to be considered as Missing information for VAXZEVRIA.

Use of VAXZEVRIA in pregnant and breastfeeding women / Use during pregnancy and while breastfeeding will be primarily investigated in the ongoing non-interventional pregnancy Registry Study (**D8110C00003**) of women exposed to VAXZEVRIA immediately before or during pregnancy as part of the C-VIPER Registry Consortium.

More detailed information is provided in Section 16.4.3.1

16.3.5.2 Use of VAXZEVRIA in subjects with severe immunodeficiency

Vaccines may be less effective in severely immunocompromised individuals, as the vaccinees weakened immune system may not mount a sufficient response. Additionally, immunocompromised individuals may also be at a greater risk of morbidity and mortality from vaccine-preventable disease, and consequently this population has been identified as a priority group for initial vaccination in several jurisdictions. Although there is no evidence that the safety profile of VAXZEVRIA in this population will be different than that of the general population, given the paucity of data, the possibility cannot be excluded.

WHO recommends that the primary vaccine series in moderately to severely immunocompromised persons (ICP) should be extended to include an additional dose for all COVID-19 vaccines. On the basis of available evidence, the additional dose in an extended primary series should be given at least 1 month and within 3 months after the primary series in order to increase protection for immunocompromised persons. A homologous additional dose in an extended primary series should currently be considered standard practice, but alternative heterologous platforms for the additional dose may also be considered, taking into account

current vaccine supply, vaccine supply projections, and other access considerations (WHO interim guidance 2021).

Review of Cases

A cumulative search (up to 28 December 2022) of the AstraZeneca Global Safety Database was undertaken for AE reports received for VAXZEVRIA in subjects with medical history of severe immunodeficiency and in immunocompromised patients, using the criteria mentioned in Appendix 12.

Of note, it should be noted the limitations of spontaneous data, as in most of the reports date of diagnosis or medical histories of IC conditions were not provided; therapy dates and duration of concomitant immunosuppressive agents were also not available.

The search of the AstraZeneca Global Safety database identified a cumulative total of 51475 cases from all sources, reported in subjects with severe immunodeficiency and in immunocompromised patients in association with VAXZEVRIA. Most of the reports were from post-marketting sources including 95% (48714) spontaneous cases, 5% (2739) other non-interventional studies.

Of the 51475 cases, 74% (38073) were reported in females, 24% (12214) were in males and gender was not reported in the remaining 2% (1188) of cases. Age was reported in 47902 case reports and in 57 % of the cases, the reported age was ≥ 50 years. Case reports by age and sex are provided in below.

Table 160 Age group and Sex in Immunocompromised groups

Age group/Gender	Female	Male	Gender unknown	Grand Total
Age < 17 Years	48	32	3	83
Age - 18-29 Years	3288	907	78	4273
Age - 30-39 Years	5086	1338	110	6534
Age - 40-49 Years	7695	1910	136	9741
Age - 50-59 Years	8617	2430	181	11228
Age - 60-69 Years	7145	2666	137	9948
Age - 70-79 Years	3214	1815	87	5116
Age - 80+ Years	581	379	19	979
Age Unknown	2399	737	437	3573
Grand Total	**38073**	**12214**	**1188**	**51475**

Case reports by Immunocompromised groups are presented in Table 161

Table 161 Case reports by Category of Immunocompromised groups

IC Category	Number of case reports
Inflammatory or immune mediated disorders	29740
Patients with Malignancy/neoplasm	11370
Primary immunodeficiency	6562
Inflammatory or immune mediated disorders OR Primary immunodeficiency	1384
Inflammatory or immune mediated disorders OR Patients with Malignancy/neoplasm	1013
Patients with Malignancy/neoplasm OR Primary immunodeficiency	578
Solid organ transplant	496
Other HIV/AIDs	222
Patients with Malignancy/neoplasm OR Solid organ transplant	45
Hematopoietic stem cell transplant	28
Hematopoietic stem cell transplant OR Patients with Malignancy/neoplasm	19
inflammatory or immune mediated disorders OR Primary immunodeficiency OR Solid organ transplant	7
inflammatory or immune mediated disorders OR Patients with Malignancy/neoplasm	4
Hematopoietic stem cell transplant OR Inflammatory or immune mediated disorders OR Patients with Malignancy/neoplasm	3
Patients with Malignancy OR neoplasm and Primary immunodeficiency	3
Hematopoietic stem cell transplant OR Inflammatory or immune mediated disorders	1
Grand Total	51475

One case report may have >1 IC category
AIDS Acquired immunodeficiency syndrome; IC Immunocompromised; HIV Human Immunodeficiency Virus

The most frequently reported (>100) events in immunocompromised group are provided in Table 162. There is no unusual trend seen in these events and they are similar to the events observed for VAXZEVRIA in the general vaccinated population.

Table 162 Most frequently reported events (>100) in the IC group

Event (PT)	Non-serious	Serious	Total
Headache	6708	11186	17887
Pyrexia	5423	8439	13857
Fatigue	4191	7644	11833
Chills	3523	6186	9707
Nausea	2493	5225	7718
Myalgia	2753	4098	6849
Arthralgia	2214	3750	5961
Dizziness	1564	3371	4934
Pain in extremity	2047	2809	4852
Pain	1600	2358	3955
Malaise	1592	2119	3711
Influenza like illness	1697	1459	3156
Dyspnoea	844	2043	2883
Vomiting	792	1997	2788
Diarrhoea	782	1486	2268
Tremor	360	1601	1960
Paraesthesia	750	1155	1902
Asthenia	867	981	1846
Hyperhidrosis	460	1376	1836
Rash	734	962	1692
Pruritus	764	897	1661
Migraine	296	1296	1592
Decreased appetite	415	1139	1554
Injection site pain	828	722	1550
Chest pain	335	1129	1462
Influenza	352	1017	1368
Palpitations	317	971	1288
Peripheral swelling	421	836	1256
Back pain	383	861	1242
Cough	435	787	1222
Vaccination site pain	837	327	1164
Lymphadenopathy	366	785	1151
Abdominal pain	388	762	1149
Hypoaesthesia	399	739	1133
Abdominal pain upper	271	856	1127

Table 162 Most frequently reported events (>100) in the IC group

Event (PT)	Non-serious	Serious	Total
Feeling cold	337	687	1024
COVID-19	473	518	991
Oropharyngeal pain	298	681	978
Illness	153	819	972
Lethargy	207	651	858
Erythema	428	409	837
Pulmonary embolism		788	788
Muscle spasms	223	543	765
Contusion	367	385	752
Eye pain	191	542	733
Insomnia	243	480	722
Feeling abnormal	237	466	703
Chest discomfort	219	482	700
Asthma	194	501	694
Neck pain	203	486	689
Limb discomfort	358	327	685
Tinnitus	213	467	680
Vision blurred	188	450	638
Tachycardia	221	402	623
Muscular weakness	172	451	622
Urticaria	296	308	603
Interchange of vaccine products	589	14	603
Somnolence	283	317	600
Feeling hot	262	322	584
Vertigo	221	343	564
Swelling	219	333	552
Heart rate increased	179	349	528
Epistaxis	256	271	527
Confusional state	93	429	522
Musculoskeletal stiffness	180	338	518
Syncope	96	419	515
Deep vein thrombosis		508	508
Thrombocytopenia		480	480

Table 162 Most frequently reported events (>100) in the IC group

Event (PT)	Non-serious	Serious	Total
SARS-CoV-2 antibody test negative	469	8	477
Thrombosis	69	402	471
Ear pain	106	341	447
Hot flush	145	301	446
Off label use	401	24	425
Nasopharyngitis	161	251	411
Body temperature increased	261	147	408
Dizziness postural	74	332	406
Heavy menstrual bleeding	153	250	403
Hypersensitivity	143	259	401
Tenderness	188	210	398
Hypertension	136	261	396
Abdominal discomfort	122	258	380
Dysgeusia	156	215	371
Rash erythematous	171	197	368
Bone pain	146	222	368
Night sweats	77	283	360
Herpes zoster	135	223	358
Rhinorrhoea	133	222	355
Neuralgia	84	259	342
Rash pruritic	150	182	332
Cold sweat	68	255	323
Photophobia	82	228	310
Tension headache	73	225	298
Anxiety	82	211	293
Wheezing	75	214	289
Peripheral coldness	87	197	284
Joint swelling	82	197	279
Injection site mass	85	192	277
Balance disorder	78	199	277
Menstruation delayed	154	118	272
Psoriasis	128	143	271

Table 162 Most frequently reported events (>100) in the IC group

Event (PT)	Non-serious	Serious	Total
Thirst	78	187	265
Swelling face	81	176	257
Burning sensation	103	154	257
Cerebrovascular accident		256	256
Vaccination site erythema	174	80	254
Injection site erythema	165	89	254
Condition aggravated	99	155	253
Rheumatoid arthritis	56	191	247
Vaccination site swelling	186	59	245
Inflammation	80	164	244
Menstruation irregular	116	127	243
Visual impairment	86	155	241
Arthritis	61	179	240
Ageusia	95	144	239
Haemorrhage	66	172	238
Seizure		237	237
Dry mouth	71	165	236
Disturbance in attention	86	144	230
Loss of consciousness	35	194	229
Head discomfort	81	141	222
Muscle fatigue	40	178	218
Blood pressure increased	83	129	212
Injection site swelling	155	54	209
Maternal exposure during breast feeding	68	140	208
Pain of skin	61	145	206
Feeling of body temperature change	68	138	206
Gait disturbance	73	131	204
Menstrual disorder	111	90	201
Application site pain	186	13	199
Vaccination failure	22	173	195
Paraesthesia oral	81	114	195
Anaphylactic reaction		194	194

Table 162 Most frequently reported events (>100) in the IC group

Event (PT)	Non-serious	Serious	Total
Renal pain	42	148	190
Hallucination	29	156	185
Petechiae	83	98	180
Immunisation reaction	156	23	179
Hypotension	50	128	178
Body temperature	36	141	177
Lip swelling	57	118	175
Heart rate	26	141	167
Dehydration	30	137	167
Injection site reaction	82	84	166
Dyspepsia	45	121	166
Vaginal haemorrhage	66	99	165
Drug ineffective	61	103	163
Rash macular	83	79	162
Haematoma	102	59	161
Pneumonia	12	141	153
Presyncope	51	102	153
Discomfort	84	69	153
Sinus headache	32	118	150
Immune thrombocytopenia		150	150
Axillary pain	44	106	150
Maternal exposure during pregnancy	78	71	149
Disorientation	23	126	149
Flushing	42	106	148
Nervousness	29	117	146
Injection site inflammation	138	7	145
Guillain-Barre syndrome		143	143
Hypoaesthesia oral	62	80	142
Abdominal distension	46	96	142
Poor quality sleep	37	103	140
Nasal congestion	51	89	140
Swollen tongue	45	93	138

Table 162 Most frequently reported events (>100) in the IC group

Event (PT)	Non-serious	Serious	Total
Sinus pain	21	117	138
Platelet count decreased	33	105	138
Blister	54	84	138
Sleep disorder	57	79	136
Oedema peripheral	65	71	135
Dysmenorrhoea	41	93	134
Taste disorder	61	71	132
Eye swelling	35	98	132
Cluster headache	33	99	132
Depressed mood	29	103	132
Constipation	38	93	131
Injection site warmth	71	59	130
Death		130	130
Colitis ulcerative	27	103	130
Skin burning sensation	41	88	129
Oral herpes	48	81	129
Lymph node pain	35	93	128
Muscle twitching	61	67	128
Depression	24	104	128
Restlessness	41	86	127
Pain in jaw	26	101	127
Sweating fever	15	111	126
Mouth ulceration	45	80	125
Memory impairment	39	85	124
Anosmia	62	61	123
Eczema	48	74	122
Transient ischaemic attack		121	121
Inappropriate schedule of product administration	89	32	121
Atrial fibrillation	14	106	120
Infection	29	90	119
Weight decreased	38	78	116
Joint stiffness	35	81	116
Breast pain	50	66	116

Table 162 Most frequently reported events (>100) in the IC group

Event (PT)	Non-serious	Serious	Total
Vaccination site reaction	103	12	115
Sinusitis	30	85	115
Skin warm	48	67	115
Pallor	34	81	115
Musculoskeletal chest pain	31	83	114
Dysarthria	6	108	114
Vaccination site mass	47	66	113
Pharyngeal swelling	34	78	112
Rash papular	49	62	111
Lower respiratory tract infection	21	90	111
Fall	24	86	110
Cellulitis	22	87	109
Amnesia	21	88	109
Sneezing	43	64	107
Mental fatigue	9	97	106
Alopecia	39	66	105
Myocardial infarction		104	104
Dry skin	39	65	104
Sensitive skin	27	74	101
Injection site pruritus	57	44	101
Vaccination site warmth	53	47	100
Crohn's disease	19	81	100

IC Immunocompromised; PT Preferred term

Outcome of all events is provided below.

- Died 610
- Not recovered 22990
- Recovered 25412
- Recovered with sequelae 2253
- Recovering 18302
- Unknown 16144

Cumulatively there were 610 deaths out of 51475 case reports. Out of the 610 reports with fatal outcome, age of vaccinee was reported in 579 reports and in 525 (90.7%) of the reports the vaccinee age was ≥ 50 years (median age 70 years). Most frequently (≥ 10) reported events (PTs) with fatal outcome were: Death: 129; Pulmonary embolism: 58; Dyspnoea: 37; COVID-19: 35; Myocardial infarction: 27; Cardiac arrest: 27; Vaccination failure: 25; Cerebral haemorrhage: 24; Sudden death: 22; COVID-19 pneumonia: 22; Cerebrovascular accident: 22; Thrombocytopenia: 22; Pyrexia: 20; Malaise: 20; Pneumonia: 19; Multiple organ dysfunction syndrome: 17; Headache: 16; Thrombosis: 15; Vomiting: 14; Fatigue: 13; Cerebral venous sinus thrombosis: 12; Cardio-respiratory arrest: 12; Acute myocardial infarction: 11; Nausea: 11; Deep vein thrombosis: 11; Adverse event following immunisation: 10; Immune thrombocytopenia: 10; and Sepsis: 10.

Review of AESI and COVID-19 Events in IC group

A total of 7396 cases reported AESIs (see appendix 07 for list of AESIs).Most frequently reported AESI was Embolic and thrombotic events (Thrombosis) (2137 events), Anaphylaxis (2049 events), Immune-mediated neurological conditions (857 events) and Thrombocytopenia including immune thrombocytopenia (704 events). COVID-19 events (from COVID-19 SMQ) were reported in 1167 case reports and outcome of in 65 (5.6%) out of 1167 case reports were fatal.

No signals or safety concerns were identified based on the review of events reports in this population.

Review of Literature

A search of Embase and InsightMeme was conducted to identify literature articles on "Immune and associated conditions" disease' following the use of VAXZEVRIA, cumulatively through 28 December 2022, using the following search terms.

'vaxzevria'/exp OR vazevria OR 'azd1222'/exp OR azd1222 OR 'chadox 1 ncov 19'/exp OR 'chadox 1 ncov 19' ('immunocomprom*' :ti,ab OR 'immune deficiency':ti,ab OR 'immunosup*': ti,ab OR 'immunodef*': ti,ab OR 'oncolog*': ti,ab OR 'cancer':ti,ab OR 'tumor':ti,ab OR 'autoimmun*': ti,ab OR 'chemotherapy' :ti,ab OR 'transplant*' :ti,ab OR 'corticosteroid*' :ti,ab OR 'lupus':ti,ab OR 'rheumatic disease' :ti,ab OR 'rheumatoid*' :ti,ab OR 'steroid*' :ti,ab OR 'digeorge syndrome':ti,ab OR 'wiskott-aldrich syndrome':ti,ab OR 'agammaglobulinemia' :ti,ab OR 'weak* immune system' ti,ab OR 'alps' ti,ab OR 'chronic granulomatous disease':ti,ab OR 'congenital neutropenia':ti,ab OR 'hiv' :ti,ab OR 'aids' ti,ab) AND (coronavirus disease 2019'/exp OR 'severe acute respiratory syndrome'/exp OR 'sars*:ti,ab OR 'covid*' :ti,ab OR 'corona*': ti,ab OR 'ncov*' :ti,ab) AND (vaccinee':ti,ab OR 'vaccinat*' :ti,ab OR (vaccine:ti,ab AND (inoculat*: ti,ab OR inject* ti,ab)) OR 'immunization': ti,ab)

The following literature articles were found to be relevant to the topic and have been presented in tables below.

