EMA/853699/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on the renewal of the marketing authorisation assessment report

Procedure no.: EMEA/H/C/005735/R/0137

Invented name: COMIRNATY

Common name: COVID-19 mRNA vaccine (nucleoside-modified)

Marketing authorisation holder (MAH): BioNTech Manufacturing GmbH

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	18 Jul 2022	18 Jul 2022
☐	CHMP and PRAC Rapporteurs Joint Assessment Report	16 Aug 2022	16 Aug 2022
☐	CHMP and PRAC members comments	22 Aug 2022	22 Aug 2022
☐	Updated CHMP and PRAC Rapporteurs Joint Assessment Report	25 Aug 2022	n/a
☐	PRAC endorsed relevant sections of the assessment report	01 Sep 2022	01 Sep 2022
☒	Opinion	15 Sep 2022	15 Sep 2022

Table of contents

1. Background information on the renewal

The European Commission issued on 21 December 2020, a conditional marketing authorisation (MA) for Comirnaty. This implied that, pursuant to Article 14-a of Regulation (EC) No 726/2004 and Article 5 of Commission Regulation (EC) No 507/2006, the marketing authorisation holder (MAH) has to complete ongoing studies, or to conduct new studies, as listed in Annex II.E of the MA, the so-called Specific Obligations (SOBs). These data form the basis of the renewal of the conditional MA.

A conditional MA is valid for one year and may be renewed annually upon request by the MAH. Therefore, pursuant to Article 14-a of Regulation (EC) No 726/2004 and Article 6(2) of Commission Regulation (EC) No 507/2006, the MAH BioNTech Manufacturing GmbH, submitted to the Agency on 17 June 2022 an application for renewal of the conditional marketing authorisation for Comirnaty. The expiry date of the MA is 21 December 2022.

The period covered by this annual renewal is 30 April 2021 to 29 April 2022.

2. Specific Obligations

2.1. Specific Obligations adopted by the CHMP at time of initial marketing authorisation

Table 1. Full list of SOBs as adopted with the initial marketing authorisation

Number	Description	Due date
SOB 001	In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data.	July 2021
SOB 002	In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications.	July 2021
SOB 003	In order to confirm the consistency of the finished product manufacturing process, the MAH should provide additional validation data.	March 2021
SOB 004	In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0315.	July 2021
SOB 005	In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159.	July 2021
SOB 006	In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591001.	Dec 2023

One new clinical specific obligation was introduced during the reporting period:

- SOB 007: In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591007

The following table provides a full overview of the current status of fulfilment for all specific obligations.

Table 2. Full overview of the current status of fulfilment for all specific obligations

Number	Description	Status
SOB 001	In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data.	Fulfilled
SOB 002	In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications.	Fulfilled
SOB 003	In order to confirm the consistency of the finished product manufacturing process, the MAH should provide additional validation data.	Fulfilled
SOB 004	In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0315.	Fulfilled
SOB 005	In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159.	Fulfilled
SOB 006	In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591001.	Pending: Dec 2023
SOB 007	In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591007	Pending: Dec 2024

2.2. Outstanding Specific Obligations – Status report for period covered

Since the granting of the conditional MA, the MAH has submitted the following data regarding the SOBs:

Table 3. Detailed overview of the current status of fulfilment for all specific obligations

SOB Number	Description (scope)	Due date indicated in Annex II	Date of submission	Date of resolution (if applicable)	Current status
Specific Obligation 1 (SO1)	In order to complete the characterisation of the active substance and finished product, the MAH should provide additional data.	July 2021	02.08.2021	17.02.2022	Fulfilled
SO1 (a)	Additional data is to be provided to further characterise the truncated and modified mRNA species present in the finished product. Data are expected to cover batches used in clinical trials (for which the characterisation data could be available earlier) and the PPQ batches. These data should address results from ion pairing RP-HPLC addressing 5'cap levels and presence of the poly(A) tail. These data should further address the potential for translation into truncated S1S2 proteins/peptides or other proteins/peptides. Relevant protein/peptide characterization data for predominant species should be provided. Any homology between translated proteins (other than the intended spike protein) and human proteins that may, due to molecular mimicry, potentially cause an autoimmune process should be evaluated.	July 2021	02.08.2021	17.02.2022	Fulfilled
SO1 (b)	The analysis of the main peak of the RNA integrity test representing the full-length RNA, should be also undertaken addressing 5'cap levels and presence of the poly (A) tail.	July 2021	02.08.2021	17.02.2022	Fulfilled

SOB Number	Description (scope)	Due date indicated in Annex II	Date of submission	Date of resolution (if applicable)	Current status
SO1 (c)	Additional data for the active substance are to be provided to confirm the identities of the observed Western Blot (WB) bands obtained by the in vitro expression assay. Protein heterogeneity, resulting in broad bands on the WB and uncertainties in the theoretical intact molecular weight of the spike protein, is assumed to be due to glycosylation. Therefore, to further confirm protein identities, enzymatic deglycosylation of the expressed proteins followed by WB analysis should be performed. Correlation with the calculated molecular weights of the intact S1S2 protein should be demonstrated	July 2021	02.08.2021	17.02.2022	Fulfilled
Specific Obligation 2 (SO2)	In order to ensure consistent product quality, the MAH should provide additional information to enhance the control strategy, including the active substance and finished product specifications.	July 2021	02.08.2021	17.02.2022	Fulfilled
SO2 (a)	The active substance and finished product specifications acceptance limits should be re-assessed and revised as appropriate, as further data becomes available from ongoing clinical trials and in line with manufacturing process capability and stability data of the product. Comprehensive data should be provided comprising batch analyses of a suitable number of commercial batches as well as analyses of batches that	July 2021	02.08.2021	17.02.2022	Fulfilled

SOB Number	Description (scope)	Due date indicated in Annex II	Date of submission	Date of resolution (if applicable)	Current status
	have been used in the (ongoing) clinical trials.				
SO2 (b)	Poly(A) tail length is considered a critical attribute, which should be controlled on each batch, even though comparable results were obtained until now. An active substance specification to control poly(A) length should be introduced. A suitable method should be developed and appropriate acceptance criteria should be set.	July 2021	02.08.2021	17.02.2022	Fulfilled
SO2 (c)	The poly(A) tail percentage is considered a critical attribute, but uncertainties remain on the suitability of the method. Additional data should be provided to support the suitability of the method used for %poly(A) tail or an alternative suitable assay should be developed and introduced. The %poly(A) tail should be characterised following any future active substance process changes.	July 2021	02.08.2021	17.02.2022	Fulfilled
SO2 (d)	Since mRNA integrity and polydispersity are CQAs for the efficacy of the medicinal product, the finished product acceptance criteria for these parameters should be revised as further data becomes available from ongoing clinical trials and in line with manufacturing process capability.	July 2021	02.08.2021	17.02.2022	Fulfilled