Table 163 Evidence of reduced COVID-19 vaccine effectiveness in immunocompromised persons

Study	Group	Country	Design	Vaccine(s)	Start date	End date	Outcome	VE in ICPs (95%	VE in non-ICPs	VE overall (95% CI)
Whitaker H et al 2021.	IC/IS	United Kingdom	Cohort	BNT162b2	07 December 2020	13 June 2021	Symptomatic disease	73 (34–89)	n.r.	93 (86–97)
				ChAdOx-1 S				75 (19–92)	n.r.	78 (70–84)

CI, confidence interval; IC/IS, immunocompromised/immunosuppressed; ICP, immunocompromised person; n.r., not reported; VE, vaccine effectiveness.

Table 164 Evidence of reduced immunogenicity of vectored and inactivated WHO Emergency Use Listing (EUL) COVID-19 vaccines in immunocompromised persons

Study	Group	Country	Design	Vaccine(s)	Time of sampling after primary series (weeks)	Definition of response	Assay	Response rate after primary series, % (N)		GMC (95% CI) [N] or median concentration (IQR) (marked as *) [N] after primary series	
								ICPs	Non-ICPs	ICPs	Non-ICPs
Prendecki M et al 2021.	SOT	United Kingdom	OBS	ChAdOx-1 S	4	S-IgG ≥7.1 BAU/ml	Abbott	44% (358)	100% (8)	ICPs	88* (47–395) [8]
Clarke CL et al 2021	DIAL	United Kingdom	OBS	ChAdOx-1 S	6	S-IgG ≥7.1 BAU/ml	Abbott	83% (272)	100% (8)	7.1* (7.1–39) [358]	88* (47–395) [8]
Shenoy P et al 2021	IC/IS	India	OBS	ChAdOx-1 S	4	Detectable S1-IgG	Roche	95% (120)	100% (30)	79* (20–213) [272]	278* (205–603.1) [30]
Whitaker H et al 2021	IC/IS	United Kingdom	OBS	ChAdOx-1 S	>1	Detectable S-Ig	Roche	97% (39)	99% (493)	238* (70.5–825.5) [93]	1778* (552–3,189) [493]
Madhi SA et al 2021	HIV	South Africa	RT	ChAdOx-1 S	2	S-IgG ≥32 BAU/ml	Luminex	94% (32)	96% (23)	832* (85.6–>2,500) [39]	504.9 (337.1–

BAU, binding antibody units; CI, confidence interval; DIAL, dialysis; IC/IS, immunocompromised/immunosuppressed; GMC Geometric Mean Concentration; ICP, immunocompromised person; IQR, interquartile range; n.r., not reported; OBS, observational study; RBD, receptor binding domain; RT, randomised trial; S, spike; SOT, solid organ transplant.

Table 165 Evidence on the immunogenicity of an additional COVID-19 vaccine dose in immunocompromised persons

Study	Group	Country	Design	Vaccine(s)	Interval, primary series to additional dose (months)	Time of sampling after additional dose (weeks)	Definition of response	Assay	Overall response rate after primary series, % (N)	Response rate after additional dose, % (N)	
										Overall	Subset with low/absent response after primary series
Schrezenmeier E et al 2021	SOT	Germany	OBS	BNT162b2	4	3	S1-IgG S/Co ≥1.1	Euro-immun	n.r.	n.r.	28% (14)
				ChAdOx-1 S	3				n.r.	n.r.	45% (11)
Bonelli M et al 2021.	IC/IS	Austria	RT	BNT162b2/ mRNA-1273	≥1	4	RBD-IgG ≥0.8 BAU/ml	Roche	n.r.	n.r.	32% (28)
				ChAdOx-1 S					n.r.	n.r.	22% (27)

BAU, binding antibody units; IC/IS, immunocompromised/immunosuppressed; n.r., not reported; OBS, observational study; RBD, receptor binding domain; RT, randomised trial; S, spike; S/Co, signal-to-cut-off ratio; SOT, solid organ transplant.

Table 166 Neutralizing antibody response after a third SARS-CoV-2 vaccine dose

Study	Group	Country	Design	Vaccine(s)	All patients (N = 49)	Seropositive after third dose (N = 35)	Seronegative after third dose (N = 14)	p Value
Benning et al 2022	SOT (solid organ transplant)	Germany	Observational cohort study	3 × mRNA	40 (82)	28 (80)	12 (86)	>.99
				ChAdOx1 + 2 × mRNA	7 (14)	6 (17)	1 (7)	0.66
				2 × ChAdOx1 + mRNA	2 (4)	1 (3)	1 (7)	0.49

SARS Severe Acute Respiratory Syndrome; C0V2 Corona virus 2; mRNA messenger ribonucleic acid, N number

Table 167 Risk-adjusted vaccine effectiveness (VE) in solid organ transplant (SOT) recipients following SARS-CoV-2 vaccines organ transplant (SOT)

Study	Group	Country	Design	Vaccine(s)	Unvaccinated		Two vaccine doses		Risk-adjusted incidence rate ratio (95% CI)	P Value	Vaccine efficacy (95% CI)
					Cases	Incidence rate per 100000 person-days	Cases	Incidence rate per 100000 person-days			
Callagen et al 2022	SOT (solid organ transplant)	England	Retrospective observational study	All	85	34.4	1283	39.2	1.29 (1.03-1.61)	0.02	–29% (–61 to –3)
				ChAdOx-1 S			793	41.9	1.37 (1.10-1.72)	0.006	–37% (–72 to –10)
				mRNA			490	35.5	1.18 (0.93-1.48)	0.17	–18% (–48 to 7)

CI Confidence Interval; SOT Solid Organ Test

The review and analysis of the available literature did not highlight any particular safety concerns with VAXZEVRIA when used in immunocompromised patients (ICPs). The safety data in ICPs have generally been consistent with those observed for the Non-ICPs. There were no articles identified with a specific reference to any new safety concerns associated with VAXZEVRIA. However a reduced response to the primary vaccination series in ICPs compared with non-ICPs has been reported from above studies, based on immunogenicity and VE data for VAXZEVRIA. Overall, based on the current data suggests that an additional dose increases the immune response rate of the primary vaccination series in ICPs. In several jurisdictions, ICPs have been prioritised for additional doses after the standard primary vaccination series.

Summary

Of the 51475 cases cumulatively of subjects with severe immunodeficiency and in immunocompromised patient's reported globally and included in AstraZeneca's post-marketing database. Cases were assessed by age, sex, type of event, and outcome.

Cumulatively 610 cases had a fatal outcome. COVID-19 and related events were reported in (1210 cases) 2.35% of the patients.

The review and analysis of the available literature did not highlight any particular safety concerns with VAXZEVRIA when used in immunocompromised patients. There were no articles identified with a specific reference to any new safety concerns associated with VAXZEVRIA. However a reduced response to the primary vaccination series in ICPs compared with non-ICPs has been reported from above studies, based on immunogenicity and VE data for VAXZEVRIA. Overall, based on the current data suggests that an additional dose increases the immune response rate of the primary vaccination series in ICPs. In several jurisdictions, ICPs have been prioritised for additional doses after the standard primary vaccination series.

In summary, the review of available data from spontaneous reports regarding subjects with severe immunodeficiency and in immunocompromised patient's did not identify an index case or other evidence of a new or emerging signal.

Conclusion

This cumulative review of the Use of VAXZEVRIA in subjects with severe immunodeficiency/Use in immunocompromised patients did not indicate any new safety concerns. Overall, the review of the currently available data did not reveal any new safety information in immune-compromised individuals that has not been identified in the overall population.

Use of VAXZEVRIA in subjects with severe immunodeficiency/Use in immunocompromised patients will be monitored in the Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU]) and systematic literature review (D8111R00020). Refer to Appendix 4 for additional details.

AstraZeneca will continue to monitor safety information in vaccinees with severe immunodeficiency and in immunocompromised patients as part of the routine safety surveillance activities for VAXZEVRIA and take further actions as deemed appropriate.

Additional information regarding the Use of VAXZEVRIA in immuno-compromised individuals is provided in Section 16.4.3.2.

16.3.5.3 Use of AZD1222 in subjects with severe and / or uncontrolled underlying disease / Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorder)

Subjects with severe and/or uncontrolled underlying diseases are potentially at risk of developing a more severe manifestation of COVID-19 and, as a consequence, have been included as a priority group for initial vaccination in several jurisdictions. Although there is no evidence that the safety profile of VAXZEVRIA in this population will be different to that of the general population, given the paucity of data, the possibility cannot be excluded.

Indicators of frailty used in the review of cases were defined in the protocol for the VAXZEVRIA PASS: A post-authorisation/post-marketing observational study to evaluate the association between exposure to VAXZEVRIA and safety concerns using existing secondary health data sources. This protocol was approved by EMA on 27 January 2022, as no follow-up questionnaires are sent for this missing information concept, no scale of frailty was used for the assessment of the spontaneous cases. Rather, a case narrative text search of VAXZEVRIA reports in the AstraZeneca global safety database using the parameters for each indicator of frailty in Table 168 was used to identify cases for review in the sub-sections below:

Table 168 Indicators of Frailty

Frailty Indicator	Search Parameter
Frailty	"Frailty" "Bedridden"
Dispensing of or reimbursement for durable medical equipment (eg, wheelchairs, home oxygen)	"oxygen" "O2" "scooter" "walker" "wheelchair" "wheel-chair"

Table 168 Indicators of Frailty

Frailty Indicator	Search Parameter
Residence in long-term facility or nursing home	"long term" "nursing home" "skilled care" "skilled-care"
Hip fracture	"hip fracture" "fractured hip" "broken hip" "hip broken"
Palliative care	"palliative" "hospice" "palliate"
Metastatic cancer	"metastatic" "metastasis" "metastases" "metastasise" "cancer spreading" "cancer spread"
Cachexia	"cachexia" "wasting" "waste"
Dementia	"dementia" "Alzheimer" "memory" "cognitive" "cognition"
Pressure ulcers	"ulcer"
Bladder incontinence	"bladder" "urine" "leak"

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database through 28 December 2022 was undertaken to review AEs reported after vaccination with VAXZEVRIA in individuals identified as having severe and/or uncontrolled underlying disease or were identified as frail. All the categories are described below:

16.3.5.3.1 Frailty

Reporting Period (29 June 2022 – 28 December 2022)

The search identified a total of 38 cases (86.8% spontaneous cases, 7.9% noninterventional/post-marketing cases, and 5.3% literature) for the topic use of VAXZEVRIA in individuals with frailty_frail.

Of the 38 cases, 23 (60.5%) were reported in females, 14 (36.8%) in males and gender was not reported in the remaining 1 (2.6%) case. Age ranged from 18 years to <65 years in 63.2% (24), and 28.9% (11) in 65^{+} years. In 7.9% (3) cases the age was reported as unknown. Of the 38 reports, 36.8% (14) were medically confirmed, with remaining 63.2% (24) being consumer reports.

Of these 38 cases, 27 (71.1%) were serious, reported seriousness criteria were medically important (18), disability (12), hospitalization (11), life threatening (3), and death (2). Cases may have met more than one criteria for seriousness. The remaining 11 (28.9%) reports were non-serious.

The top 20 reported events were Fatigue (17), Pyrexia (17), Bedridden (16), Headache (15), Dyspnoea (10), Malaise (10), Myalgia (10), Nausea (9), Pain (7), Asthenia (7), Dizziness (6), Musculoskeletal stiffness (5), Arthralgia (5), Chills (5), Diarrhoea (5), Heart rate increased (5), Hyperhidrosis (5), Pain in extremity (5), Palpitations (5), and Disturbance in attention (5).

Of the 38 cases, there were 2 (5.3%) cases with fatal outcome reported during this period. The assessment of these 2 fatal case reports are presented below:

Case ID [redacted]: This medically confirmed case concerns a 91-year-old female patient. The patient's medical history included non-insulin dependent diabetes mellitus, essential (primary) hypertension unspecified and other and unspecified seizures. Concomitant medication included B complex, gabapentin, fenobarbital, acetylsalicylic acid, captopril, simvastatin and metformin. On 30 June 2021, the patient received an unknown dose of Covishield vaccine. On 31 January 2021, the patient experienced fever, asthenia, general malaise, appetite absent and melaena, and died on 13 February 2021. The cause of death included fever, appetite absent, melaena and malnutrition protein-calorie. It was not known whether an autopsy was performed. The outcome of all the events was reported as fatal.

AstraZeneca Comment: Fatal events of Pneumonia, Severe acute respiratory syndrome, Bradycardia, Hypotension. Melaena, Malnutrition, Faeces discoloured and Mucous stools are not listed in the company core data sheet of AZD1222. Pyrexia, Decreased appetite, Asthenia, Malaise and Diarrhoea are listed in the company core data sheet of AZD1222. However, since the events are reported with fatal outcome, they are considered unlisted. Advanced age of the vaccine and medical history of non-insulin dependent diabetes mellitus, essential (primary) hypertension unspecified, unspecified seizures and stroke could be considered as contributory factors to the events. The case is further confounded by polypharmacy. Due to limited information on baseline health condition of the vaccinee, other risk factors, circumstances

surrounding the events, detailed etiological and diagnostic workup, the evaluation did not find evidence to suggest a causal relationship between the events and AZD1222.

Case ID [redacted] This consumer report concerns a 44-year old female, with a medical history of nicotine dependence, and tobacco user. Concomitant medications were not reported. On 27 April 2021, the user received first dose of VAXZEVRIA. On an unknown date, the user experienced erythematous lesions on the skin and back of the hands. On 23 July 2021, the user received second dose of VAXZEVRIA. On an unknown date, the user experienced dermatomyositis. On 27 November 2021, the user experienced discomfort in the throat region, and died on the same day. It was not known whether an autopsy was performed. The cause of death was dermatomyositis.

AstraZeneca Comment: Fatal event of Dermatomyositis is not listed in the company core data sheet of AZD1222. Cause of death was further specified as DERMATOMYOSITIS. Case further confounded by polypharmacy. Due to limited information on baseline health condition prior to vaccine administration, concurrent conditions, detailed etiological and diagnostic workup, autopsy report if available, the evaluation did not find evidence to suggest a causal relationship between the event and AZD1222.

Cumulative Review (29 December 2020 – 28 December 2022)

The search of the AstraZeneca global safety database identified a cumulative total of 1509 cases (98.7% spontaneous cases, 0.9% non-interventional/post-marketing cases, and 0.4% literature) for the topic use of VAXZEVRIA in individuals with frailty_frail.

Of the 1509 cases, 1146 (75.9%) were reported in females, 311 (20.6%) in males and gender was not reported in the remaining 52 (3.4%) of cases. Age ranged from 18 years to <65 years in 64.0% (966), 65+ years in 22.5% (340), 0 to <18 years in 0.1% (1), in adult 0.3% (5), and in elderly 0.5% (8). In 12.5% (189) cases the age was reported as unknown. Of the 1509 reports, 16.7% (252) were medically confirmed, with remaining 83.3% (1257) being consumer reports.

Of these 1509 cases, 1069 (70.8%) were serious, reported seriousness criteria were medically important (779), disability (301), hospitalization (156), life threatening (59), and death (140). Cases may have met more than one criteria for seriousness. The remaining 440 (29.2%) reports were non serious.

The top 20 reported PTs were Pyrexia (765), Headache (754), Bedridden (682), Fatigue (652), Chills (484), Nausea (451), Myalgia (351), Dizziness (346), Pain (307), Malaise (302), Arthralgia (284), Asthenia (230), Pain in extremity (221), Vomiting (212), Dyspnoea (176), Decreased appetite (165), Hyperhidrosis (147), Diarrhoea (121), Influenza like illness (120), and Tremor (114).

Outcome was reported as fatal for 140 (9.3%) cases, of which 2 were reported during the interval period, as described in the previous section.

16.3.5.3.2 Hip Fracture

Search Strategy

A cumulative and periodic search of the global safety database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited reporting and literature) for the topic use of VAXZEVRIA in individuals with Hip fracture.

Reporting Period (29 June 2022 – 28 December 2022)

The search identified 6 case reports in frail vaccinees with hip fracture who received VAXZEVRIA, and all cases were spontaneously reported. Of the 6 cases, 83.3% (5) of were reported in females and 16.7% (1) were in males. Age ranged from 18 years to <65 years in 50% of the reports and 65+ years in 50%. Of these 6 reports 3 were not medically confirmed and 3 were medically confirmed.

Of these 6 cases, 4 (66.7%) were serious, reported seriousness criteria were medically important (3), hospitalization (1), and death (1). Cases may have met more than one criteria for seriousness. The remaining 2 (33.3%) reports were non-serious.

There was one fatal case (16.7%) reported in individuals with hip fracture during the interval. Age of the 1 vaccinee was 67 years. The reported PTs in 1 case with a fatal outcome were Pyrexia and Acute myocardial infarction.

The reported PTs were singularly reported [Arthralgia (1), Cardiovascular disorder (1), Decreased appetite (1), Heavy menstrual bleeding (1), Osteoporosis (1) and Pyrexia (1)].

Cumulative Review (29 December 2020 – 28 December 2022)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 30 spontaneous cases for the topic use of VAXZEVRIA in individuals with hip fracture.

Of the 30 cases, 70% (21 cases) were reported in females and 30% (9 cases) were in males. Age ranged from 18 years to <65 years in 33.3%, 65+years in 60.0% and gender was missing in 6.7% of the reports.

The majority of reports (70%) were from consumers with the remaining 30% being medically confirmed. Of these 30 cases, 23 (76.7%) were serious, reported seriousness criteria were medically important (17), disability (5), hospitalization (8), life threatening (2), and death (5). Cases may have met more than one criteria for seriousness. The remaining 7 (23.3%) reports were non serious.

The top 20 reported PTs were Deep vein thrombosis (3), Pulmonary embolism (3), Pyrexia (2), Abdominal pain upper (1), Arthralgia (1), Balance disorder (1), Cardiovascular disorder (1), Cerebrovascular accident (1), Contusion (1), Death (1), Decreased appetite (1), Disturbance in attention (1), Epilepsy (1), Epistaxis (1), Fall (1), Femur fracture (1), Hallucination (1), Headache (1), Heavy menstrual bleeding (1) and Hip fracture (1). The most common PTs of Deep vein thrombosis (3), Pulmonary embolism (3) can be also attributed to the complications of hip fracture.

There were 5 fatal cases reported cumulatively in individuals with hip fracture.

16.3.5.3.3 Cachexia

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited reporting and literature) for the topic use of VAXZEVRIA in cachexic individuals.

Reporting Period (29 June 2022 – 28 December 2022)

The search identified a total of 19 cases (89.5% spontaneous cases, and 10.5% literature) for the topic use of VAXZEVRIA in cachexic individuals.

Of the 19 cases, 11 (57.9%) were reported in males, and 8 (42.1%) in females. Age ranged from 18 years to <65 years in 57.9% (11), 31.6% (6) in 65^{+} years, and 5.3% (1) in adult age group. In 5.3% (1) case the age was reported as unknown. Of the 19 reports, 31.6% (6) were medically confirmed, with remaining 68.4% (13) being consumer reports.

Of these 19 cases, 13 (68.4%) were serious, reported seriousness criteria were medically important (9), hospitalization (7), disability (3), and life threatening (2). Cases may have met more than one criteria for seriousness. The remaining 6 (31.6%) reports were non-serious.

The top 20 reported events were Muscle atrophy (8), Myalgia (7), Fatigue (6), Pain in extremity (6), Dizziness (5), Headache (5), Hypoaesthesia (5), Asthenia (4), Nausea (4), Paraesthesia (4), Arthralgia (3), Dyspnoea (3), Muscular weakness (3), Weight decreased (3), Back pain (2), Blood creatine phosphokinase increased (2), Cachexia (2), Chills (2), COVID-19 (2), and Erythema (2).

There were no fatal cases reported.

Cumulative Review (29 December 2020 – 28 December 2022)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 221 cases (99.1% spontaneous cases, and 0.9% literature) for the topic use of VAXZEVRIA in cachexic individuals.

Of the 221 cases, 124 (56.1%) were reported in females, 92 (41.6%) in males and gender was not reported in the remaining 5 (2.3%) of cases. Age ranged from 18 years to <65 years in 71.5% (158), 65^{+} years in 19.5% (43), and in adult 0.9% (2). In 8.1% (18) cases the age was reported as unknown. Of the 221 reports, 22.2% (49) were medically confirmed, with remaining 77.8% (172) being consumer reports.

Of these 221 cases, 161 (72.9%) were serious, reported seriousness criteria were medically important (93), hospitalization (59), disability (37), life threatening (16), and death (11). Cases may have met more than one criteria for seriousness. The remaining 60 (27.1%) reports were non serious.

The top 20 reported events were Headache (68), Fatigue (54), Pyrexia (45), Muscle atrophy (41), Dizziness (37), Myalgia (37), Muscular weakness (34), Chills (30), Pain in extremity (25), Nausea (24), Pain (24), Arthralgia (22), Asthenia (21), Malaise (21), Hypoaesthesia (18), Dyspnoea (17), Influenza like illness (17), Paraesthesia (17), Vomiting (16), and Diarrhoea (15).

There were 11 (5.0%) fatal cases reported cumulatively in individuals with cachexia.

16.3.5.3.4 Bladder Incontinence

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited and literature) for the topic use of VAXZEVRIA in individuals with underlying Bladder incontinence.

Reporting Period (29 June 2022 – 28 December 2022)

The search identified a total of 908 case reports in individuals with underlying bladder incontinence who received COVID-19 VACCINE ASTRAZENECA (90.4% spontaneous cases, 6.9% literature, 1.7% non-interventional/post-marketing, and 1 % each from the study (ChAdOx1-nCoV-19_ZA_phI/II, COV002, COV003, D8110C00001 and D8111C00013.

Of the 908 cases, 85.8% (779) were reported in females, 13.8% (125) in males and gender was not reported in the remaining 0.4% (4) of cases. Age ranged from, 18 to <65 years in 88.4% (803), 65+ years in 8.7% (79) cases; in 0.6% (5) cases reported foetus, infant, adult and elderly and age was not reported in the remaining 2.3% (21 cases). The majority of cases 80.3% (729) were consumer reports with the remaining 19.7% (179) cases being medically confirmed.

Of these 908 cases, 719 (79.2%) were serious, reported seriousness criteria were medically important (585), disability (125), hospitalization (190), life threatening (48), and death (18).

Cases may have met more than one criteria for seriousness. The remaining 189 (20.8%) reports were non serious. he outcome was reported as fatal in 18 (2%) of the total case count.

Of the 908 reports, there were 18 cases with fatal outcome reported during this period. Age of the 18 vaccinees with a fatal outcome ranged from 29 to 93 years with a median of 46 years. The reported PTs in the 18 cases with a fatal outcome in order of frequency (>1) were as follows:). Acute myocardial infarction (2), Cerebral haemorrhage (2), Cerebral venous sinus thrombosis (2), Haemophagocytic lymphohistiocytosis (2) and Thrombosis with thrombocytopenia syndrome (2). There were 11 cases where a fatal event occurred after 1st dose of vaccine, 4 cases – after 2nd dose and 1 case after booster dose. The dose was missing in 3 cases.

The top 20 events reported were Abdominal discomfort (8), Abdominal distension (5), Abdominal injury (1), Abdominal pain (3), Abdominal pain upper (2), Abdominal rigidity (1), Abnormal loss of weight (1), Accident at work (1), Acquired claw toe (1), Acute disseminated encephalomyelitis (2), Acute kidney injury (5), Acute myeloid leukaemia (1), Acute myocardial infarction (1), Ageusia (1), Aggression (1), Allodynia (1), Alopecia (1), Anal incontinence (1), Anosmia (1), and Anti-neutrophil cytoplasmic antibody positive vasculitis (2).

Cumulative Review (29 December 2020 – 28 December 2022)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 5194 cases (94.1% spontaneous cases, 2.3% non-interventional/post-mark pet, 3.3% from literature and 2 cases each from the study ChAdOx1 nCoV-19_ZA_phI/II, COV003 and D8111C00013; 4 case from COV002, D8110C00001 and 1 case from ICMR/SII-AZD-COVID-19/2020) in individuals with underlying bladder incontinence.

Of the 5194 cases, 66.9% (3475) were reported in females, 30.8% (1600) in males and gender was not reported in the remaining 2.3% (119) of cases. Age ranged from 0 to <18 years in 0.1% (3) of the reports; 18 to <65 years in 65.8% (3420) cases, 65+ years in 25.3% (1314) and age was not reported in the remaining 8% (414) of cases. The age group of adolescent, adult and elderly and foetus (age was not specified) was reported for 0.8% (43) cases. The majority of reports (79.9%) were from consumers with the remaining 20.1% being medically confirmed.

Of these 5194 cases, 3759 (72.4%) were serious, reported seriousness criteria were medically important (2910), disability (574), hospitalization (1074), life threatening (291), and death (174). Cases may have met more than one criteria for seriousness. The remaining 1435 (27.6%) reports were non serious.

The top 20 reported PTs were Blood urine present (128), Paraesthesia (115), Headache (90), Chromaturia (75), Pyrexia (72), Pain in extremity (69), Dyspnoea (67), Urinary tract infection (67), Pulmonary embolism (59),Influenza (58), Hypoaesthesia (56), Muscular weakness (53), Renal pain (53), Pain (52), Vomiting (50), Fatigue (49), Seizure (49), Chest pain (45) and Chills (45).

Outcome was reported as fatal in 174 (3.4%) of the total case count, of which 18 cases with fatal outcome were reported during the interval period, as described in the previous section.

16.3.5.3.5 Dementia

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited and literature) for the topic of use of VAXZEVRIA in individuals with Dementia.

Reporting Period (29 June 2022 – 28 December 2022)

The search identified a total of 519 case reports (93.8% spontaneous, 4.0% literature and 1.5% noninterventional/ post-market) and 0.6% from the study COV003 and D8110C00001 in individuals with underlying dementia who received COVID-19 VACCINE ASTRAZENECA. Of the 519 cases, 77.6% (403) were reported in females, 19.1% (99) in males and gender was not reported in the remaining 3.3% (17) of cases.

Age ranged from 18 to <65 years in 82.3% (427); 65+ years in 11.6% (60) and age was not reported in the remaining 5.4% (28) of cases. The age group of adult (age was not specified) was reported for 0.8% (4 cases). The majority of reports 416 (80.2%) were from consumers, with the remaining 19.8% (103) cases being medically confirmed.

Of these 519 cases, 416 (80.2%) were serious due to reported seriousness criteria were medically important (313), disability (136), hospitalization (131), life threatening (39), and death (13). Cases may have met more than one criteria for seriousness. The remaining 103 (19.8%) reports were non serious. Outcome was reported as fatal in 13 (2.5%) of the total case count.

Of the 519 reports, there were 13 cases with fatal outcome reported during this period. Age of the 28 vaccinees with a fatal outcome ranged from 56 to 90 years with a median of 80 years. The reported PTs in the 13 cases with a fatal outcome in order of frequency (≥2) were: Death (2), Diarrhoea (2), Pyrexia (2) and Vomiting (2), however the exact cause of death could not comprehensively determined due to insufficient information on exact clinical course or autopsy . There were 7 cases were a fatal outcome occurred after 1st dose of vaccine. There was limited information in 6 cases.

The top 20 events reported were co-manifestations of dementia [Memory impairment (36), Amnesia (32), Cognitive disorder (24)], Cerebrovascular accident (14), Dyspnoea (11), Confusional state (10), Guillain-Barre syndrome (10), Aphasia (8), Disturbance in attention (8), Balance disorder (7), COVID-19 (7), Muscular weakness (7), Chest pain (6), Fatigue (6), Hypoaesthesia (6), Vision blurred (6), Palpitations (5), Thrombosis with thrombocytopenia syndrome (5), Adverse drug reaction (4) and Anxiety (4).

Cumulative Review (29 December 2020 – 28 December 2022)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 3611 cases (96.5% spontaneous, 2.1% non-interventional/post-marketing, 1.2% from literature and 0.1% (4) from the study D8110C00001 and 0.0% (1 case) each from COV003 and ICMR/SII-AZD-COVID-19/2020) in individuals with dementia who received VAXZEVRIA.

Of the 3611 cases, 66.4% (2396) were reported in females, 31.0% (1120) in males and gender was not reported for the remaining 2.6% (95) of cases. Age ranged from 0 to <18 years in 0.1% (2) of the reports; 18 to <65 years in 57.5% (2075), 65+ years in 32.7% (1180) and age was not reported in the remaining 8.8% (316) of cases. The age group of adult and elderly (age was not specified) was reported for 38 (1.1%) cases. The majority of reports 2794 (77.4%) were from consumers with the remaining 817 cases (22.6%) being medically confirmed.

Of these 3611 cases, 2580 (71.4%) were serious, reported seriousness criteria were medically important (1805), disability (662), hospitalization (781), life threatening (251), and death (210). Cases may have met more than one criteria for seriousness. The remaining 1031 (28.6%) reports were non serious.

The top 20 reported events were co-manifestations of dementia [Memory impairment (312), Amnesia (235), Cognitive disorder (122), Confusional state (103)], Cerebrovascular accident (83), Disturbance in attention (74), Aphasia (61), Seizure (61), Pulmonary embolism (50), Dyspnoea (48), Muscular weakness (48), Paraesthesia (47), COVID-19 (45), Balance disorder (44), Death (44), Dementia (44), Hypoaesthesia (44), Headache (37), Pyrexia (36) and Fatigue (35).

Outcome was reported as fatal in 210 (5.8%) of the total case count, of which 13 cases with fatal outcome were identified during the reporting period, as described in the previous section.

16.3.5.3.6 Residence in long-term facility or nursing home

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited and literature) for the topic use of VAXZEVRIA in Residence in long-term facility or nursing home.

Reporting Period (29 June 2022 – 28 December 2022)

The search identified a total of 187 case reports in vaccinees with metastatic cancer who received COVID-19 VACCINE ASTRAZENECA (63.1% spontaneous,17.1% non-interventional and 19.8% literature).

Of the 187 cases, 65.8% (12) were reported in females, 23% (43) in males. The gender was missing in 11.2% cases. Age ranged from 18 to <65 years in 80.% (150) cases; 65+ years in 7.5% (14) reports and for 12.3% (23) the age group was missing. The majority of reports 83 (44.4%) were from consumers with the remaining 104 cases (55.6%) being medically confirmed.

Of these 187 cases, 140 (74.9%) were serious were serious, reported seriousness criteria were medically important (115), disability (25), hospitalization (34), life threatening (13), and death (3). Cases may have met more than one criteria for seriousness. The remaining 47 (25.1%) reports were non serious.