SOB Number	Description (scope)	Due date indicated in Annex II	Date of submission	Date of resolution (if applicable)	Current status
SO2 (e)	Additional data should be provided to support the suitability of the method used for potency determination or an alternative suitable assay for this purpose should be developed and introduced. Then the finished product acceptance criteria for potency should be revised accordingly.	July 2021	02.08.2021	17.02.2022	Fulfilled
SO2 (f)	Lipid-related impurities should be further evaluated. An appropriate control strategy should be introduced, suitably justified and provided for assessment during Q2 2021.	July 2021	26.07.2021	16.12.2021	Fulfilled
Specific Obligation 3 (SO3)	In order to confirm the consistency of the finished product manufacturing process, the MAH should provide additional validation data.	March 2021	29/03/2021	20.05.2021	Fulfilled
SO3 (a)	Full commercial scale finished product PPQ-batches will be manufactured at the commercial facility Pfizer Puurs, Belgium. The applicant should provide the summary report on the completed commercial scale process validation activities.	March 2021	29/03/2021	20.05.2021	Fulfilled
SO3 (b)	The applicant should perform testing of future process validation-batches of finished product according to the extended comparability testing protocol and the results should be provided for assessment.	March 2021	29/03/2021	20.05.2021	Fulfilled
Specific Obligation 4 (SO4)	In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional	July 2021	06/01/2021 26/07/2021	16.12.2021	Fulfilled

SOB Number	Description (scope)	Due date indicated in Annex II	Date of submission	Date of resolution (if applicable)	Current status
	information about the synthetic process and control strategy for the excipient ALC-0315.				
SO4 (a)	A detailed description of the chemical synthesis of ALC-0315 (e.g. information on reagents and process conditions) should be provided.	January 2021	06/01/2021	27.01.2021	Fulfilled
SO4 (b)	Differences in the manufacturing process between two suppliers should be described and possible impact on impurity profile should be discussed by July 2021.	July 2021	26/07/2021	16.12.2021	Fulfilled
SO4 (c)	Information and justification of quality control of starting materials (e.g. general synthetic route, supplier and specifications) and solvents should be provided.	July 2021	26/07/2021	16.12.2021	Fulfilled
SO4 (d)	Information and justification on critical steps and intermediates (including specifications) should be provided.	July 2021	26/07/2021	16.12.2021	Fulfilled
SO4 (e)	Specified impurities should be further evaluated and appropriate specification limits for individual impurities should be included when more data are available. Acceptance criteria for specified and un-specified impurities should be added to the specification for ALC-0315 and should also be evaluated during stability studies.	July 2021	26/07/2021	16.12.2021	Fulfilled
SO4 (f)	The specification limit for total impurities should be re-evaluated as more batch data becomes available and revised, as appropriate.	July 2021	26/07/2021	16.12.2021	Fulfilled

SOB Number	Description (scope)	Due date indicated in Annex II	Date of submission	Date of resolution (if applicable)	Current status
SO4 (g)	The specification limit for assay should be tightened based on the provided batch data to improve the quality control strategy of the finished product.	July 2021	26/07/2021	16.12.2021	Fulfilled
SO4 (h)	Detailed method validation reports for assay, impurities, and residual solvents for ALC-0315 should be provided.	July 2021	26/07/2021	16.12.2021	Fulfilled
SO4 (i)	Results of stability studies in accordance with ICH guidelines should be provided.	July 2021	26/07/2021	16.12.2021	Fulfilled
Specific Obligation 5 (SO5)	In order to confirm the purity profile and ensure comprehensive quality control and batch-to-batch consistency throughout the lifecycle of the finished product, the MAH should provide additional information about the synthetic process and control strategy for the excipient ALC-0159.	July 2021	06/01/2021 26/07/2021	16.12.2021	Fulfilled
SO5 (a)	A detailed description of the chemical synthesis of ALC-0159 (e.g. information on reagents and process conditions) should be provided.	January 2021	06/01/2021	27.01.2021	Fulfilled
SO5 (b)	Information and quality control of starting materials (e.g. general synthetic route, supplier and specifications) and solvents should be provided. Relevant acceptance criteria for molecular weight and polydispersity should be included in the specification for the starting material carboxy-MPEG.	July 2021	26/07/2021	16.12.2021	Fulfilled
SO5 (c)	Information and justification of critical steps and intermediates (including specifications) should be provided.	July 2021	26/07/2021	16.12.2021	Fulfilled

SOB Number	Description (scope)	Due date indicated in Annex II	Date of submission	Date of resolution (if applicable)	Current status
SO5 (d)	The specification limit for assay should be tightened based on batch data in order to provide a more stringent quality control of the finished product.	July 2021	26/07/2021	16.12.2021	Fulfilled
SO5 (e)	Specified impurities should be further evaluated and appropriate specification limits for individual impurities should be included when more data are available. Acceptance criteria for specified and un-specified impurities should be added to the specification for ALC-0159 and should also be evaluated during stability studies.	July 2021	26/07/2021	16.12.2021	Fulfilled
SO5 (f)	The specification limit for total impurities should be re-evaluated as more batch data are available and revised, as appropriate.	July 2021	26/07/2021	16.12.2021	Fulfilled
SO5 (g)	Acceptance criteria for tetrahydrofuran should be added to the specification for ALC-0159, unless otherwise justified, as it is included as a solvent in step 2 of the synthesis.	January 2021	06/01/2021	27.01.2021	Fulfilled
SO5 (h)	Detailed method validation reports for assay, impurities and residual solvents for ALC-0159 should be provided.	July 2021	26/07/2021	16.12.2021	Fulfilled
SO5 (i)	Results of stability studies in accordance with ICH guidelines should be provided.	July 2021	26/07/2021	16.12.2021	Fulfilled
Specific Obligation 6 (SO6)	In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591001.	December 2023			Pending

SOB Number	Description (scope)	Due date indicated in Annex II	Date of submission	Date of resolution (if applicable)	Current status
Specific Obligation 6 (SO7)	In order to confirm the efficacy and safety of Comirnaty, the MAH should submit the final Clinical Study Report for the randomized, placebo-controlled, observer-blind study C4591007.	December 2024			Pending

Quality SOBs (SOB 001, SOB 002, SOB 003, SOB 004 and SOB 005)

During the period covered by this annual renewal, data on the quality SOBs have been submitted and assessed. The CHMP is of the view that all quality SOBs adopted with the initial marketing authorisation have been fulfilled.

Clinical SOBs (SOB 006 and SOB 007)

The MAH believes that as of now, comprehensive data are available from multiple sources, including but not limited to clinical trials, exhaustively informing about the safety, reactogenicity, immunogenicity and efficacy of Comirnaty and supporting the favourable benefit/risk profile of in all approved populations.

The MAH has therefore requested to take the opportunity of the present renewal of Comirnaty's conditional marketing authorisation to remove the submission of the final Clinical Study Reports of studies C4591001 and C4591007 from the list of specific obligations and to adopt an opinion recommending the granting of a marketing authorisation in accordance with Article 14(1) of Regulation (EC) No 726/2004 ('marketing authorisation not subject to specific obligations').

The MAH's justification for the request above has been assessed in the post authorisation measure procedures EMEA/H/C/005735/SOB/043 and EMEA/H/C/005735/SOB/044.

Considering the vaccination of a large proportion of the control arm patients in study C4591001, which was unavoidable, it is agreed that the continued follow-up would no longer be informative on the safety and efficacy profile of Comirnaty. Thus, the MAH's justification for early termination of study C4591001 is considered justified. Similarly, due to further interventions after the primary series, is not expected that the remaining outstanding data from study C4591007 will alter the benefit-risk profile of Comirnaty for the presently approved use in paediatric subjects.
Therefore, the justification for removal of study C4591001 and study C4591007 from the list of specific obligations is considered acceptable by the Committee.

In summary, it is not expected that the remaining outstanding data from study C4591001 and study C4591007 will bring substantial additional confirmatory evidence impacting the benefit-risk profile of Comirnaty in the respective age groups. The remaining clinical SOBs may therefore be reclassified as category 3 studies in the RMP, with the final CSRs to be submitted at a later stage as supportive data, notwithstanding the premature closure of the dedicated studies.