Of the 187 reports, there were 3 cases with fatal outcome reported during this period. Age of the 3 vaccinees who died ranged from 65 to 89 years with a median of 65 years. The reported events in the 3 cases with a fatal outcome in order of frequency were: Pulmonary embolism (2), Atrial septal defect (1), Brain injury (1), Cardiac arrest (1), Cardiac septal hypertrophy (1), Cardiopulmonary failure (1), Cerebrovascular accident (1), COVID-19 immunisation (1), Death; Cough (1), Haemorrhagic stroke (1), Hypoxia (1), Left ventricular dysfunction (1), Palpitations (1) and Respiratory failure (1). There were 2 cases were a fatal event occurred after 1st dose of vaccine and 1 case– after 2nd dose.

The top 20 reported events were Breakthrough COVID-19 (21), Hepatitis acute (13), COVID-19 (7), Pulmonary embolism (5), Amnesia (4), Guillain-Barre syndrome (4), Cerebral venous sinus thrombosis (3), Headache (3), Myocarditis (3), Rheumatoid arthritis (3), Thrombosis with thrombocytopenia syndrome (3), Arrhythmia (2), Blood pressure increased (2), Burning sensation (2), Chest pain (2), Colitis ulcerative (2), Dyspnoea (2), Heavy menstrual bleeding (2), Herpes zoster (2) and Insomnia (2).

Cumulative Review (29 December 2020 – 28 December 2022)

The search of the AstraZeneca global safety database identified a cumulative total of 950 cases (88.8% spontaneous, 4.7% non-interventional/post-marketing, 6.3% literature and 0.1% from study COV002) in Residence in long-term facility or nursing home.

Of the 950 cases, 60.8% (578) were reported in females, 34.6% (329 cases) in males and gender was not reported in the remaining 4.5% (43) of cases. Age ranged from 0 to <18 years in 0.1% (1 case); 18 to <65 years in 66.2% (629) cases; 65+ years in 23.1% (219) cases and age was not reported in the remaining 9.6% (91) of cases. The age group of adult and elderly (age not specified) was reported for 1.1% (10) cases. The majority of reports 742 (78.1%) were from consumers with the remaining 208 cases (21.9%) being medically confirmed.

Of these 950 cases, 831 (79.0%) were serious, reported seriousness criteria were medically important (615), disability (183), hospitalization (250), life threatening (96), and death (66). Cases may have met more than one criteria for seriousness. The remaining 119 (12.5%) reports were non serious.

The top 20 reported events were Death (29), Pulmonary embolism (28), Breakthrough COVID-19 (21), Deep vein thrombosis (21), Bell's palsy (18), COVID-19 (17), Guillain-Barre syndrome (16), Hypoaesthesia (16), Myocardial infarction (16), Paraesthesia (16), Dyspnoea (15), Hepatitis acute (13), Pericarditis (12), Headache (11), Influenza (11), Cerebral venous sinus thrombosis (10), Cerebrovascular accident (10), Chest pain (10), Muscular weakness (10) and Neuralgia (10)

Outcome was reported as fatal for 66 (6.9%) of the total case count, of which 3 cases with fatal outcome were identified during the reporting previous, as described in the previous section.

16.3.5.3.7 Metastatic Cancer

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited reporting and literature) for the topic use of VAXZEVRIA in individuals with metastatic cancer.

Reporting Period (29 June 2022 – 28 December 2022)

The search identified a total of 48 case reports in vaccinees with metastatic cancer who received COVID-19 VACCINE ASTRAZENECA (87.5% spontaneous, 8.3% from the study COV002, 2.1% non-interventional and 2.1% literature).

Of the 48 cases, 72.9% (35) were reported in females, 25% (12) in males. Age ranged from 18 to <65 years in 68.8% (33)cases; 65+ years in 29.2% (14) reports and 2.1% (1) for the age group adult. The majority of reports 29 (60.4%) were from consumers with the remaining 19 cases (39.6%) being medically confirmed.

Of these 48 cases, 34 (70.8%) were serious, reported seriousness criteria were medically important (25), disability (5), hospitalization (8), life threatening (3), and death (8).. Cases

may have met more than one criteria for seriousness. The remaining 14 (29.2%) reports were non serious.

Outcome was available for 73.6 % (53 events) of the 48 cases, with 20.8% reported as Recovered, 13.9% as Recovering, 22.2% Not recovered and 5.6% as Recovered with sequelae. Outcome was unknown in 26.4% of reports and was reported as fatal in 8 (11.1%)of the total case count.

Of the 48 reports, there were 8 cases with fatal outcome reported during this period. Age of the 8 vaccinees who died ranged from 46 to 81 years with a median of 60 years. The reported PTs in the 8 cases with a fatal outcome in order of frequency (>1) were: Intracranial pressure increased (2) and Photophobia (2). There was insufficient information on exact clinical course of photophobia (reported from spontaneous.source) for a comprehensive assessment. There were 4 cases were a fatal event occurred after 1st dose of vaccine and 1 case– after 2nd dose. There was limited information in 3 cases.

The top 20 reported events were Administration site pain (3), Oesophageal cancer metastatic (3), Breast cancer metastatic (2), Cough (2), Lymphadenopathy (2), Muscular weakness (2), Pyrexia (2), Therapeutic response unexpected (2), Abdominal mass (1), Adverse drug reaction (1), Blister (1), Cerebral venous sinus thrombosis (1), Chest pain (1), Colon cancer metastatic (1), Contusion (1), COVID-19 (1), Drug interaction (1), Drug resistance (1), Dyspnoea (1) and Flatulence (1).

Cumulative Review (29 December 2020 – 28 December 2022)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 446 cases (95.3% spontaneous, 1.6% non-interventional/post-marketing, 2.0% literature and 1.1% from the study COV002) in individuals with metastatic cancer who received VAXZEVRIA.

Of the 446 cases, 57.0% (254 cases) were reported in females, 41.5% (185 cases) in males and gender was not reported in the remaining 1.6% (7) cases. Age ranged from 0 to <18 years in0.2% (1 case); 18 years to <65 years in 50% (223) of the reports and 65+ years in 43.9% (196) cases. The age group of adult and elderly (age not specified) was reported in 1.1% and age was not reported in the remaining 4.7% (21) of cases. The majority of reports 273 (61.2%) were from consumers with the remaining 173 cases (38.8%) being medically confirmed.

Of these 446 cases, 380 (85.2%) were serious, reported seriousness criteria were medically important (258), disability (43), hospitalization (138), life threatening (51), death (65). Cases may have met more than one criteria for seriousness. The remaining 66 (14.8%) reports were non serious.

The top 20 reported PTs were Pulmonary embolism (32), Deep vein thrombosis (13), Thrombocytopenia (12), Headache (11), Immune thrombocytopenia (11), Dyspnoea (10), Pyrexia (10), Thrombosis (9), COVID-19 (8), Lymphadenopathy (8), Chest pain (6), Oesophageal cancer metastatic (6), Back pain (5), Cerebrovascular accident (5), Metastatic neoplasm (5), Muscular weakness (5), Pain (5), Paraesthesia (5), Cough (4) and Death (4).

Outcome was available for 90.1% (402 cases) of the total 446 cases, with 17.7% (79 cases) reported as Recovered, 24.0% (107) as Recovering, 30.5% (136 cases) Not recovered, 3.4% (15 cases) as Recovered with sequelae and unknown in 9.9% (44 cases). The outcome was reported as fatal in 65 (14.6%) of the total case count, of which 8 cases with fatal outcome were identified during the reporting period, as described in the previous section.

16.3.5.3.8 Supplementary Oxygen Use

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited reporting and literature) for the topic use of VAXZEVRIA in individuals with frailty_ Oxygen (periodic search) and frailty_ Supplementary Oxygen Use (cumulative search).

Reporting Period (29 June 2022 – 28 December 2022)

The search identified a total of 477 case reports (89.7% spontaneous, 8.4% literature, 0.8% non-interventional/post-marketing, and 0.2% each from studies COV002, COV003, D8110C00001, D8111C00010, and D8111C00013) for the topic use of VAXZEVRIA in individuals with frailty_ Oxygen.

Of the 477 cases, 359 (75.3%) were reported in females, 110 (23.1%) in males and gender was not reported in the remaining 8 (1.7%) cases. Age ranged from 18 years to <65 years in 79.2% (359), 13.6% (65) in 65^{+} years, and 1.0% (5) in adult age group. In 6.1% (29) cases the age was reported as unknown. Of the 477 reports, 41.9% (200) were medically confirmed, with remaining 58.1% (10) being consumer reports.

Of these 477 cases, 404 (84.7%) were serious, reported seriousness criteria were medically important (254), hospitalization (162), disability (58), life threatening (57), and death (36). Cases may have met more than one criteria for seriousness. The remaining 73 (15.3%) reports were non serious.

The top 20 reported events were Headache (121), Dyspnoea (115), Pyrexia (115), Fatigue (104), Dizziness (77), Oxygen saturation decreased (72), Myalgia (65), Nausea (62), Chills (60), Arthralgia (48), Pain (46), Pain in extremity (41), Hypoaesthesia (40), Chest pain (38),

Paraesthesia (37), Malaise (32), Vomiting (32), Diarrhoea (30), Palpitations (30), and Asthenia (29).

Of the 477 cases, there were 36 (7.5%) cases with fatal outcome reported during this period. Age of the 36 vaccinees who died ranged from 28 to 90 years with a median of 60 years. The reported PTs for the 36 fatal cases were COVID-19 pneumonia (3), Dyspnoea (3), COVID-19 (2), Death (2), Hypoxia (2), Pneumonia (2), and 1 each for Acute myeloid leukaemia, Acute myocardial infarction, Angina pectoris, Cardiac arrest, Cerebral haemorrhage, Cerebral thrombosis, Chronic obstructive pulmonary disease, Cough, Decreased appetite, Dementia Alzheimer's type, Encephalitis, Gastric cancer, Haemorrhagic stroke, Hemiparesis, Hyperthermia, Hypoxia, Loss of consciousness, Obstructive pancreatitis, Pulmonary embolism, Pyrexia, SARS-CoV-2 test positive, Septic shock, and Thrombosis with thrombocytopenia syndrome. There were 17 cases were a fatal outcome occurred after the 1st dose of vaccine, and 4 cases after 2nd dose. In 1 case both doses were reported. There was limited information in 14 cases.

Cumulative Review (29 December 2020 – 28 December 2022)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 3910 cases (95.5% spontaneous, 3.1% literature, 0.9% non-interventional/post-marketing, and 0.3% from study D8110C00001, 0.1% from study D8111C00013, and 1 case each from studies COV002, COV003, D8111C00003, D8111C00010, and ICMR/SII-AZD-COVID-19/2020) for the topic use of VAXZEVRIA in individuals with frailty_ Supplementary Oxygen Use.

Of the 3910 cases, 2341 (59.9%) were reported in females, 1471 (37.6%) in males and gender was not reported in the remaining 98 (2.5%) cases. Age ranged from 18 years to <65 years in 63.4% (2477), 23.1% (903) in 65^{+} years, 0 to <18 years in 0.3% (12), 0.4% (16) in adult, 0.2% (17), 0.1% (3) in neonate. In 12.6% (492) cases the age was reported as unknown. Of the 3910 reports, 45.4% (1775) were medically confirmed, with remaining 54.6% (2135) being consumer reports.

Of these 3910 cases, 2853 (73.0%) were serious, reported seriousness criteria were medically important (1782), hospitalization (1303), disability (347), life threatening (409), and death (325). Cases may have met more than one criteria for seriousness. The remaining 1057 (27.0%) cases were non serious.

The top 20 reported events were Pyrexia (1171), Headache (1027), Dyspnoea (919), Oxygen saturation decreased (739), Fatigue (673), Chills (516), Myalgia (494), Dizziness (451), Nausea (451), Cough (348), Malaise (327), Asthenia (315), Arthralgia (296), Pain (288), Pulmonary embolism (264), Chest pain (254), Pain in extremity (245), Vomiting (232), Tachycardia (201), and COVID-19 (199).

There were 325 (8.3%) fatal cases reported cumulatively in individuals with frailty_ Supplementary Oxygen Use, of which 36 were reported during the interval period, as described in the previous section.

16.3.5.3.9 Palliative Care

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited reporting and literature) for the topic use of VAXZEVRIA in individuals with Palliative care needs.

Reporting Period (29 December 2021 – 28 December 2022)

The search identified a total of 11 case reports (54.5% spontaneous, 18.2% literature, 18.2% from study COV002, and 9.1% from study COV0003) for the topic use of VAXZEVRIA in individuals with Palliative care needs.

Of the 11 cases, 7 (63.6%) were reported in females, 2 (18.2%) in males and gender was not reported in the remaining 2 (18.2%) cases. Age ranged from 18 years to <65 years in 36.4% (4), and 54.5% (6) in 65^{+} years. In 9.1% (1) case the age was reported as unknown. Of the 11 reports, 54.5% (6) were medically confirmed, with remaining 45.5% (5) being consumer reports.

All of the 11 cases, were serious, reported seriousness criteria were medically important (7), hospitalization (5), life threatening (4), disability (2), and death (5). Cases may have met more than one criteria for seriousness.

The top 20 reported events were Confusional state (2), Malaise (2), Pulmonary embolism (2), and 1 each for Arthritis bacterial, Atrial fibrillation, Blood viscosity increased, Cardiac failure, Cellulitis, Cerebral haemorrhage, Cerebral venous thrombosis, Chronic obstructive pulmonary disease, Cluster headache, Dizziness, Dizziness postural, Gout, Guillain-Barre syndrome, Headache, Infection, Lower respiratory tract infection, and Malignant neoplasm progression.

Of the 11 cases, there were 5 (45.5%) cases with fatal outcome reported during this period. Age of the 5 vaccinees who died ranged from 42 to 77 years with a median of 74 years. The reported PTs (1 each) for the 5 fatal cases were Guillain-Barre syndrome, Metastatic neoplasm, Pancreatic carcinoma, Sarcoma, and Thrombosis with thrombocytopenia syndrome. There was 1 case were a fatal outcome occurred after the 1st dose of vaccine. There was limited information in 4 cases.

Cumulative Review (29 December 2020 – 28 December 2022)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 122 cases (90.2% spontaneous, 6.6% literature, 0.8% non-interventional/post-marketing, 1.6% from study COV002, and 0.8% from study COV003) for the topic use of VAXZEVRIA in individuals with Palliative care needs.

Of the 122 cases, 57 (46.7%) were reported in females, 63 (51.6%) in males and gender was not reported in the remaining 2 (1.6%) cases. Age ranged from 18 years to <65 years in 23.0% (28), and 72.1% (88) in 65^{+} years. In 4.9% (6) cases the age was reported as unknown. Of the 122 reports, 57.4% (70) were medically confirmed, with remaining 42.6% (52) being consumer reports.

Of these 122 cases, 119 (97.5%) were serious, reported seriousness criteria were medically important (69), hospitalization (56), disability (21), life threatening (27), and death (68). Cases may have met more than one criteria for seriousness. The remaining 3 (2.5%) cases were non serious.

The top 20 reported events were Cerebrovascular accident (15), Dyspnoea (14), Malaise (14), Death (13), Headache (11), Cerebral haemorrhage (9), Pyrexia (9), Thrombocytopenia (9), Fatigue (8), Vomiting (8), Confusional state (7), Pulmonary embolism (7), Syncope (7), Facial paralysis (6), Nausea (6), Pneumonia (6), Depressed level of consciousness (5), Myalgia (5), Pain (5), and Pain in extremity (5).

There were 68 (55.7%) fatal cases reported cumulatively in individuals with palliative care needs, of which 5 were reported during the interval period, as described in the previous section.

16.3.5.3.10 Pressure Ulcers

Search Strategy

A cumulative and periodic search of the AstraZeneca Global Safety Database was conducted to review AEs reported from all sources (clinical, spontaneous, solicited reporting and literature) for the topic use of VAXZEVRIA in individuals with pressure ulcers.

Reporting Period (29 June 2022 – 28 December 2022)

The search identified a total of 890 case reports (97.4% spontaneous, 1.5% literature, 0.8% non-interventional/post-marketing, and 0.1% each from studies COV001, COV002, and COV003) for the topic use of VAXZEVRIA in individuals with pressure ulcers.

Of the 890 cases, 797 (89.6%) were reported in females, 85 (9.6%) in males and gender was not reported in the remaining 8 (0.9%) cases. Age ranged from 18 years to <65 years in 91.5% (814), 6.3% (56) in 65^{+} years, 0.2% (2) in 0 to <18 years, and 0.1% (1) in adult. In 1.9% (17)

case the age was reported as unknown. Of the 890 reports, 19.1% (170) were medically confirmed, with remaining 80.9% (720) being consumer reports.

Of the 890 reports, 57.8% (154) cases were serious, reported seriousness criteria were medically important (453), disability (72), hospitalization (71), life threatening (16), and death (3). Cases may have met more than one criteria for seriousness. The remaining 42.2% (376) cases were non-serious.

The top 20 reported events were Headache (326), Pyrexia (280), Mouth ulceration (253), Fatigue (236), Chills (168), Nausea (144), Arthralgia (127), Myalgia (124), Pain in extremity (88), Dizziness (81), Malaise (74), Pain (64), Oropharyngeal pain (54), Aphthous ulcer (52), Diarrhoea (44), Pruritus (44), Colitis ulcerative (41), Lymphadenopathy (39), Dyspnoea (37), and Paraesthesia (37).

Of the 890 cases, there were 3 (0.3%) cases with fatal outcome reported during this period. Age of the 3 vaccinees who died ranged from 46 to 82 years with a median of 68 years. The reported PTs (1 each) for the 3 fatal cases were Adverse Event Following Immunisation, Cerebral venous sinus thrombosis, and Pyrexia. There was 1 case were a fatal outcome occurred after the 1st dose of vaccine. There was limited information in 2 cases.

Cumulative Review (29 December 2020 – 28 December 2022)

The search of the AstraZeneca Global Safety Database identified a cumulative total of 4254 cases (96.4% spontaneous, 2.6% non-interventional/post-marketing, 0.9% literature, and 1 case each from studies COV001, COV002, COV003, D8110C00001, and ICMR/SII-AZD-COVID-19/2020) for the topic use of VAXZEVRIA in individuals with pressure ulcers.

Of the 4254 cases, 3007 (70.7%) were reported in females, 1145 (26.9%) in males and gender was not reported in the remaining 102 (2.4%) cases. Age ranged from 18 years to <65 years in 73.9% (3143), 17.7% (753) in 65+ years, 0.2% (9) in 0 to <18 years, 0.5% (22) in adult, and 0.1% (6) in elderly. In 7.5% (321) cases the age was reported as unknown. Of the 4254 reports, 20.4% (867) were medically confirmed, with remaining 79.6% (3387) being consumer reports.

Of these 4254 cases, 2363 (55.5%) were serious, reported seriousness criteria were medically important (1924), hospitalization (395), disability (334), life threatening (99), and death (59). Cases may have met more than one criteria for seriousness. The remaining 1891 (44.5%) cases were non serious.

The top 20 reported events were Headache (1387), Pyrexia (1129), Fatigue (977), Mouth ulceration (968), Chills (726), Myalgia (577), Nausea (570), Arthralgia (485), Dizziness (398), Pain in extremity (386), Aphthous ulcer (366), Malaise (338), Pain (269), Diarrhoea (245),

Vomiting (194), Oropharyngeal pain (192), Colitis ulcerative (183), Influenza like illness (179), Pruritus (162), and Paraesthesia (158).

There were 59 (1.4%) fatal cases reported cumulatively in individuals with underlying pressure ulcers, of which 3 were reported during the interval period, as described in the previous section.

Overall Conclusion

This review of the cumulative and periodic data in individuals with frailty, severe and/or uncontrolled underlying disease and comorbidities did not reveal any new safety concern. There was no increase in events seriousness (for all discussed topics) or severity.

In individuals with frailty, there was an increase of 51 fatal cases (34 new, 17 follow ups) reported cumulatively from the previous PBRER (88) covering the period 29 December 2021 to 28 June 2022. Due to search strategy update 51 cases were retrieved in the current cumulative output. Of note, out of the 34 new reports received by AstraZeneca, of which 32 had the onset date at an earlier point during 2021 before the start of the reporting interval. On review, there were no significant safety concerns identified.

In individuals with dispensing of or reimbursement for durable medical equipment, there was an increase of 54 fatal cases (18 new, 36 follow ups) reported cumulatively from the previous PBRER (251) covering the period 29 December 2021 to 28 June 2022. Due to search strategy update 54 cases were retrieved in the current cumulative output. Of note, out of the 18 new reports received by AstraZeneca, of which 16 had the onset date at an earlier point during 2021 before the start of the reporting interval. On review, there were no significant safety concerns identified.

In summary, no abnormal trends or significant new safety concerns were identified in the interval period with respect to the cumulative data. Majority of the adverse events reported in patients with frailty and/or uncontrolled underlying disease were either related or heavily confounded by patients' medical history and underlying disorders or were consistent with the known safety profile of the vaccine.

This cumulative and periodic review of currently available data from the use of VAXZEVRIA in subjects with frailty, severe and/or uncontrolled underlying diseases and comorbidities did not identify any new safety concerns.

This topic will continue to be considered missing information and will be kept under close surveillance by AstraZeneca.

Use of VAXZEVRIA in subjects with severe or uncontrolled underlying disease/Use in frail patients will be investigated primarily in the ongoing non-interventional post-marketing

observational study using existing secondary health data sources (D811110R00002 [US] and D8111R00006 [EU/UK]) study of subgroups exposed to VAXZEVRIA. Refer to Appendix 4 for additional details.

More detailed information is provided in Section 16.4.3.3.

16.3.5.4 Use of VAXZEVRIA with other vaccines

During the period covered by this PBRER, the missing information on the topic of "Use of VAXZEVRIA with other vaccines" has been reclassified and removed from the list of safety concerns (Core RMP V8.0 dated 10 November 2022).The safety, immunogenicity, and efficacy of VAXZEVRIA when co-administered with other vaccines has not been evaluated in clinical trials. Therefore, while there is currently no evidence to suggest the safety profile of the subjects receiving VAXZEVRIA when co-administered with other vaccines would be impacted, given the paucity of data, the possibility cannot be excluded.

The review of this topic for this PBRER covering period is presented below: A cumulative search of the AstraZeneca Global Safety Database through 28 December 2022 was undertaken to review AEs reported after vaccination with VAXZEVRIA with other non-COVID-19 vaccines, including seasonal influenza vaccine, herpes vaccine, varicella vaccine, and pneumococcal pneumonia vaccine. Reports were identified in the Global Safety Database through a search of the concomitant medications for: seasonal Influenza vaccine, Herpes vaccines, Pneumococcal vaccine and Varicella vaccine.

16.3.5.4.1 Influenza Vaccine

Assessment for cases received with Influenza Vaccine (reporting interval):

This search identified a total of 855 cases (71.0% spontaneous cases, 28.8% non-interventional/post-marketing cases, and 0.2% from study D8110C00001) for the topic use of VAXZEVRIA with seasonal influenza vaccine.

Of the 855 cases, 66.7% (570) were reported in females, 31.9% (273) in males, and gender was not reported in the remaining 1.4% (12) of cases. The age ranged from 18 years to <65 years in 52.9% (452), 65^{+} years in 39.9% (341), 0.5% (4) in 0 to <18 years, and 0.1% (1) each in elderly and neonate. In 6.5% (56) cases the age was reported as unknown. Of the 855 reports, 15.8% (135) were medically confirmed, with the remaining 84.2% (720) being consumer reports.

Of the 855 cases, 221 (25.8%) were serious, reported seriousness criteria were medically important (176), hospitalization (49), disability (18), life threatening (3), and death (8). Cases may have met more than one criteria for seriousness. The remaining 74.2% (634) cases were non-serious.

A total of 3644 events were reported within the 855 cases. The top 20 reported events were Headache (337), Fatigue (333), Injection site pain (217), Myalgia (201), Pyrexia (201), Chills (165), Arthralgia (146), Malaise (138), Pain in extremity (131), Nausea (110), Dizziness (85), Injection site swelling (82), Diarrhoea (51), Lymphadenopathy (48), Pain (43), COVID-19 (38), Influenza like illness (38), Feeling cold (30), Limb discomfort (28), and Nasopharyngitis (26).

The time to onset from vaccination to the event was available for 65.3% events of which 15.2% of events occurred within day 0 of vaccination, 10.5% occurred on day 1 post vaccination, 4.5% events occurred within days 2-15 post-vaccination, 19.0% events occurred between 16-200 days post-vaccination, 16.1% events occurred > 200 days post-vaccination, and for 34.7% events the time from vaccination to AE onset was not reported.

Outcomes of events were reported as 51.7% (1883) recovered, 22.0% (801) recovering, 12.8% (466) not recovered, 0.6% (23) recovered with sequelae, 0.2% (8) fatal, and 12.7% (463) as unknown.

Of the 855 cases, there were 8 (0.6%) cases with fatal outcome reported during this period. Age was reported in 5 out of 8 cases with a median age of 82 years; range 72 to 93 years. The reported PTs for the 8 fatal cases were Death (2), and 1 each for Adverse event following immunisation, Cerebral infarction, Dyspnoea, Guillain-Barre syndrome, Loss of consciousness, and Myocardial infarction.

Assessment for cases received with Influenza Vaccine (cumulative search):

This search identified a total of 13679 cases (89.1% spontaneous cases, 10.7% non-interventional/post-marketing cases, 0.09% literature, and 0.03% Clinical trial) for the topic use of VAXZEVRIA with seasonal influenza vaccine.

Of the 13679 cases, 73.4% (10035) were reported in females, 24.3% (3318) in males, and gender was not reported in the remaining 2.4% (326) of cases. The age ranged from 18 years to <65 years in 66.4% (9082) of the reports, 65+ years in 27.2% (3718), and 0.4% (49) in less than 18 years of age. In 5.8% (792) cases the age was reported as unknown. Of the 13679 reports, 8.9% (1222) were medically confirmed, with remaining 91.1% (12457) being consumer reports.

Of the 13679 reports, 61.4% (8401) were serious and reported seriousness criteria were medically important (7697), disability (726), hospitalization (463), life threatening (148), and death (77); 8 of 77 fatal cases occurred in the reporting period. Cases may have met more than one criteria for seriousness. The remaining 38.6% (5278) cases were non-serious.

A total of 59047 events were reported within the 13679 cases. The top 20 reported events were Headache (6055), Fatigue (4163), Pyrexia (3926), Chills (3513), Nausea (2515), Myalgia (2288), Arthralgia (1754), Pain in extremity (1575), Dizziness (1375), Malaise (1056), Pain (1033), Influenza like illness (792), Tremor (743), Vomiting (688), Injection site pain (665), Diarrhoea (587), Hyperhidrosis (569), Decreased appetite (504), Influenza (478), and Paraesthesia (474).

The time to onset from vaccination to the event was available for 70.8% events of which 29.5% occurred the same day as vaccination, 22.3% occurred on day 1 post-vaccination, 8.5% events occurred within days 2-15 post-vaccination, 6.5% events occurred between 16-200 days post-vaccination, 4.0% events occurred > 200 days post-vaccination, and for 29.2% events the time from vaccination to AE onset was not reported.

Outcomes for events were reported as 42.0% (24332) recovered, 20.7% (11970) recovering, 1.2% (698) recovered with sequelae, 21.6% (12500) not recovered, 0.3% (163) fatal, and 14.3% (8301) as unknown.

There were 75 (0.5%) fatal cases reported cumulatively with seasonal influenza vaccine, of which 8 were reported during the interval period, as described in the previous section.

16.3.5.4.2 Herpes Vaccine

Assessment for cases received with Herpes vaccine (Reporting Interval):

There were no cases were reported involving use of VAXZEVRIA with Herpes vaccine in the reporting interval.

Assessment for cases received with Herpes vaccine (Cumulative search):

Cumulatively, this search has identified a total 3 cases from the previous PBRERs covering the period 29 December 2021 to 28 June 2022 (2 cases) and 29 June 2021 to 28 December 2021 (1 case).

16.3.5.4.3 Pneumococcal Vaccine

Assessment for cases received with Pneumococcal vaccine (Reporting interval):

This search identified a total of 70 cases (all spontaneous) for the topic use of VAXZEVRIA with Pneumococcal vaccine.

Of the 70 cases, 72.9% (51) were reported in females, 25.7% (18) in males, and 1.4% (1) of unknown gender. The age ranged from 18 years to <65 years in 41.4% (29) of the reports and 65^{+} years in 34.3% (24). In 24.3% (17) cases the age was not reported. Of the 70 reports, 67.1% (47) cases were medically confirmed with remaining 32.9% (23) being consumer reports.

Of the 70 reports, 18.6% (13) were serious and reported seriousness criteria were medically important (9), disability (3), hospitalization (2), life threatening (1), and death (1). Cases may have met more than one criteria for seriousness. The remaining 81.4% (57) cases were non-serious.

A total of 172 events were reported within the 70 reports. The top 20 reported events were Oedema (19), Pyrexia (19), Headache (16), Fatigue (7), Flushing (7), Myalgia (7), Application site pain (6), Chills (6), Erythema (4), Hyperaemia (4), Abdominal pain (3), Arthralgia (3), Feeling hot (3), Pain (3), Pain in extremity (3), Pruritus (3), Vomiting (3), Abscess (2), Decreased appetite (2), and Dizziness (2).

The time to onset from vaccination to the event was available for 88.9% events, of which 20.6% occurred within day 0 of vaccination, 8.6% occurred on day 1 post vaccination, 5.2% events occurred within days 2-15 post-vaccination, 19.5% events occurred between 16-200 days post-vaccination, 34.9% events occurred > 200 days post-vaccination. For 11.1% events, the time to onset post vaccination was not reported.

Outcomes for events were reported as 90 (52.3%) recovered, 19 (11.0%) recovering, 10 (5.8%) not recovered, 1 (0.6%) recovering with sequelae, 1 (0.6%) fatal, and 51 (29.7%) as unknown.

There was 1 case with fatal outcome reported during this period. The assessment of the fatal case is presented below:

Case ID [redacted] This consumer report concerns a 71 years old patient of unknown gender. The medical history was not reported. On 09 February 2021, the patient received first dose of VAXZEVRIA for an unknown indication. On 26 April 2021, the patient received second dose VAXZEVRIA for an unknown indication. On 11 June 2021, the patient started treatment with Pneumococcal Vaccine. On 20 October 2021, the patient experienced Guillain-Barre syndrome. On an unknown date, the patient experienced Hypertension and Pneumonia aspiration. The patient died from the event of Guillain-Barre syndrome. It was not known whether an autopsy was performed. The cause of death was Guillain-Barre syndrome and Pneumonia aspiration.

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Comment: Fatal events of Guillain-Barre syndrome and Pneumonia aspiration and non-fatal event of Hypertension are not listed in the company core data sheet of VAXZEVRIA. Elderly age of vaccinee could be considered a risk factor for fatal outcome. Guillain-Barre syndrome can be a confounding factor to the events of Pneumonia aspiration and Hypertension. Vaccinee died on 20 October 2021. The cause of death was Guillain-Barre syndrome and Pneumonia aspiration. Due to limited information on, onset date of events, risk factors (viral

infection, surgery, trauma), circumstances surrounding the events, concurrent conditions, concomitant medications, therapeutic measures taken with respect to the events, relevant medical history, detailed etiological and diagnostic work-up (complete blood analysis, physical examination, neurological workup, radiological investigations including imaging studies, autopsy report with confirmed final diagnosis), the evaluation did not find evidence to suggest a causal relationship between the events and VAXZEVRIA.