As part of this annual renewal the CHMP is of the opinion that SOBs 006 and 007 can therefore be deleted

from Annex II.

2.3. Overall conclusion on Specific Obligations

During the period covered by this annual renewal, new data on all SOBs have been generated. The new data provided to address the SOBs are compliant in terms of adherence to deadlines and have been considered acceptable to address the SOBs. All quality SOBs are now considered fulfilled. The clinical safety profile, as well as the efficacy of this product, is considered comprehensively characterised and supportive of a positive benefit-risk balance. The clinical SOBs 006 and 007 may therefore be reclassified as category 3 studies in the RMP and deleted from Annex II, with the final CSRs to be submitted at a later stage as supportive data.

3. Additional scientific data provided relevant for the assessment of the benefit/risk balance

3.1. Quality

All SOBs on quality have been fulfilled during the period from 30 April 2021 until 29 April 2022.

The major variations submitted to solve the SOBs are listed in Table 4. Information on the data submitted and the conclusions drawn can be found in the corresponding assessment reports.

Table 4. Variations submitted to fulfil the SOBs on quality issues

Number	Variations submitted to fulfil the SOBs
SOB 001	EMEA/H/C/005735/II/0056/G
SOB 002	EMEA/H/C/005735/IB/0031/G, EMEA/H/C/005735/II/0054/G, EMEA/H/C/005735/II/0056/G
SOB 003	EMEA/H/C/005735/II/0023/G
SOB 004	EMEA/H/C/005735/II/0003/G, EMEA/H/C/005735/IB/0031/G, EMEA/H/C/005735/II/0054/G
SOB 005	EMEA/H/C/005735/II/0003/G, EMEA/H/C/005735/II/0054/G

3.2. Clinical efficacy

3.2.1. Specific Obligations

During the period covered by this annual renewal, data on the remaining clinical SOBs have been submitted as follows:

- SO6: An Interim Clinical Study Report for study C4591001 has been submitted with the dossier for the Conditional Marketing Application.

- Further updates to the C4591001 CSR have been submitted to the Marketing Authorization with Variation EMEA/H/C/005735/II/0030 (submitted 30 Apr 2021) and Variation EMEA/H/C/005735/II/0036 (submitted 18 May 2021), reporting the data in subjects 12-15 years old and the 6-months post-dose-2 update for study subjects 16 and above, respectively.
- After the first annual renewal of the CMA (submitted 18 June 2021), further updates to the C4591001 CSR have been submitted to the Marketing Authorization of Comirnaty with Variation EMEA/H/C/005735/II/0067 (submitted 02 September 2021) and Variation EMEA/H/C/005735/II/0102 (submitted 23 December 2021) reporting data on the 3rd dose (booster) post-dose-2 and the 6-months post-dose-2 update for subjects 12-15 years of age, respectively.

- SO7: The Specific Obligation (SO) 7 relevant to the completion of study C4591007 was added on 26 November 2021 with the approval of procedure EMEA/H/C/005735/X/0077 extending the indication starting from paediatric subjects 5 years and older. This was recommended in the Assessment Report of the above procedure, considering the limited safety data and limited duration of follow-up available at the time of CHMP Opinion. The intent of the SO introduced with this procedure was to confirm the efficacy and safety of Comirnaty in this paediatric indication and ensure delivery of the final study report for the paediatric study C4591007, which has also been included in the RMP as Category 2 study accordingly.
    - An update to the C4591007 CSR has been submitted to the Marketing Authorization with Variation EMEA/H/C/005735/II/0129 (submitted 12 May 2022), reporting the 1-month post-dose-3 data for study subjects 5-11 years of age.

3.3. Clinical safety

The MAH submitted the Addendum to the Clinical Overview (ACO), covering the period from 30 April 2021 until 29 April 2022.

Worldwide Marketing Authorisation Status

BNT162b2 received the first temporary authorisation for emergency supply under regulation 174 in the UK on 01 December 2020.

BNT162b2 received the first regulatory conditional marketing authorisation approval for use in individuals 16 years and older in Switzerland on 19 December 2020 and in the EU on 21 December 2020.

Actions Taken for Safety Reasons During the Period Covered Since the Last Renewal

Actions taken for safety reasons during the reporting interval are summarised in the table below and include actions taken from the beginning of the reporting period of this ACO through the DLP of the most recently PSUR submitted in the EU. There were no actions taken following the DLP of the most recent PSUR submitted in the EU up to the DLP of this ACO. The last PSUR submitted in the EU covered the reporting interval 19 June 2021 through 18 December 2021.

Table 5. Regulatory Actions Taken for Safety Reasons During the Reporting Interval

Issue	Country	Action Taken	Date
Actions Taken from the Beginning of the Reporting Period of this ACO through DLP of the most recently PSUR submitted (19 June 2021 through 18 December 2021)			
Final recommendation from PRAC on the myocarditis, pericarditis signal for the BNT162b2 (EMEA/H/C/5735/SDA/032)	EU	A joint DHPC for both Comirnaty and Spikevax, distributed in all Member States, Amendment to the Product Information (Variation EMEA/H/C/005735/II/050, already effective, introducing myocarditis and pericarditis in sections 4.4 and 4.8 of the SmPC).	08 July 2021
Risk of myocarditis and pericarditis (Joint DHPC Pfizer and Moderna)	Switzerland	With Decision dated 30 July 2021 Swissmedic requested a joint DHPC (Pfizer, Moderna) on myocarditis/pericarditis. Distribution of DHPC 12 August 2021. The label was updated in parallel, approval from Swissmedic on 3 August 2021.	Distribution of DHPC on 12 August 2021
Risk of myocarditis and pericarditis Brazilian Health Authority (ANVISA)	Brazil	A DHPC was issued to ensure that HCPs are aware of the risk for myocarditis and pericarditis associated with COVID-19 mRNA vaccine use.	08 December 2021

Significant Changes to the Reference Safety Information

The RSI for this ACO is the COVID-19 mRNA Vaccine CDS version 12.0 dated 23 March 2022 in effect at the end of the reporting interval. There were 9 previous CDS versions in effect during the reporting interval.

The safety-related changes made to the RSI during the reporting interval are summarised in the table below.

Table 6. Safety-Related Changes Made to the RSI During the Reporting Interval

Safety-Related Changes made to the RSI during the Reporting Interval Covered through the DLP of the most recently submitted PSUR (19 June 2021 through 18 December 2021)

Section Number	Revision Type	Revision
19 May 2021 version 4.0		
4.4	Addition	Stress-related responses under General recommendations
4.8	Modification	Decreased appetite, Lethargy, Hyperhidrosis, Night sweats, Asthenia were added to Table 1 (clinical trial experience); Anaphylaxis, Hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema) were removed from Table 1. Anaphylaxis, Hypersensitivity reactions (e.g., rash, pruritus, urticaria, angioedema) were added to Table 2 (post-marketing experience).
Appendix A, Appendix B, Appendix C	Addition	Table A-1 (ADR and frequency in participants 16 years of age and older) Table A-2 (ADR and frequency in participants 12 through 15 years of age) Table B-1 (ADR by frequency category in participants 16 years of age and older) Table B-2 (ADR by frequency category in participants 12 through 15 years of age) Table C-1 (Frequency and percentage of solicited local reactions in HIV positive participants 16 years of age and older) Table C-2 (Frequency and percentage of solicited systemic reactions in HIV positive participants 16 years of age and older).
14 July 2021 version 5.0		
4.4	Addition	Myocarditis and pericarditis under General recommendations
08 September 2021 version 7.0		
4.8 Appendix A, Appendix B	Addition	Booster dose (third dose) data for participants 16 years of age and older. Table A-3 (ADR and frequency – Booster safety population) Table B-3 (ADR by frequency category – Booster safety population)
19 October 2021 version 8.0		
4.2	Addition	Tris/Sucrose 10 mcg presentation for individuals 5 through <12 years of age.
4.8	Addition	C4591007 paediatric data for participants 5 through <12 years of age after 2 doses.
5.1	Addition	Immunogenicity data after 2 doses, in paediatric participants aged 5 through <12 years
Appendix A, Appendix B	Addition	Table A-4 (ADR and frequency in paediatric participants 5 through <12 years of age) Table B-4 (ADR and frequency category in paediatric participants 5 through <12 years of age).