Assessment for cases received with Pneumococcal vaccine (Cumulative search):

This search identified a total of 445 cases (93.9% spontaneous cases, 5.8% non-interventional/post-marketing cases, and 0.2% literature cases) for the topic use of VAXZEVRIA with Pneumococcal vaccine.

Of the 445 cases, 73.5% (327) were reported in females, 24.9% (111) in males, and gender was not reported in the remaining 1.6% (7) of cases. The age ranged from 18 years to <65 years in 43.4% (193) of the reports, 65+ years in 37.8% (168), and 0.4% (2) in less than 18 years of age. In 17.8% (79) cases the age was not reported. Of the 445 reports, 39.3% (175) cases were medically confirmed with remaining 60.7% (270) being consumer reports.

Of the 445 reports, 45.8% (204) were serious and reported seriousness criteria were medically important (175), disability (23), hospitalization (19), life threatening (7), and death (3). Cases may have met more than one criteria for seriousness. The remaining 54.2% (241) cases were non-serious.

A total of 1774 events were reported within the 445 reports. The top 20 reported events were Headache (142), Pyrexia (108), Fatigue (95), Chills (80), Myalgia (64), Nausea (55), Oedema (51), Pain in extremity (50), Dizziness (41), Arthralgia (40), Pain (36), Malaise (27), Erythema (20), Feeling hot (20), Tremor (19), Flushing (18), Influenza like illness (18), Application site pain (16), Pruritus (16), and Asthenia (15).

The time to onset from vaccination to the event was available for 74.6% events, of which 26.4% occurred within day 0 of vaccination, 14.1% occurred on day 1 post vaccination, 6.6% events occurred within days 2-15 post-vaccination, 14.5% events occurred between 16-200 days post-vaccination, 13.0% events occurred > 200 days post-vaccination. For 25.4% events, the time to AE onset post vaccination was not reported.

Outcomes of events were reported as 726 (41.4%) recovered, 342 (19.5%) not recovered, 226 (15.2%) recovering, 21 (1.2%) recovering with sequelae, 8 (0.5%) fatal, and 391 (22.3%) as unknown.

There were 3 fatal cases (8 events) reported cumulatively with pneumococcal vaccine, of which 1 was reported during the interval period, as described in the previous section.

16.3.5.4.4 Varicella Vaccine

Assessment for cases received with Varicella vaccine (Reporting interval):

This search identified a total of 42 cases (all spontaneous) for the topic use of VAXZEVRIA with Varicella vaccine.

Of the 42 cases, 73.8% (31) were reported in females, 19.0% (8) in males, and 7.1% (3) in unknown gender. The age ranged from 18 years to <65 years in 35.7% (15) of the reports, 65^{+} years in 31.0% (13), and 33.3% (14) of unknown age. Of the 42 reports, 66.7% (28) cases were medically confirmed with remaining 33.3% (14) being consumer reports.

Of the 42 reports, 11.9% (5) were serious and reported seriousness criteria were medically important (3), hospitalization (2), and death (1). Cases may have met more than one criteria for seriousness. The remaining 88.1% (37) cases were non serious.

A total of 114 AEs were reported within the 42 reports. The top 20 reported PTs were Oedema (9), Application site pain (8), Flushing (6), Pain (6), Herpes zoster (5), Application site erythema (4), Headache (4), Vaccination failure (4), Abdominal pain (3), Application site warmth (3), Erythema (3), Pruritus (3), Pyrexia (3), Vomiting (3), Application site oedema (2), Asthenia (2), Pain in extremity (2), Product administered to patient of inappropriate age (2), Abdominal discomfort (1), and Abdominal hernia (1).

The time to onset from vaccination to the was available for 87.6% of AEs, of which 8.7% occurred within day 0 of vaccination, 12.4% occurred on day 1 post vaccination, 6.0% occurred within days 2-15 post-vaccination, 23.5% events occurred between 16-200 days post-vaccination and 36.9% events occurred >200 days post-vaccination. For 12.4% events, the time to onset post vaccination was not reported.

Outcomes for AEs were reported as 35 (30.7%) recovered, 26 (22.8%) recovering, 12 (10.5%) not recovered, 1 (0.9%) fatal, and 40 (35.1%) as unknown.

The 1 fatal case ([redacted]) has been identified as a duplicate during the reporting period, which has been described in the previous PBRER covering the period 29 December 2021 to 28 June 2022.

Assessment for cases received with Varicella vaccine (Cumulative search):

This search identified a total of 96 cases (94.8% spontaneous cases, 4.2% non-interventional/post-marketing cases, and 1.0% Clinical trial) for the topic use of VAXZEVRIA with Varicella vaccine.

Of the 96 cases, 67.7% (65) were reported in females, 26.0% (25) in males, and gender was not reported in the remaining 6.3% (6) of cases. The age ranged from 18 years to < 65 years in

30.2% (29) of the reports, and 65^{+} years in 52.1% (50). In 17.7% (17) cases the age was not reported. Of the 92 reports, 43.8% (42) were medically confirmed with remaining 56.3% (54) being consumer reports.

Of the 96 reports, 34.4% (33) were serious and reported seriousness criteria were medically important (28), hospitalization (5), disability (2), life threatening (2), and death (1). Cases may have met more than one criteria for seriousness. The remaining 65.6% (63) cases were non-serious.

A total of 316 AEs were reported within the 96 reports. The top 20 reported PTs were Pyrexia (18), Headache (16), Herpes zoster (15), Chills (10), Pain (10), Vaccination failure (10), Oedema (9), Nausea (9), Fatigue (9), Application site pain (9), Pain in extremity (8), Flushing (7), Pruritus (6), Rash (5), Asthenia (5), Vomiting (5), Arthralgia (5), Myalgia (5), Erythema (4), and Blister (4).

Time to onset from vaccination to the event was available for 74.5% of AEs, of which 11.7% of events occurred within day 0 of vaccination, 12.8% occurred on day 1 post vaccination, 5.9% events occurred within days 2-15 post-vaccination, 20.3% events occurred between 16-200 days post-vaccination, and 23.8% events occurred > 200 days post-vaccination. For 29.3% events, the time to onset post vaccination was not reported.

Outcomes for AEs were reported as 97 (30.7%) recovered, 65 (20.6%) recovering, 5 (1.6%) recovered with sequelae, 48 (15.2%) not recovered, 1 (0.3%) fatal, and 100 (31.9%) as unknown.

Discussion

The most common adverse events reported of VAXZEVRIA when co-administered with other vaccines were similar to VAXZEVRIA when given alone. In most cases, there was limited information. There were no additional reports received regarding Use of VAXZEVRIA with other vaccines.

At the end of the reporting period, this missing information is reclassified in the Core RMP and removed from the list of safety concerns and the justification for removal is presented below:

Adequate safety data are available to evaluate whether the VAXZEVRIA safety profile differs when taken concomitantly with other vaccines. The safety of VAXZEVRIA taken concomitantly with other vaccines was evaluated based on the cumulative post-marketing experience as of 28 December 2022 in individuals who concomitantly received non-covid-19 vaccines including 13679 reports with influenza vaccines, 3 reports with herpes vaccines, 445 with pneumococcal vaccines and 96 reports with varicella vaccines. There is no evidence to

suggest that the use with other vaccines results in a specific safety concern, or a different outcome to previously identified risks. Furthermore, there is no reasonable expectation that ongoing pharmacovigilance activities could further characterize the safety profile with respect to interactions with other vaccines. Therefore, interactions with other vaccines is no longer considered relevant for inclusion as missing information.

Conclusion

Based on the evaluation of the available data during the reporting period and considering the cumulative experience, this missing information of: Use of AZD1222 with other vaccines is removed from the list of safety concerns.

16.4 Characterisation of risks

At the end of the reporting period, the VAXZEVRIA safety specification (presented in the global AstraZeneca Core Risk Management Plan, Version no. 8.0, dated 10 November 2022) included the following important identified and important potential risks, and missing information (see Table 169). Characterisations of the safety concerns are presented in Sections 16.4.1, 16.4.2 and 16.4.3 respectively.

Table 169 Summary of safety concerns – AstraZeneca Core Risk Management Plan for VAXZEVRIA (Version no. 8.0, dated 10 November 2022)

Risk Category	Safety concern
Important identified risks	Thrombosis in combination with thrombocytopenia
Important potential risks	Immune mediated neurological conditions
	Cerebrovascular venous sinus thrombosis without thrombocytopenia
Missing information	Use of VAXZEVRIA in pregnant and breastfeeding women
	Use of VAXEVRIA in subjects with severe immunodeficiency
	Use of VAXEVRIA in subjects with severe and/or uncontrolled underlying disease

In the following sections, detailed information is given on the important identified and potential risks, and missing information included in Table 169 above.

16.4.1 Important identified risks

The following safety concern is considered as important identified risk:

- Thrombosis in combination with thrombocytopenia

16.4.1.1 Thrombosis in combination with thrombocytopenia

Table 170 *Important identified risk* - Thrombosis in combination with thrombocytopenia

Characterisation	Summary
Frequency	There were no reports of thrombosis concurrent with thrombocytopenia in the VAXZEVRIA clinical development programme. Very rare events of serious thrombosis concurrent with thrombocytopenia (including fatal events), have been observed following vaccination with VAXZEVRIA during post-authorisation use. The majority of the events occurred within the first 21 days following vaccination and some events had a fatal outcome. The reporting rates after the second dose are lower compared to after the first dose.
Potential mechanisms	The exact mechanism of thrombosis concurrent with thrombocytopenia following immunisation with VAXZEVRIA is unknown. Several hypothetical biologic mechanisms have been proposed to explain the pathophysiology of thromboembolic events with thrombocytopenia following vaccination (Greinacher et al 2021 (NEJM)). Among them a study by Baker et al 2021, proposes an interaction between the ChAdOx1 vaccine vector used in VAXZEVRIA and PF4; however, it is unknown if the adenoviral ChAdOx1 interaction with PF4 is actually platelet activating or thrombogenic (causal of blood clots). Greinacher et al 2021 (NEJM) suggested that ChAdOx1 itself or proteins contained within the vaccine can bind to PF4 to form immune complexes which may drive a B-cell response causing high-titer anti-PF4 antibodies resulting in TTS. However, none of these hypotheses have been confirmed.
Risk group or risk factors	There are no known risk factors for the development of thrombosis with thrombocytopenia following vaccination.
Preventability	Prevention of thrombosis concurrent with thrombocytopenia in the context of COVID-19 vaccination is currently unknown. As described in Section 4.4 of the CDS, HCPs should be alert to the signs and symptoms of thromboembolism and thrombocytopenia, as well as coagulopathies. Vaccinated individuals should be instructed to seek immediate medical attention if they develop symptoms such as a severe or persistent headaches, blurred vision, confusion, seizures, shortness of breath, chest pain, leg swelling, leg pain, persistent abdominal pain, or unusual skin bruising and/or petechia a few days after vaccination.
Impact on the risk-benefit balance of the product	Thrombosis with thrombocytopenia is a potentially life-threatening event if not recognised or managed appropriately, may result in persistent or significant disability or incapacity. Thrombosis with thrombocytopenia requires immediate medical intervention.

Table 170 ***Important identified risk*** **- Thrombosis in combination with thrombocytopenia**

Characterisation	Summary
Public health impact	The public health benefit of vaccination is considered to outweigh the very rare occurrence of these events.

CDS Core Data Sheet; HCP Healthcare Professional; TTO Tine To Onset

16.4.2 Important potential risks

The following 2 safety concerns are considered as important potential risks:

- Immune-mediated neurological conditions (Section 16.4.2.1)
- Cerebrovascular venous sinus thrombosis (CVST) without thrombocytopenia (Section 16.4.2.2)

16.4.2.1 Immune-mediated neurological conditions

Table 171 ***Important potential risk - Immune mediated neurological conditions***

Characterisation	Summary
Frequency	Overall, in clinical studies there were no clinically meaningful imbalances in the incidence of neurological AESIs. In the US study, neurologic or neuroinflammatory AESIs were reported in 0.6% (121/21,587 participants) in the VAXZEVRIA (formerly AZD1222) group and 0.4% (48/10,792 participants) in the placebo group. In the pooled Oxford studies as of 07 December 2020, neurologic or neuroinflammatory AESIs were reported in 0.7% (81/12,282 participants) in the VAXZEVRIA (formerly AZD1222) group and 0.8% (90/11,963 participants) in the control group. Furthermore, in the pooled Oxford studies no clinically meaningful imbalance was noted in the incidence of AESIs of neuroinflammatory disorders, which were reported in 7 participants (0.1%) in the VAXZEVRIA (formerly AZD1222) group and 4 participants (< 0.1%) in the control group in the pooled safety dataset (any dose group). Of these, the most frequently reported events were nonserious AEs of facial paralysis occurred in 4 participants in the VAXZEVRIA (formerly AZD1222) group and 3 participants in the control group. In the US study, there were 5 nonserious AEs of facial paralysis, all in the VAXZEVRIA (formerly AZD1222) group. In the US study, there was 1 SAE of a demyelinating event: a participant in the VAXZEVRIA (formerly AZD1222) group had an AE initially reported as Guillain-Barre syndrome, which was subsequently diagnosed as an SAE of Chronic inflammatory demyelinating polyradiculoneuropathy. In the pooled Oxford studies, there were 3 SAEs of demyelinating events: 2 cases in the VAXZEVRIA (formerly AZD1222) group (1 case of transverse

Table 171 ***Important potential risk - Immune mediated neurological conditions***

Characterisation	Summary
	myelitis, and 1 case of multiple sclerosis in a participant with pre-existing, but previously unrecognised, multiple sclerosis), and 1 case of myelitis in the control group.
Potential mechanisms	Several hypothetical biologic mechanisms have been proposed to explain the pathophysiology of neurologic adverse reactions following immunisation; most involve the concept of autoimmunity and the possibility that the vaccine's immunostimulatory effect results in an aberrant immunologic response (Stratton et al 1994).
Risk groups or risk factors	There are no known risk factors for the development of immune-mediated neurological conditions following vaccination.
Preventability	Prevention of immune-mediated neurological conditions in the context of SARS-COV-2 vaccination is unknown.
Impact on the risk-benefit balance	Severe immune-mediated neurological conditions, if not recognised or managed appropriately, may result in persistent or significant disability or incapacity.
Public health impact	Immune-mediated neurological disorders are very rare, and as such the public health benefit of vaccination is considered to outweigh the very rare potential occurrences of such events.

AESI Adverse Event of Special Interest; SARS-COV-2 Severe Acute Respiratory Coronavirus 2;SAE Serious Adverse Event; US United States

16.4.2.2 Cerebrovascular venous sinus thrombosis (CVST) without thrombocytopenia

Table 172 ***Important potential risk*** **- Cerebrovascular venous sinus thrombosis (CVST) without thrombocytopenia**

Characterisation	Summary
Frequency	There were no reports of CVST identified in the VAXZEVRIA (formerly AZD1222) group in the US study (D8110C00001 [DCO: 15 March 2021] and D8111C00002 [DCO: 10 January 2021]), and in the pooled Oxford studies (COV001, COV002, COV003 and COV005; DCO: 07 December 2020). In the post-marketing setting, CVST without thrombocytopenia have been reported very rarely following vaccination with VAXZEVRIA.
Potential mechanisms	The exact mechanism of CVST without thrombocytopenia following administration with VAXZEVRIA is unknown.
Risk groups or risk factors	There are no known risk factors for the development of CVST without thrombocytopenia following vaccination.

Table 172 *Important potential risk* - Cerebrovascular venous sinus thrombosis (CVST) without thrombocytopenia

Characterisation	Summary
Preventability	Prevention of CVST without thrombocytopenia in the context of COVID-19 vaccination is currently unknown. The events of CVST without thrombocytopenia can be fatal and may require different treatment approaches than thrombosis in combination with thrombocytopenia.
Impact on the risk-benefit balance of the product	CVST without thrombocytopenia is a potentially life-threatening event, and if not recognised or managed appropriately, may result in persistent or significant disability or incapacity, and hence requires immediate medical intervention.
Public health impact	The public health benefits of vaccination are considered to outweigh the very rare occurrence of these events.

COVID-19 Coronavirus Disease of 2019; CVST- Cerebral Venous Sinus Thrombosis.

16.4.3 Missing information

The following 3 safety concerns are considered as missing information:

- Use of VAXZEVRIA in pregnant and breastfeeding women (Section 16.4.3.1)
- Use of VAXZEVRIA in subjects with severe immunodeficiency (Section 16.4.3.2)
- Use of VAXZEVRIA in subjects with severe and/or uncontrolled underlying disease (Section 16.4.3.3)

16.4.3.1 Use of VAXZEVRIA in pregnant and breastfeeding women

Evidence source

As per the VAXZEVRIA CDS Section 4.6, data from more than 400 case reports of pregnant women or women who became pregnant after receiving VAXZEVRIA do not suggest unusual patterns of pregnancy complications or foetal/neonatal outcomes. No increased risk of maternal thrombosis in combination with thrombocytopenia has been observed. Preliminary non-clinical safety studies have not indicated any concern to date, and available non-clinical, clinical and post-marketing data do not suggest a risk to breastfed newborns/infants. As VAXZEVRIA is intended for use in mass vaccination campaigns in a large proportion of the global population, the collection of pregnancy and infant outcomes data with the aim of further characterising the safety profile in this population, is still considered necessary.

Population in need of further characterisation

Although there are data in the post-marketing setting in pregnant and breastfeeding women, use of VAXZEVRIA in pregnant and breastfeeding women will continue to be investigated in

the ongoing PASS (EAS, a post-marketing observational study using existing secondary health data sources, and a pregnancy registry).

16.4.3.2 Use of VAXZEVRIA in subjects with severe immunodeficiency

Evidence source

Vaccines may be less effective in severely immunocompromised subjects, as the vaccinees weakened immune system may not mount a sufficient response; however, immunocompromised individuals may also be at greater risk of morbidity and mortality from vaccine-preventable disease, and consequently this population have been identified as a priority group for initial vaccination in several jurisdictions following vaccine availability.

Although there is no evidence that the safety profile of this population receiving VAXZEVRIA will be different to that of the general population, given the paucity of data, the possibility cannot be excluded.

Population in need of further characterisation

Use of VAXZEVRIA in subjects with severe immunodeficiency will continue to be investigated in the ongoing PASS and additional Pharmacovigilance activity (a post-marketing observational study using existing secondary health data sources and systematic literature review).

16.4.3.3 Use of VAXZEVRIA in subjects with severe and/or uncontrolled underlying disease

Evidence source

Subjects with severe and/or uncontrolled underlying disease are potentially at risk of developing a more severe manifestation of COVID-19, and as a consequence have been included as a priority group for initial vaccination in several jurisdictions following vaccine availability. Although there is no evidence that the safety profile of this population receiving VAXZEVRIA will be different to that of the general population, given the paucity of data, the possibility cannot be excluded.

Population in need of further characterisation

Use of VAXZEVRIA in patients with severe and/or uncontrolled disease will continue to be investigated in the ongoing PASS program (post-marketing observational study using existing secondary health data sources).

16.5 Effectiveness of risk minimisation

No information on the effectiveness of risk minimisation activities relevant to the benefit-risk assessment became available during the reporting period.

17 BENEFIT EVALUATION

17.1 Important baseline efficacy/effectiveness information

At the beginning of the reporting period, COVID-19 ASTRAZENECA VACCINE was authorised for the prevention of COVID-19 in adults.

A summary of the information supporting the efficacy and effectiveness in this authorised indication is provided in the sub-sections below.

17.1.1 Active immunisation of individuals ≥18 years old for the prevention of COVID-19

COVID-19 VACCINE ASTRAZENECA is able to elicit a strong immune response capable of preventing serious symptomatic infections with SARS-COV-2, the causative agent of COVID-19, a life-threatening disease, particularly in older age groups.

COVID-19 VACCINE ASTRAZENECA has been shown to be efficacious in preventing severe disease, avoiding hospitalization and death.

A summary of new information supporting the effectiveness of COVID-19 VACCINE ASTRAZENECA against COVID-19 is provided in section 17.2.1.

17.2 Newly identified information on efficacy/effectiveness

17.2.1 Newly Identified Information on immunogenicity of VAXZEVRIA against omicron obtained in Clinical Trials

During the reporting period, data analyses for Oxford studies data was conducted by AstraZeneca to estimate the efficacy of VAXZEVRIA against Omicron variant of concern. As described in detail in section 13. there were no new clinical trial efficacy data available during the reporting period.

17.3 Vaccine effectiveness of a 2 dose primary series vaccination with against dominant SARS-COV-2 variant of concern Omicron

Real world studies have demonstrated high vaccine effectiveness (VE) of a 2-dose primary series vaccination with AZD1222 against the Omicron variant in a variety of settings and populations, particularly with regard to prevention of severe disease. Table 173 summarises VE in studies that focused on severe outcomes in a general adult population (≥ 18 years) and/or an older population (≥ 65 years), during a period when Omicron was the dominant variant.

Table 173 Real-World Vaccine Effectiveness (VE) of a 2-Dose Primary Series Vaccination with AZD1222

Study	Days Post Dose 2	Outcome	Country	Population	VE	95% Lower CI	95% Upper CI	Vaccine Sequence
Kirsebom et al 2022	175+	Hospitalization	UK	65+ years	61	49.8	69.7	AZ+AZ
Stowe et al 2022	14-174	Hospitalization with ARI	UK	18-64 years	59	31.9	75.3	AZ+AZ
Stowe et al 2022	175+	Hospitalization with ARI	UK	18-64 years	53	41.7	62	AZ+AZ
Stowe et al 2022	14-174	Hospitalization with ARI	UK	≥ 65 years	71.2	50	83.4	AZ+AZ
Stowe et al 2022	175+	Hospitalization with ARI	UK	≥ 65 years	53.1	43.4	61.2	AZ+AZ
Cerqueira-Silva et al 2022	14-69	Hospitalization or death	Brazil	≥ 18 years	41	-8.1	67.8	AZ+AZ (previously infected)
Cerqueira-Silva et al 2023	140+	Hospitalization or death	Brazil	≥ 18 years	55.4	44.6	64.1	AZ+AZ (previously infected)
Cerqueira-Silva et al 2023	14-69	Hospitalization or death	Brazil	≥ 18 years	67.5	-7.9	90.2	AZ+AZ (previously infected)
Cerqueira-Silva et al 2023	140+	Hospitalization or death	Brazil	≥ 18 years	63.2	39	77.8	AZ+AZ (previously infected)
Cerqueira-Silva et al 2023	14-59	Severe disease	Brazil	≥ 18 years	77.1	72.9	80.6	AZ+AZ
Cerqueira-Silva et al 2023	150+	Severe disease	Brazil	≥ 18 years	67.8	66.7	69	AZ+AZ
Cerqueira-Silva et al 2023	60-149	Severe disease	Scotland	≥ 18 years	78.8	31.8	93.4	AZ+AZ
Cerqueira-Silva et al 2022	150+	Severe disease	Scotland	≥ 18 years	52.8	33.3	66.7	AZ+AZ

AZ AstraZeneca; ARI Acute Respiratory Infection; CI Confidence interval; VE Vaccine effectiveness.

In addition, a small study in a prison population in Zambia (including over 10.5% of individuals who were living with HIV) assessed effectiveness against infection with Omicron

(any infection or symptomatic infection). Effectiveness of an AZD1222 primary series against infection with Omicron was 89.4% (95% CI: 59.5-97.8%), whilst effectiveness against symptomatic infection with Omicron was 85.1% (95% CI: 19.5-98.0%;Simwanza et al 2022).

More recently, a public-private partnership, COVIDRIVE, reported data on the effectiveness of VAXZEVRIA against an early SARS-COV-2 ancestral variant (DELTA) and the currently predominant omicron variant of concern. COVIDRIVE was launched in the fourth quarter of 2020 to monitor VE against SARS-COV-2 by utilizing an existing vaccine effectiveness platform, DRIVE, established to obtain yearly brand-specific influenza vaccine effectiveness estimates to the European Medicines Agency (EMA). COVIDRIVE's first study is a multi-country (Belgium, Italy, Spain, and Austria) hospital-based case-control study with a test-negative case-control design (TNCC), investigating brand-specific VE against hospitalisation. A total of 561 test-positive cases and 200 test-negative controls are included in the primary analysis for the 'fully vaccinated with two doses' exposure definition. Data collection is a combination of data collected prospectively (ie. from Site Initiation Visit onwards) and data collected retrospectively (ie, prior to the Site initiation Visit). The overall data collection period is from 01 June 2021 to 05 September 2022

Disease-onset occurred between November 2021 and end of January 2022. Delta was the dominant SARS-CoV-2 variant during the initial months of the study for 44% of patients and it was also the most sequenced variant among the cases. Omicron predominated during the last eight months of the study period.

Disease-onset occurred between November 2021 and end of January 2022. Delta was the dominant SARS-CoV-2 variant during the initial months of the study for 44% of patients and it was also the most sequenced variant among the cases. Omicron predominated during the last eight months of the study period.

For Delta, the adjusted VE against COVID-19 hospitalisation for those 'fully vaccinated with two doses' is estimated at 92.9% (95% CI: -15.8; 99.6), 85.0%(95% CI: 41.3; 96.2), 71.0% (95% CI: 30.7; 87.9), and 71.8% (95% CI: 34.0; 87.9) for ≤8 weeks, ≤16weeks, ≤24 weeks and ≤32 weeks since the last dose, respectively.

For Omicron, adjusted VE against COVID-19 hospitalization for those 'fully vaccinated with two doses' is estimated at 74.8% (95% CI: -548.9; 99.1) and -9.5% (95% CI: -462.6; 78.7) for ≤24 weeks and ≤32 weeks since the last dose, respectively. The VE estimates for Omicron are to be interpreted with caution due to an insufficient sample size.

17.3.1 Real-world effectiveness of AZD1222 as a Booster against emerging variants of concern

17.3.1.1 Vaccine effectiveness of VAXZEVRIA administered as a Third Dose Booster

Real world studies have also demonstrated high VE of AZD1222 in prevention of severe outcomes when administered as a third dose in both homologous and heterologous settings during the Omicron-dominant phase of the COVID-19 pandemic.

Table 174 summarises VE against severe outcomes, again in studies in a general adult population (≥ 18 years) and/or an older population (≥ 65 years).

Table 174 Real-World Vaccine Effectiveness (VE) of a First Booster (Third Dose) Vaccination with AZD1222

Study	Days Post 1st Booster	Outcome	Country	Population	VE	95% Lower CI	95% Upper CI	Vaccine Sequence
Cerqueira-Silva et al 2022	14-69	Hospitalization or death	Brazil	≥ 18 years	84.5	79.4	88.4	AZ+AZ+AZ (previously infected)
Cerqueira-Silva et al 2022	70+	Hospitalization or death	Brazil	≥ 18 years	81.2	72.5	87.1	AZ+AZ+AZ (previously infected)
Cerqueira-Silva et al 2022	14-69	Hospitalization or death	Brazil	≥ 18 years	89.7	81.5	94.3	AZ+AZ+AZ (previously infected)
Cerqueira-Silva et al 2022	70+	Hospitalization or death	Brazil	≥ 18 years	86.3	71.6	93.4	AZ+AZ+AZ (previously infected)
Kirsebom et al 2022	7+	Hospitalization	UK	≥ 65 years	82.3	64.2	91.3	AZ+AZ+AZ
Nittayasoot et al 2022	14+	Pneumonia requiring invasive ventilation	Thailand	≥ 18 years	94.9	61.9	99.3	Sino+Sino+AZ

AZ AZD1222; CI Confidence interval; Sino COVID-19 vaccine BIBP developed by China National Biotec Group (CNBG), Sinopharm; VE Vaccine effectiveness.

In these studies, a third dose booster of AZD1222 had VE comparable to that of mRNA vaccines against emerging variants of concern.

A test-negative design study in Malaysia on third dose booster effectiveness against infection demonstrated a similar marginal VE (during Omicron-dominant period) for AZD1222 boosting on top of a Coronavac primary series versus a BNT162b2 primary series and for

BNT162b2 boosting on top of Coronavac primary series versus BNT162b2 primary series (Suah et al 2022).

A test-negative design study in Thailand on third dose and fourth dose booster effectiveness against infection reported similar adjusted VE (during Omicron-dominant period) for a third-dose booster of 3 vaccines (AZD1222 26%; BNT162b2 and mRNA-1273 both 31%;Intawong et al 2022). A fourth-dose booster increased adjusted VE to a similar extent across all 3 vaccines (AZD1222 73%; BNT162b2 and mRNA-1273 both 71%).

Another study in Thailand during the Omicron-dominant period (Nittayasoot et al 2022) used a case-control design and a nationwide database to investigate the protection conferred by COVID-19 vaccines against infection, pneumonia requiring invasive ventilation, and death. Third and fourth dose boosters with either AZD1222 or mRNA vaccines provided a high degree of protection of 87% to 100% against pneumonia requiring invasive ventilation or death, whereas 2 doses provided a moderate degree of protection (70%).

17.4 Characterisation of benefits

The original clinical development program allowed us to demonstrate robust efficacy of COVID-19 VACCINE ASTRAZENECA against SARS-COV-2 variants circulating early in the COVID-19 pandemic.

Worldwide, more than 6 billion of people have had confirmed SARS-COV-2 infection and over 13 billion doses of COVID-19 vaccines of different platform technologies were administered. In this context, it has been widely demonstrated that vaccines that are able to booster immunity in previously immunized individuals are beneficial in the control against COVID-19.

A recent estimates derived from a mathematical modelling study has recently estimated that VAXZEVRIA was responsible for saving 6 million lives (Watson et al 2022 and Airfinity 2023).

Since its original identification in November 2021 in South Africa, omicron has become the predominant SARS-COV-2 circulant variant during the reporting period of current PBRER, with over 95% of infection associated with this variant worldwide. Several sub-variants have been under monitoring to better understand their pathogenesis and potential to cause severe disease.

In addition to robust efficacy data demonstrated through Clinical Development programme, further studies found that VAXZEVRIA continues to protect against hospitalization and severe disease in the real-world setting even in the omicron era. More specifically, RWE studies have recently confirmed that, although omicron is able to escape vaccine immunity, VAXZEVRIA offers protection against omicron when administered as booster dose similarly

to vaccines using different vaccine platforms, including RNA vaccines. This was demonstrated in a large meta-analysis of 20 observational studies, consisting of 4 cohorts and 16 test-negative case-control studies from seven different Countries in North America, Europe and Middle East (Pratama et al 2022). In this study, the effectiveness of different types of vaccine (including VAXZEVRIA) against omicron was shown to be protective when administered as booster even though the protection of primary series was confirmed to be low for the same types of vaccines investigated. Furthermore, data on effectiveness of third and fourth booster of VAXZEVRIA have emerged from Thailand. This Country offers the opportunity to examine representative data from their National surveillance system that included populations vaccinated with heterologous third and fourth booster regimens with ASTRAZENCA COVID VACCINE. In a large test-negative case control study of over 27,000 individuals, they found that during omicron period, there was an increase in vaccine effectiveness from third to fourth dose when any vaccine platform was analysed, including AZTRAZENECA COVID-19 VACCINE (Intawong et al 2022).

In a large study including over 3 million records from the National health care data base in Thailand during omicron era (Nittayasoot et al 2022), the authors found in this test-negative case control study, that ASTRAZENECA COVID-19 VACCINE was able to provide protection against COVID-19 pneumonia requiring hospitalization when included in a heterologous regimen yielding VE= (92.1%; CI: 80.5-96.9) as third or fourth dose (VE=100%; CI:99.9-100).