Relevant Safety-Related Changes Made to the RSI following the DLP of the last PSUR submitted up to the DLP of this ACO

Section Number	Revision Type	Revision
21 December 2021 version 10.0		
4.8	Addition	Updated booster information for participants 16 years of age and older.

5.1	Addition	Updated vaccine efficacy information after booster dose in participants 16 years of age and older.
Appendix A, Appendix B	Addition	Table A-5 (ADR and frequency from C4591031 – Booster safety population) Table B-5 (ADR and frequency category for participants 16 years of age and older from C4591031).
14 January 2022 version 11.0		
4.8	Addition	Updated long-term safety follow-up study participants' number.
5.1	Addition	Updated vaccine efficacy information after second dose in adolescents 12 through 15 years of age Vaccine efficacy information after second dose in children 5 through <12 years of age.

The MAH also reported that **after the DLP of this ACO**, the CDS has been further updated (CDS version 13.0 dated 10 May 2022) reflecting the 5 through <12 years old booster inclusion.

Table 7. Safety-Related Changes Made to the RSI after the DLP of the ACO

Section Number	Revision Type	Revision
10 May 2022 version 13.0		
4.2	Addition	Booster dose in 5 through <12 year olds.
4.8	Addition	Safety profile in children 5 through <12 years after booster dose.
5.1	Addition	Immunogenicity data (including Omicron variant) in children 5 through <12 years after booster dose.
Appendix A, Appendix B	Addition	Table A-6 (ADR and frequency in participants 5 through <12 years of age after booster dose). Table B-6 (ADR by frequency category in participants 5 through <12 years after booster dose)

Post DLP, an updated version of the EU SmPC was approved on 04 May 2022 by EMA.
This updated version includes the introduction of heterologous booster after adenoviral vector vaccines and mRNA vaccines in the primary course in adults and the reduction of the interval between primary vaccination course and booster vaccination from currently 6 months to 3 months.

The SmPC is in line with the CDS.

As an outcome of the 14th Summary Safety Report (MEA 002.13), the MAH was requested to submit a variation (or justify otherwise) within 30 days to update the occurrence of myocarditis as more information is available in the age group 5-11 years and to update the statement in the SmPC section 4.4 regarding the risk of myocarditis after a third dose of Comirnaty. For this, the MAH has submitted the type II variation (EMEA/H/C/005735/II/0141).

Patient exposure

Clinical studies

Cumulatively through 21 April 2022, 63,910 participants have participated in the BNT162b2 clinical development program comprising several clinical candidates, as outlined below:

- BNT162b2: 56,795 participants of which
    - 30,631 had received BNT162b2;
    - 25,205 had received BNT162b2 post-unblinding and had received placebo before;
    - 959 had received BNT162b2/placebo.
- Variant vaccines based on BNT162b2: 3016 participants of which
    - 747 had received BNT162b2 (B.1.351);
    - 372 had received BNT162b2 (B.1.617.2);
    - 545 had received BNT162b2 (B.1.1.7 + B.1.617.2);
    - 20 had received BNT162b2 (B.1.1.7);
    - 667 administered with BNT162b2 (B.1.1.529);
    - 665 administered with BNT162b2/ BNT162b2 OMI.
- Early development candidates: 633 participants of which
    - 30 had received BNT162a1;
    - 411 had received BNT162b1, including 48 participants at 10 µg and 363 participants at 30 µg;
    - 96 had received BNT162b3;
    - 96 had received BNT162c2.
- Blinded therapy: 7493 participants.
- Placebo: 3367 participants.

Post-marketing experience worldwide

It is not possible to determine with certainty the number of individuals who received BNT162b2 during the period of this review. Estimated worldwide cumulative shipped doses may serve as a reasonable indicator of the cumulative subject exposure, considering that approximately 77% of the cumulative shipped doses were administered; this estimation is a weight average considering the proportion of cumulative doses administered out of those shipped upon review of the cumulative data currently available for the EU-EEA countries and the US.

With these caveats in mind, it is estimated that approximately 3,352,695,090 doses of BNT162b2 were shipped worldwide from the receipt of the first temporary authorisation for emergency supply on 01 December 2020 through 15 April 2022, corresponding to 2,581,772,503 estimated administered doses.

The estimated cumulative number of shipped and administered doses of BNT162b2 by region based on data provided in the shipment tracker (Order Book), from the receipt of the first temporary authorisation for emergency supply on 01 December 2020 through 15 April 2022, are summarized in Table 8.

Table 8. Cumulative Estimated Shipped/Administered Doses of BNT162b2 by Region Worldwide

Region/Country/Other	% of Doses	Total Number of Shipped Doses	Total Number of Administered Doses
Europe	**32.9%**	**1103352420**	**841258282**
European Union (27)	24.5%	821088015	624026891
European Economic Area Countries (3)	0.3%	11220165	8527325
Switzerland	0.3%	10197450	7852037
UK	3.3%	110562585	85133190
Other Countries[a]	3.3%	111276945	85683248
Commonwealth of Independent States[b]	1.2%	39007260	30035590
North America	**14.8%**	**496619635**	**390917484**
US	12.7%	426018255	336554421
Canada	2.1%	70601380	54363063
Central and South America[c]	**14.3%**	**479530385**	**369238396**
Asia	**30.2%**	**1012725750**	**779798828**
Japan	8.0%	268808340	206982422
Other Countries[d]	22.2%	743917410	572816406
Oceania	**2.2%**	**72356640**	**55714613**
Australia/New Zealand	2.1%	71552850	55095695
Other Countries[e]	0.0%	803790	618918
Africa[f]	**5.6%**	**188110260**	**144844900**
Total	**100.0%**	**3352695090[g]**	**2581772503**

a. Includes Albania, Andorra, Bosnia, Kosovo, Montenegro, North Macedonia, Serbia, Turkey and Vatican;
b. Includes Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Tajikistan, Ukraine and Uzbekistan;
c. Includes Antigua&Barbuda, Argentina, Bahamas, Barbados, Belize, Bolivia, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, Ecuador, El Salvador, Grenada, Guatemala, Guyana, Haiti, Honduras, Jamaica, Mexico, Nicaragua, Panama, Paraguay, Peru, St Kitts&Nevis, St. Lucia, StVin&Grenadine, Suriname, Trinidad & Tobago and Uruguay;
d. Includes Bahrain, Bangladesh, Bhutan, Brunei, Cambodia, Indonesia, Iraq, Israel, Jordan, Korea, Kuwait, Laos, Lebanon, Malaysia, Maldives, Mongolia, Nepal, Oman, Pakistan, Palestine, Philippines, Qatar, Saudi Arabia, Singapore, Sri Lanka, Thailand, Timor-Leste, United Arab Emirates and Vietnam;
e. Includes Fiji, Nauru, Samoa, Solomon Islands, Tonga and Tuvalu;
f. Includes Angola, Benin, Botswana, Burkina Faso, Cabo Verde, Cameroon, Cen African Rep, Chad, Comoros, Congo, Djibouti, DR Congo, Egypt, Eswatini, Ethiopia, Gabon, Gambia, Ghana, Guinea, Ivory Coast, Kenya, Lesotho, Liberia, Libya, Madagascar, Malawi, Mali, Mauritania, Mauritius, Morocco, Namibia, Niger, Nigeria, Rwanda, Senegal, Seychelles, Sierra Leone, Somalia, South Africa, Sudan, Tanzania, Togo, Tunisia, Uganda and Zambia;
g. Out of these shipped doses, 34,966,620 doses were shipped for COVAX, 371,084,580 doses were shipped for USG Donation program and 40,880,760 doses were shipped for EC Donation program.

Additionally, as per data provided by LP, in the Fosun Territories (Hong Kong, Macau and Taiwan) the following approximate doses of BNT162b2 were administered cumulatively through 15 April 2022:

- Hong Kong: 9,221,575 doses;
- Macau: 230,477 doses;
- Taiwan: 15,669,512 doses.

Post-marketing experience in the EU-EEA

Estimated cumulative shipped doses in the EU-EEA countries may serve as a reasonable indicator of the cumulative subject exposure in these countries, considering that approximately 76% of the cumulative shipped doses were administered; this estimation is based on the proportion of the cumulative doses administered out of those shipped upon review of the cumulative data currently available for the EU-EEA countries.

With these caveats in mind, it is estimated that approximately 832,308,180 doses of BNT162b2 were shipped in the EU-EEA countries from the receipt of the first conditional marketing authorisation approval on 21 December 2020 through 15 April 2022, corresponding to 632,554,217 estimated administered doses.

Table 9 provides the estimated number of shipped and administered doses for BNT162b2, cumulatively from the receipt of the first conditional marketing authorisation approval through 15 April 2022.

Table 9. Cumulative Estimated Shipped/Administered Doses of BNT162b2 by EU-EEA Countries (30)

EU Country	Total Number of Cumulative Shipped Doses	Total Number of Cumulative Administered Doses
EU (27)	**821088015**	**624026891**
AT	18926715	14384303
BE	18424095	14002312
BG	5793540	4403090
HR	5532780	4204913
CY	1836165	1395485
CZ	19912170	15133249
DK	14082450	10702662
EE	1921155	1460078
FI	11120745	8451766
FR	132209880	100479509
DE	174508785	132626677
EL	22787400	17318424
HU	13107675	9961833
IE	10578360	8039554
IT	106806720	81173107
LV	2487855	1890770
LT	5223435	3969811
LU	1173975	892221
MT	1194240	907622
NL	31273770	23768065
PL	71819175	54582573
PT	20316930	15440867
RO	19784580	15036281
SK	8062860	6127774
SI	3549150	2697354
ES	78469830	59637071
SE	20183580	15339521
EEA (3)	**11220165**	**8527325**
IS	710145	539710
LI	0	0
NO	10510020	7987615
Total	**832308180**	**632554217**

Stratified data on the administered first and second doses, paediatric doses, and booster dose were not reproduced here.

The CHMP noted that up to 15 April 2022, it is estimated that approximately 2,6 billion doses of BNT162b2 were administered worldwide. Of these, over 632 million doses were administered in the EU and EEA countries.

Data in Summary Tabulations

Cumulatively, there have been 2245 clinical trial cases (2943 SAEs) reported. During the reporting interval, there have been 20 clinical trial cases (22 SAEs) reported.

Cumulatively, there have been 1,389,181 post-marketing cases (4,674,419 ADRs) reported. During the reporting interval, there have been 1,280,485 post-marketing cases (4,252,051 ADRs) reported.

Significant findings from clinical trials and non-interventional studies

Completed clinical trials

No clinical trials were completed up to 21 April 2022.

Ongoing clinical trials

There were 15 ongoing clinical trials up to 21 April 2022. For 9 interventional trials, BioNTech is the sponsor and Pfizer acts as lead development party. Additionally there are 4 BioNTech interventional trials and 2 studies from Fosun (BioNTech LP) with BioNTech third party acting as lead development party.

Clinically important emerging efficacy and safety findings were identified for Study C4591031 Substudy A and are summarized below.

Study C4591031 Substudy A is a Phase 3 randomized, placebo-controlled, observer-blind substudy aimed at evaluating the safety, tolerability, and efficacy of a booster dose of BNT162b2. Participants ≥16 years of age who had completed a 2-dose primary series of BNT162b2 in Study C4591001 at least 6 months prior to randomization, were enrolled and randomized at a ratio of 1:1 to receive either BNT162b2 or placebo. Randomization was stratified by age, such that approximately 60% of participants enrolled were ≥16 to 55 years of age and approximately 40% of participants >55 years of age. Considering the observation of waning effectiveness and recommendation for booster doses in some countries, per the protocol, participants could be unblinded from 24 September 2021 onwards and those randomized to placebo were offered a dose of BNT162b2 30 µg. The efficacy results were not reproduced here. With regard to safety, within 1 month after the administration of Dose 3, AEs were more frequent in the vaccine group than in the placebo group. Injection site pain was the most frequently reported AE in the 2 groups and was reported more often in the vaccine group vs the placebo group (risk difference, 11.3 percentage points). From Dose 3 through the data cut-off date, SAEs were reported by slightly more participants in the placebo group than in the vaccine group (0.5% vs 0.3%). No cases of myocarditis or pericarditis were reported at the time of this interim analysis.

No new clinically important information has emerged from the CT C4591030 ongoing following the DLP of the most recently submitted PSUR up to the DLP of this ACO.

The CHMP noted that no new safety information was identified from the ongoing clinical trials.

Non-interventional studies

During this reporting period, there were no NISs completed with a final CSR. Six NI safety studies, including 5 PASSs denoted in bold, were ongoing (Table 10). No new safety information was reported regarding these ongoing non-interventional studies.

Table 10. Non-Interventional Studies Ongoing During the Reporting Period

Study No.	Study Title and Country(ies)
Safety Studies	
C4591008[a] PASS	**Study Title**: HERO Together: A post-Emergency Use Authorization observational cohort study to evaluate the safety of the Pfizer-BioNTech COVID-19 vaccine in US healthcare workers, their families, and their communities. **Country**: United States
C4591010[b] PASS	**Study Title**: A Non-Interventional Post-Authorization Safety Study (PASS) for Active Safety Surveillance of Recipients of the Pfizer-BioNTech COVID-19 mRNA vaccine in the EU. **Countries**: Germany; Italy; Spain
C4591012[b,c] PASS	**Study Title**: Post-Emergency Use Authorization Active Safety Surveillance Study among Individuals in the Veteran's Affairs Health System Receiving Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine **Country**: United States
C4591021[b,d] PASS	**Study Title**: Post Conditional Approval Active Surveillance Study Among Individuals in Europe Receiving the Pfizer-BioNTech Coronavirus Disease 2019 (COVID-19) Vaccine **Country**: Italy; Netherlands; Norway; Spain; United Kingdom.
C4591022[b,c] PASS	**Study Title**: Pfizer-BioNTech COVID-19 Vaccine Exposure during Pregnancy: A Non-Interventional Post-Approval Safety Study of Pregnancy and Infant Outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry **Country**: Canada; United States
C4591025[d]	**Study Title**: A prospective single-arm, open-label, non-interventional, multicenter study to assess the safety of BNT162b2 in domestic post-marketing surveillance. **Country**: Republic of Korea

a. Voluntary PASS. Included in the US-Pharmacovigilance Plan as post-authorization safety study addressing the important potential risk of VAED/VAERD
b. Committed PASS (Category 3 Study in the EU).
c. Committed PASS to the US FDA
d. Required PASS for the US FDA. This NIS was ongoing following the DLP of the most recently submitted PSUR up to the DLP of this ACO.