In summary, it has been acknowledged that the robust vaccine efficacy of any COVID-19 vaccine against SARS-COV-2 reported earlier in the COVID-19 pandemic, are not reproducible against variants and sub-variants of omicron that emerged in November 2021. The currently predominant variant of SARS-COV-2, omicron, has increase transmission within populations and it has the ability to escape vaccine and natural immunity, but worsening of severity in comparison with its ancestral strains have not yet observed. ASTRAZENECA COVID-19 VACCINE remains beneficial to individuals who are vaccinated as part of heterologous regimens in the omicron era.

18 INTEGRATED BENEFIT-RISK ANALYSIS FOR APPROVED INDICATIONS

The analysis of the benefit-risk balance incorporates an evaluation of the safety and efficacy/effectiveness information that became available during the reporting period, in the context of what was known previously. This evaluation involves the following:

- Critically examining information that has emerged during the reporting period to determine whether it has generated new signals, led to the identification of new potential or identified risks, or contributed to knowledge of previously identified risks.

- Critically summarising relevant new safety and efficacy/effectiveness information that could have an impact on the benefit-risk balance.
- Conducting an integrated benefit-risk analysis for all approved indication(s) based on the cumulative information available since the DIBD (where the DIBD is unknown or AstraZeneca does not have access to data from the clinical development period, the earliest possible applicable date is used as the starting point for inclusion and evaluation of the cumulative information).
- Summarising any risk minimisation actions that may have been taken or implemented during the reporting period, as well as risk minimisation actions that are planned to be implemented.
- Outlining plans for signal or risk evaluations, including timelines and/or proposals for additional pharmacovigilance activities.

18.1 Benefit-risk context - medical need and important alternatives

A description of the medical need for VAXZEVRIA and important alternatives available is provided for each of the approved indications below.

18.1.1 Active immunisation of individuals ≥18 years old for the prevention of COVID-19

- **Medical need for the product**

Soon after the 2019 report of the then unknown pneumonia occurring in clusters of patients in Hubei province of Wuhan, Gov.cn 2023 show Detail/2019123108989], the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the causative agent of COVID-19 in January 2020 (Na Zhu 2020). Following the WHO declaration of the COVID-19 pandemic on 11 March 2020, COVID-19 has been reported in 223 Countries, devastating lives and causing economic chaos across the Globe.

As of 06 January 2023, WHO reported that worldwide, over 650 million cases of COVID-19 had been confirmed and nearly 7 million people had lost their lives to COVID-19 (WHO Coronavirus (COVID-19) Dashboard). Airfinity estimated the impact of VAXZEVRIA on lives saved to be 6.3 million based on data from Watson et al 2022.

There is a medical need to also maintain and/or increase protection in vaccinated individuals in the face of waning immunity and emerging variants of SARS-CoV-2. For many infectious diseases, multiple or additional 'booster' doses beyond those prescribed by the original vaccination protocol are a standard part of the vaccination schedule. For example, booster vaccines are given for tetanus, diphtheria, and polio (NHS 2021). Boosters can help to elevate the level of antibodies and memory immune cells, and in some instances, strengthen their potency (Callaway 2021).

As recommendations and regulatory authorizations for booster dosing with COVID-19 vaccines continue to expand, the authorization of AZD1222 for booster vaccination will help address the demand for COVID-19 vaccine doses, when a substantial number of people, particularly in low and low-to-middle income countries, have not received or completed a primary vaccination series (Ritchie et al 2020).

Later in the COVID-19 pandemic, viral mutations led to the emergence of more efficiently transmissible versions of SARS-COV-2, actively monitored by WHO and categorized as variants of interest or variants of concern, depending on their epidemiological characteristics and pathogenesis. During previous reporting (June to December 2021), AstraZeneca reported on WHO-labelled variants of concerns, ie, Alpha (B.1.1.7); Beta (B.1.351); Gamma (P.1) and Delta (B.1.617.2). The epidemiological landscaped has now changed and more recently, further mutations in SARS-COV-2 led to the identification of more (Nyberg et al 2022) rapidly transmissible Omicron variants of concern, now dominating transmission within communities worldwide (ie, Omicron BA.1, BA.2, BA.3, BA.4 and BA.5) CDC 2022.

It has been noticed that hybrid immunity conferred by a mix of natural infection and immunization is not as effective against Omicron variants in comparison with the earlier strains of SARS-COV-2. Once infected with SARS-COV-2, the majority of individuals may remain asymptomatic or will experience light to mild symptoms. When severely affected, patients may need hospitalization to primarily treat pneumonia and acute respiratory distress syndrome (ARDS). Systemic failure of multiple organs may ensue, leading to death. Certain comorbidities and older age are known to increase the risk for severe COVID-19 and death (Coopersmith et al 2021). Recently included in the therapeutic arsenal to treat COVID-19 are: antiviral medications (eg, molnupiravir, ritonavir in combination with nirmatrelvir, remdesivir), anti-SARS-CoV-2 monoclonal antibodies (eg, Evusheld (Tixagevimab and cilgavimab), sotrovimab), anti-inflammatory drugs (eg, dexamethasone), and immunomodulators agents (eg, baricitinib, tocilizumab). Although the contribution of the available therapeutic armamentarium towards the treatment of Covid-19 or prophylaxis from infection is significant and growing as new therapeutics are being developed, vaccines to prevent severe COVID-19 and death remain the primary agents of choice to control the COVID-19 pandemic.

Important alternatives available

Following the WHO declaration of the COVID-19 pandemic on 11 March 20, acceleratedvaccine development began worldwide to prevent infection with the causative agent, SARS-COV-2. Until the end of the reporting period (28 June 2022), 344 Covid-19 vaccine candidates had either been developed or were in development. (London School of Hygiene & Tropical Medicine).

Currently, five main technologies are included in approved worldwide: messenger RNA [mRNA], viral-vectored, inactivated whole virus, protein subunit, and plasmid DNA approaches (Nohynek and Wilder 2022). VAXZEVRIA is among vaccines that do not need added adjuvant to enhance immune response, unlike some whole-virus and protein subunit vaccines.

Apart from VAXZEVRIA, there are 5 other vaccines are currently approved in the EU/EEA and UK: Comirnaty (Pfizer), Spikevax (Moderna), Nuvaxovid (Novavax), JCOVDEN (Janssen), and VLA2001 (Valneva) and VidPrevtyn Beta (Sanofi Pasteur).

18.2 Benefit-risk analysis evaluation

An evaluation of the benefit-risk profile for the use of VAXZEVRIA in authorised indications cited in Section 17.1 (Important baseline efficacy/effectiveness information) is provided below.

18.2.1 Active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older

18.2.1.1 Context of use of the medicinal product

Since its identification in South Africa in November/2021, the SARS-COV-2 omicron variant spread rapidly across continents and, together with various subvariants, is now the predominant variant of concern sustaining the COVID-19 pandemic. As it was reported in the previous PBRER, active primary immunizations against SARS-COV-2 omicron variant failed to demonstrate efficacy against symptomatic infection with SARS-COV-2, regardless the brand of COVID-19 vaccine investigated in clinical trials [WHO Coronavirus Dashboard]. Nonetheless, it has been demonstrated that COVID-19 ASTRAZENECA vaccine continues to protect against hospitalization, severe disease and death as described in section 17.1.

Currently, over 13 billion of doses of vaccines of any technology were administered to the world population (WHO Coronavirus (COVID-19) dashboard 2023). A mathematical modelling study performed to estimate the number of deaths avoided by vaccination before the omicron era, estimated that nearly 20 million of deaths were averted following the introduction of a handful of COVID-19 vaccination programmes around the world up to the end of year 2021 (Watson et al 2022). As part of Covid-19 Vaccines Global Access (COVAX) vaccination programme to distribute COVID-19 vaccines to Low- And Middle-Income Countries (LMIC), ASTRAZENECA vaccine will have contributed to avert millions of deaths worldwide. In Brazil alone, a Country that utilized Coronavac and ASTRAZENECA COVID-19 vaccine in their first year at the start of the immunization campaign, a significant number of deaths due to COVID-19 were averted in the first year of the national vaccination campaign (Santos et al.2023).

There has been no new data or information received during the reporting period that impacts the previously established efficacy and effectiveness of COVID-19 VACCINE ASTRAZENECA in the approved indication of prevention of COVID-19 in adults 18 years of age and older.

18.2.1.2 Considerations relating to key benefit(s)

ASTRAZENECA COVID-19 vaccine was developed to address an urgent public health need. As the pandemic evolve, world-wide efforts to develop effective vaccines against the omicron SARS-COV-2 variant of concern are ongoing.

The COVID-19 VACCINE ASTRAZENECA vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks after the first dose. It is recommended that individuals who receive a first dose of COVID-19 VACCINE ASTRAZENECA complete the vaccination course with COVID-19 VACCINE ASTRAZENCA. A booster dose (third dose) of 0.5 ml may be given to individuals who completed the primary vaccination course with COVID-19 VACCINE ASTRAZENECA at least 3-months after completing the primary 2-dose vaccination course (homologous boosting). COVID-19 VACCINE ASTRAZENECA may be given as a booster dose after completion of a primary vaccination course with any other COVID-19 vaccine (heterologous boosting).

The repeated and on-going waves of COV-SARS-2 infections in the form of the evolving Omicron variants around the globe continue to present a challenge. In particular the ability of the Omicron variants to evade vaccine generated immunity is of concern. In this respect, data from RWE studies (see section 17.4) have become available that support the effectiveness of VAXZERVIA when administered as a fourth dose booster against progression to severe disease, hospitalization and death.

18.2.1.3 Considerations relating to risk

The important identified risks associated with VAXZEVRIA are characterised in detail in Section 16.4.

Considerations regarding the key important identified and potential risks are summarized below:

- **Thrombosis in combination with thrombocytopenia**: A very rare and serious combination of thrombosis and thrombocytopenia, including thrombosis with thrombocytopenia syndrome (TTS), in some cases accompanied by bleeding, has been observed following vaccination with VAXZEVRIA during post-authorisation use. The majority of the events occurred within the first 21 days following vaccination and some events had a fatal outcome. The reporting rates after the second dose are lower compared to the first dose. No new or emerging concern regarding TTS has been identified with booster doses of AZD1222. Based on the available data, thrombosis in combination with

thrombocytopenia is considered a very rare adverse reaction of VAXZEVRIA. The CDS reflects AstraZeneca's position on this risk.

- **Immune-mediated neurological conditions:** There is a theoretical concern that vaccination could be associated with immune-mediated neurological conditions. Very rare events of demyelinating disorders were reported in the VAXZEVRIA clinical development programme and in the post-marketing use, however, there is no evidence suggesting a causal relationship between VAXZEVRIA and demyelinating disorders. Severe neurological conditions may result in persistent or significant disability or incapacity and require early detection, careful monitoring, and timely medical intervention. CDS reflects AstraZeneca's position on this risk.
- **CVST without thrombocytopenia:** Events of cerebrovascular venous and sinus thrombosis (CVST) without thrombocytopenia have been reported very rarely in the post-authorisation setting following vaccination with VAXZEVRIA. The exact mechanism of CVST without thrombocytopenia following administration with VAXZEVRIA is unknown. There are no known risk factors for the development of CVST without thrombocytopenia following vaccination. Events of CVST without thrombocytopenia may require different treatment approaches than thrombosis in combination with thrombocytopenia (eg, use of heparin or warfarin). Based on the available data, a causal association has not been established between VAXZEVRIA and CVST without thrombocytopenia. However, such events are considered an important potential risk and CDS reflects AstraZeneca's position on this risk.
- **Vaccine-associated enhanced disease (VAED) / Vaccine-associated enhanced respiratory disease (VAERD):** This safety concern is currently theoretical in relation to VAXZEVRIA administration, and based on the available data, a causal association has not been established between VAXZEVRIA and VAED / VAERD. Therefore, there is no public health impact noted at this time.

The significance of the information that became available during the reporting period has been evaluated in the context of what was known previously. An integrated evaluation of the key benefits and risks continue to suggest an overall positive benefit-risk profile for the use of VAXZEVRIA. The data gathered during the reporting period of this PBRER did not provide any additional evidence which would alter the efficacy or safety evaluation of VAXZEVRIA

18.2.1.4 Strengths, weaknesses, and uncertainties of the evidence

AZD1222 confers a strong immunogenicity response when administered as a booster both in the homologous or heterologous primary series settings and considered safe for use. The accumulating evidence of the effectiveness of VAXZEVRIA against the landscape of constantly mutating omicron variants indicates that booster doses continue to provide significant protection against progression to severe disease, hospitalization and associated mortality. This evidence is derived primarily from RWE studies (see section 17.4) coming from disparate locations across the world.

18.2.1.5 Methodology and reasoning used to develop the benefit-risk evaluation

A qualitative assessment of the benefit-risk balance for the use of VAXZEVRIA for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals >18 years of age has been performed.

The basis for efficacy of Vaxzevia given as a primary series has already been provided in previous PBRERs. Evidence primarily from RWE studies indicates that booster doses of Vaxzervia (3rd and/or 4th doses) continue to safeguard and provide a considerable degree of protection against critical outcomes such as progression to severe disease, hospitalization and death.

AstraZeneca's pharmacovigilance system provides the framework for the identification of any risks associated with the use of VAXZEVRIA in the approved indication. All information that has emerged during the reporting period has been reviewed and evaluated by AstraZeneca, irrespective of reporting source, seriousness, or causality. This has included an analysis of clinical trials, literature studies, safety topics that are kept under close surveillance, as well as an assessment of any new safety issues.

The significance of the information that became available during the reporting period has been evaluated in the context of what was known previously. An integrated evaluation of the key benefits and risks give an overall positive benefit-risk profile for the use of VAXZEVRIA.

The data gathered during the reporting period of this PBRER did not provide any additional evidence which would alter the efficacy or safety evaluation of VAXZEVRIA.

19 CONCLUSIONS AND ACTIONS

VAXZEVRIA is used for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals >18 years of age, as described in the previous sections.

There has been no new efficacy related information received during the reporting period that impacts previously established efficacy and effectiveness of VAXZEVRIA in the approved indication. VAXZEVRIA confers a strong immunogenicity response when administered as a booster both in the homologous or heterologous primary series settings and considered safe for use.

During the reporting period, CDS Section 4.8 (undesirable effects) was updated to include ADRs Tinnitus with a frequency of 'uncommon', Cutaneous vasculitis with a frequency of 'not known' and Immune thrombocytopenia with a frequency of 'not known', and CDS section 4.4 (Special warnings and special precautions for use) was updated with the addition of relevant text of thrombocytopenia including immune thrombocytopenia.

After the DLP, based on a review of safety data from the final pooled clinical studies (COV001, COV002, COV003, COV005) DCO3, the signal Decreased appetite was validated. VAXZEVRIA CDS is currently in the progress to be updated to include Decreased appetite as ADR in Section 4.8 with frequency of 'uncommon' and also section 4.8 of the CDS will be updated with the frequency changes for Dizziness, Abdominal pain, Vomiting, Pain extremity and Urticaria.

The summary of safety concerns were reclassified during the reporting period in the Core RMP (version 8), the important potential risk of VAED and the missing information the 'use of AZD1222 with other vaccines' were removed from the list of safety concerns.

The benefit of vaccination VAXZEVRIA has been weighed against the safety experience in the clinical programmes as well from post-authorization use. The data received during this reporting period, combined with analyses of the cumulative efficacy and safety data available, does not indicate a change in the positive benefit-risk profile of VAXZEVRIA. It is AstraZeneca's opinion that the information in the current document and the CDS accurately reflects the known benefit-risk profile for VAXZEVRIA.

20 APPENDICES TO THE PBRER

A full list of Appendices and Regional Appendices is provided in the List of Appendices presented in the Table of Contents.

Where submitted, Regional Appendices R1 to R8 provide information meeting local requirements.

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