The CHMP noted that the interim report of the PASS study C4591012, which is listed in the RMP of Comirnaty, is currently under assessment (procedure EMEA/H/C/005735/MEA/010.4). Study C4591008 is not part of the EU-RMP.

Medication errors

During the reporting period 88,782 cases (including 114,763 medication errors) were reported. Among the 85,114 relevant medication error cases (including 107,492 medication errors), the following scenarios, categorized according to the EMA guidance "Good practice guide on recording, coding, reporting and assessment of medication errors" (EMA/762563/2014), were described:

- 2148 medication errors associated with harm [i.e., resulting in adverse reaction(s)] were reported in 2141 cases (2.5% of relevant medication error cases); 144 of them were serious.
- 105,136 medication errors without harm [i.e., not resulting in adverse reaction(s)] were reported in 83,020 cases (97.3% of relevant medication error cases), of which 33,066 cases involved co-reported AEs;
- 205 potential medication errors were reported in 173 cases (0.2% of relevant medication error cases).
- 3 intercepted medication errors were reported in 3 cases (0.004% of relevant medication error cases).

The 85,114 relevant medication error cases originated mostly (≥1000 cases) from the following countries: the US (20,602 cases), Austria (13,930), the UK (11,466), Germany (11,029), Netherlands

(4594), Sweden (3297), Canada (3258), France (2832), Japan (2724), Australia (1506), and Brazil (1084).

The most commonly (≥1000 events) reported medication errors were coded to the PTs Inappropriate schedule of product administration (49,614), Poor quality product administered (18,325), Product temperature excursion issue (11802), Incorrect route of product administration (3981), Product administration error (3678), Expired product administered (3017), Product administered to patient of inappropriate age (2682), Product preparation error (2646), Underdose (2371), Product preparation issue (1945), Incorrect dose administered (1437) and Product storage error (1331).

During the reporting interval, there were 2 relevant serious clinical trial cases that reported one medication error each [no harm; Accidental overdose (serious and unrelated to BNT162b2) and Inappropriate schedule of product administration (non-serious)].

The CHMP noted that no new safety signal was identified from the cases reporting medication errors. Medication errors have been assessed in the PSUSAs and SSRs.

Non-clinical data

During this reporting interval, no new safety information regarding non-clinical data were reported.

Literature

Non-clinical (Published)

According to the MAH, a search of the Medline and Embase databases did not identify non-clinical studies that presented important new safety findings for COVID-19 vaccine up to 29 April 2022.

Clinical (Published)

A search of the Medline and Embase databases identified 7 clinical trials that presented important new safety findings for COVID-19 vaccine. These are presented in Table 11 below grouped as follows: a) At risk patients; b) Special patient population/Pregnancy; c) Other

Table 11. Clinical Literature Articles that Presented New Safety Information in the Reporting Interval

Citation/Abstract
a) At Risk Patients
Four articles (1-4) described a reduced immune response to BNT162b2 in patients with immunocompromised conditions/treated with immunosuppressants. Section 4.4. *Special warnings and precautions for use (Immunocompromised individuals)* of the EU SmPC includes a warning regarding vaccination in immunocompromised patients, as follows, "*The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty may be lower in immunocompromised individuals.*" Use in immunocompromised patients is categorized as missing information in the EU-RMP v 5.0. 1. Ruggeri EM, Nelli F, Fabbri A, et al. Antineoplastic treatment class modulates COVID-19 mRNABNT162b2 vaccine immunogenicity in cancer patients: a secondary analysis of the prospective Vax-On study. ESMO Open. 2022; 7(1):100350. 2. Terpos E, Gavriatopoulou M, Fotiou D, et al. Poor Neutralizing Antibody Responses in Patients with CLL, NHL and HL after Vaccination Against SARS-CoV-2; A Prospective Study in 132 Patients. Blood 2021; 138 (S1):3752. 3. Majcherek M, Matkowska-Kocjan A, Szymczak D, et al. Two Doses of BNT162b2 mRNA Vaccine in Patients after Hematopoietic Stem Cell Transplantation: Humoral Response and Serological Conversion Predictors. Cancers (Basel). 2022; 14(2):325. 4. Majcherek M, Matkowska-Kocjan A, Szymczak D, et al. Two Doses of BNT162b2 mRNA Vaccine in Patients after Hematopoietic Stem Cell Transplantation: Humoral Response and Serological Conversion Predictors. Cancers (Basel). 2022; 14(2):325.
b) Special Patients Population (Pregnancy)
5. Citu IM, Citu C, Gorun F, et al. The Risk of Spontaneous Abortion Does Not Increase Following First Trimester mRNA COVID-19 Vaccination. J Clin Med. 2022; 11(6):1698. This article contributes to the growing evidence that risk of spontaneous abortion after COVID-19 vaccine immunization during the first trimester of pregnancy is commensurate with the predicted risk in nonvaccinated pregnant women. Use in pregnancy is categorised as missing information in the EU-RMP v 5.0.
c) Other Safety Information
6. Yanir Y, Doweck I, Shibli R, et al. Association Between the BNT162b2 Messenger RNA COVID-19 Vaccine and the Risk of Sudden Sensorineural Hearing Loss. JAMA Otolaryngol Head Neck Surg. 2022;148(4):299–306. This study suggests that the COVID-19 vaccine might be associated with increased risk of Sudden Sensorineural Hearing Loss; however, the effect size is very small. The study had various limitations and no causality assessment has been conducted. The MAH will continue to monitor using routine pharmacovigilance.

7. Visser C, Biedermann JS, Nierman M et al. The Immediate Effect of COVID-19 Vaccination on Anticoagulation Control in Patients Using Vitamin K Antagonists. Thromb Haemost 2022; 122:377–385.

In this study, BNT162b2 was associated with an immediate negative effect on anticoagulation control in patients treated with vitamin K antagonists. The author though, cannot exclude the possibility that the effect on anticoagulation control was due to dose adjustments to avoid complications and patients themselves could have decided to decrease the dosage in the days following COVID-19 vaccination as they might be afraid for bleeding complications after intramuscular injection. This could result in a higher percentage of subtherapeutic INRs after vaccination. In addition, the authors use a surrogate variable for bleeding complications (INR >5).

The possible effects of vaccines on anticoagulation control remain debated even though several prospective studies have been performed (mostly on the effect of the influenza vaccine on anticoagulation control), but overall results were conflicting. As of now, there is no biological or pharmacological plausibility for a vaccine – drug interaction. The MAH will continue to monitor using routine pharmacovigilance.

All other published sources

A search of the Medline and Embase databases identified no new information that presented important new safety findings for BNT162b2.

Unpublished manuscripts/abstracts/scientific meeting findings

During the reporting interval, no new safety findings were identified.

In summary, the MAH identified a total of seven relevant literature articles. Of these, four articles report results of studies in immunocompromised patients and one in pregnant women. No new safety information was identified from these studies. The 6th article describing a study on the association between sudden sensorineural hearing loss and Comirnaty was previously discussed in the 3rd bi-monthly SSR. Within this procedure, the MAH was requested to provide a cumulative review on sudden sensorineural hearing loss within the next PSUR (DLP: 18/06/2022), which is currently under assessment. The last article described an association of BNT162b2 with an immediate negative effect on anticoagulation control in patients treated with vitamin K antagonists, a topic which the MAH will continue to monitor using routine pharmacovigilance.

Overview of Signals: New, Ongoing, or Closed

Table 12. Overview of Signals

Signal *Source*	Signal Type	Data	Category
Overview of Closed Signals from the Beginning of the Reporting Period of this ACO through the DLP of the most recently PSUR submitted (19 June 2021 through 18 December 2021)			
Closed Signals - Potential Risks			
Myocarditis and Pericarditis[a] *Enquiry from a competent authority (UK MHRA, EMA PRAC, New Zealand MedSafe, Others)*	Ongoing and Closed	Post-authorization safety data, clinical study safety data, and pre-clinical data review, literature review, and O/E analysis	Identified Potential Risk[a]
Closed Signals - No Risks			
Thrombosis with Thrombocytopenia Syndrome (TTS) *Commitment to monitor (EMA PRAC)*	New and Closed	Post-authorization safety data, clinical study safety data, and medical literature review	No risk
Erythema multiforme[b] *Enquiry from a competent authority (EMA PRAC)*	New and Closed	Post-authorization safety data, clinical study safety data, medical literature O/E analyses	No risk
Glomerulonephritis and nephrotic syndrome[c] *Enquiry from a competent authority (EMA PRAC)*	New and Closed	Post-authorization safety data, clinical study safety data, medical literature O/E analyses	No risk
Hypoesthesia/Paraesthesia *Enquiry from a competent authority (EMA PRAC)*	New and Closed	Post-authorization safety data, clinical study safety data, medical literature	No risk
Rhabdomyolysis *Enquiry from a competent authority (EMA PRAC)*	New and Closed	Post-authorization safety data, clinical study safety data, medical literature O/E analyses	No risk
Multisystem Inflammatory Syndrome (MIS) in adults (MIS-A) and children (MIS-C)[d] *Enquiry from a competent authority (EMA PRAC)*	New and Closed	Post-authorization safety data, clinical study safety data, medical literature, O/E analyses	No risk
Liver Injury/Autoimmune Hepatitis[e] *Enquiry from a competent authority (Australia TGA, EMA PRAC, US FDA)*	New and Closed	Post-authorization safety data, clinical study safety data, medical literature, O/E analyses	No risk
Herpes Zoster including Ophthalmic herpes zoster *Enquiry from a competent authority (EMA PRAC, UK MHRA)*	Ongoing and Closed	Post-authorization safety data, clinical study safety data, medical literature, O/E analyses	No risk
Immune Thrombocytopenia *Enquiry from a competent authority (EMA PRAC, US FDA)*	New and Closed	Post-authorization safety data, clinical study safety data, medical literature, O/E analyses	No risk

Signal *Source*	Signal Type	Data	Category
Myasthenia gravis *Enquiry from a competent authority (Health Canada)*	New and Closed	Post-authorization safety data, clinical study safety data, medical literature, O/E analyses	No risk
Seizure *Enquiry from a competent authority (EMA PRAC, Saudi Arabia SFDA, Health Canada)*	Ongoing and Closed	Post-authorization safety data, clinical study safety data, medical literature, O/E analysis	No risk
Overview of Ongoing or Closed Signals from the DLP of the most recent PSUR submitted up to the DLP of this ACO			
Ongoing Signals			
Corneal Graft Rejection[f] *Enquiry from a competent authority (EMA PRAC)*	New and Ongoing at ACO DLP	Post-authorization safety data, clinical study safety data, medical literature	Not yet determined
Appendicitis *Enquiry from a competent authority (Singapore BoH)*	New and Ongoing at ACO DLP	Post-authorization safety data, clinical study safety data, medical literature O/E analyses	Not yet determined
Closed Signals - Identified Risks			
Irritability *Clinical Trial C4591007 unblinded review of data (Pfizer)*	New and Closed at ACO DLP	Review of unblinded systemic reactogenicity events for doses 1 and 2 in 6-month to < 2-year-old recipients of BNT162b2 (compared to placebo)	Identified risk (not important)
Closed Signals - No Risks			
Hemolytic anemia *Enquiry from a competent authority (Saudi Arabia SFDA)*	New and Closed at ACO DLP	Post-authorization safety data, clinical study safety data, medical literature O/E analyses	No risk
Uveitis *Scientific Literature; Enquiry from a competent authority (Health Canada)*	New and Closed at ACO DLP	Post-authorization safety data, clinical study safety data, medical literature, O/E analyses	No risk
Exacerbation and/or flare of underlying autoimmune disease or inflammatory disorders *Enquiry from a competent authority (EMA PRAC)*	New and Closed at ACO DLP	Post-authorization safety data, clinical study safety data, medical literature	No risk
Capillary Leak Syndrome (CLS)[g] *Enquiry from a competent authority (EMA PRAC)*	New and Closed at ACO DLP	Post-authorization safety data, clinical study safety data, medical literature	No risk
Vasculitis *Notification from a competent authority (The Netherlands Lareb)*	New and Closed at ACO DLP	Post-authorization safety data, clinical study safety data, medical literature, O/E analyses	No risk

Signal *Source*	Signal Type	Data	Category
Cerebral venous sinus thrombosis (CVST) *Enquiry from a competent authority (Swissmedic)*	New and Closed at ACO DLP	Post-authorization safety data, clinical study safety data, medical literature, O/E analyses	No risk
Lymphocytic colitis *Scientific Literature*	New and Closed at ACO DLP	Post-authorization safety data, clinical study safety data, medical literature	No risk
Polymyalgia Rheumatica (PMR) *Enquiry from a competent authority (EMA PRAC)*	New and Closed at ACO DLP	Post-authorization safety data, clinical study safety data, medical literature, O/E analyses	No risk
Subacute Thyroiditis (SAT) *Enquiry from a competent authority (EMA PRAC)*	New and Closed at ACO DLP	Post-authorization safety data, clinical study safety data, medical literature, O/E analyses	No risk
Cerebrovascular Accident/Stroke *Enquiry from a competent authority (Australia TGA)*	New and Closed at ACO DLP	Post-authorization safety data, clinical study safety data, medical literature, O/E analyses	No risk
Amenorrhea[h] *Enquiry from a competent authority (EMA PRAC)*	New and Closed at ACO DLP[j]	Post-authorization safety data, clinical study safety data, medical literature, O/E analyses	No risk
Heavy Menstrual Bleeding[i] *Enquiry from a competent authority (EMA PRAC)*	New and Closed at ACO DLP	Post-authorization safety data, clinical study safety data, medical literature, O/E analyses	No risk
Loss of/Altered Taste and Smell *Enquiry from a competent authority (Australia TGA)*	New and Closed at ACO DLP	Post-authorization safety data, clinical study safety data, medical literature, O/E analyses	No risk

a. EPITT no: 19712, Procedure no: SDA 032. Myocarditis and pericarditis is an Important Identified Risk in the EU-RMP v 5.0.
b. EPITT no: 19721, Procedure no: SDA 034
c. EPITT no: 19722, Procedure no: SDA 035
d. EPITT no: 19732, Procedure no: SDA 038
e. EPITT no: 19749, Procedure no: SDA 042
f. EPITT no: 19789
g. EPITT no: 19743, Procedure no: SDA 051
h. EPITT no: 19784, Procedure no: SDA 052
i. EPITT no: 19783, Procedure no: SDA 053
j. Signal considered ongoing by PRAC.

The signals that were closed by the MAH for which however further evaluation is ongoing or has been requested in the remit of the PSUR/signal procedure and therefore cannot be considered closed are:

- Glomerulonephritis/nephrotic syndrome: following the assessment of the signal in the last PSUR procedure, the MAH was requested to provide, in the next PSUR (DLP: 18/06/2022), a cumulative review of cases regarding IgA nephropathy, including details of the underlying condition(s), time to onset, duration, outcome and an assessment of the causal relationship with the vaccination.
- Heavy menstrual bleeding: following assessment of the signal procedure (EPITT ref. 19783), the PRAC concluded that the current evidence was insufficient to warrant an update to the product information at present. However, an updated cumulative review within the signal procedure was requested.
- Amenorrhea: following assessment of the signal procedure (EPITT ref. 19784), the PRAC concluded that the current evidence was insufficient to warrant an update to the product information at present. However, an updated cumulative review was requested in the next PSUR (DLP: 18/06/2022).

The classification of the remaining signals is acceptable by the CHMP.

Risk evaluation

Summary of Safety Concerns

Table 13. Safety Concerns at the beginning of the reporting period (EU-RMP v 1.1)

Important Identified Risk	Anaphylaxis
Important Potential Risk	Vaccine-Associated Enhanced Disease (VAED), Including Vaccine-Associated Enhanced Respiratory Disease (VAERD)
Missing Information	Use in Pregnancy and While Breast Feeding
	Use in Immunocompromised Patients
	Use in Frail Patients With Co-Morbidities (e.g. COPD, Diabetes, Chronic Neurological Disease, Cardiovascular disorders)
	Use in Patients With Autoimmune or Inflammatory Disorders
	Interaction With Other Vaccines
	Long-Term Safety Data

Within the reporting interval, "Myocarditis and Pericarditis" was added as an important identified risk to the safety concerns.

Based on the data submitted with the renewal application, the CHMP is of the view that no changes to the summary of safety concerns listed in the RMP are warranted.
It is noted that with version 6.0 of the RMP, submitted as part of variation EMEA/H/C/005735/II/0140 (Opinion 01/09/2022), anaphylaxis has been removed from the safety concerns.
The MAH has also been requested by EMA to critically appraise if the wealth of safety data accumulated during the product use can inform rationalising the safety concerns in the RMP, at the next regulatory opportunity.

3.4. Pharmacovigilance inspections

During the renewal period, the following inspections of MAH's pharmacovigilance system were conducted:

Table 14. List of Pharmacovigilance Inspections During the Interval (30 April 2021 through 29 April 2022)

Inspecting Authority	Site Inspected	Inspection Start Date	Inspection End Date	Type of Inspection	Impact of findings on benefit/risk balance of BNT162b2
INVIMA	Pfizer Colombia Office (Virtual)	25 October 2021	25 October 2021	Routine Pharmacovigilance Inspection	No findings identified during this inspection
EMA	Headquarter Milan Office	27 September 2021	01 October 2021	Pharmacovigilance Inspection	None of the findings impacts the Benefit/Risk

				Comirnaty (COVID Vaccine)	of BNT162B2 (Comirnaty)
AGES	Pfizer Austria Office	30 June 2021	01 July 2021	Routine Pharmacovigilance Inspection	None of the findings impacts the Benefit/Risk of BNT162B2 (Comirnaty)
MHRA	Pfizer UK Office (Virtual)	21 June 2021	24 June 2021	Pharmacovigilance Inspection (COVID Vaccine PF-07302048)	None of the findings impacts the Benefit/Risk of BNT162B2 (Comirnaty)
HC	Pfizer Canada Office (Virtual)	25 May 2021	11 June 2021	Routine Pharmacovigilance Inspection	None of the findings impacts the Benefit/Risk of BNT162B2 (Comirnaty)
ARCSA	Pfizer Ecuador Office (Virtual)	19 May 2021	21 May 2021	Routine Pharmacovigilance Inspection	No findings identified during this inspection

4. Risk management plan

The MAH has confirmed the current approved RMP remains unchanged and applicable.

During the reporting interval, the following changes have been implemented in the RMP:

- Update of the therapeutic indication to include individuals 12 years of age and older;
- Inclusion of new information from interim study C4591001 results for all participants ⩾16 years of age and including participants with confirmed stable HIV disease;
- Inclusion of a new formulation and update on potential medication errors;
- Inclusion of myocarditis and pericarditis as important identified risks, with supporting data from clinical trials and safety databases and update of the information on planned/ongoing post-authorization safety studies with inclusion of 2 new studies, and the circulation of a DHPC;
- Update of the therapeutic indication to include individuals 5 years of age and older;
- Inclusion of data from the booster dose and third dose in immunocompromised as part of the primary vaccination including data in patients who have undergone a solid organ transplantation
- Discontinuation of enrolment in study C4591015

As described above, based on the data submitted with the renewal application, the CHMP is of the view that no changes to the summary of safety concerns listed in the RMP are warranted. The remaining clinical SOBs may therefore be reclassified as category 3 studies in the RMP, with the final CSRs to be submitted at a later stage as supportive data, notwithstanding the premature closure of the dedicated studies. Thus, as an outcome of the renewal procedure, the MAH is requested to submit an updated RMP at the next regulatory opportunity.

5. Changes to the Product Information

Annexes I, II and IIIB of the current marketing authorisation were amended to reflect the granting of a marketing authorisation not subject to Specific Obligations for Comirnaty.

Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Comirnaty (tozinameran) is included in the additional monitoring list as it contains a new active substance which, on 01 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

6. Overall conclusions and benefit-risk balance

6.1. Specific Obligations (SOBs)

Compliance of SOB data submitted

During the period covered by this annual renewal data on the SOBs have been submitted that overall are compliant in terms of adherence to deadlines and are compliant in terms of acceptability of data submitted.

All quality SOBs are now considered fulfilled. The clinical safety profile, as well as the efficacy of this product, is considered comprehensively characterised and supportive of a positive benefit-risk balance. The clinical SOBs 006 and 007 may therefore be reclassified as category 3 studies in the RMP and deleted from Annex II, with the final CSRs to be submitted at a later stage as supportive data.

Updated list of Specific Obligations (SOBs)

The CHMP is of the opinion that the comprehensive existing data package for this vaccine warrants conversion of the current conditional approval into a marketing authorisation not subject to specific obligations. The clinical SOBs 006 and 007 will be reclassified as category 3 studies in the RMP, with the final CSRs to be submitted at a later stage as supportive data.

6.2. Benefit-risk Balance

During the period covered by this annual renewal, new data have emerged. However, these data do not have an impact on the benefit-risk of COMIRNATY in the approved indication.

The data collected as part of the specific obligations for Comirnaty during the period covered by this annual renewal confirmed its positive benefit-risk balance in the approved indication.

Favourable effects

The favourable effects were demonstrated in the initial marketing authorisation for persons 16 years of age and older and updated in a type II variation to extend its use to adolescents 12-15 years of age. Since the last renewal, type II variations have been submitted:

- to also include homologous and heterologous booster doses and,

- to extend to children from 5 years of age in the indication using a lower dose (10 µg/dose).

The most important favourable effects are briefly summarised below.

The overall vaccine efficacy against symptomatic laboratory confirmed COVID-19 from 7 days after dose 2 was 95.0% (95% CI 90.0, 97.9) in subjects ≥16 years of age without prior evidence of SARS CoV-2 infection and 94.6% (95% CI 89.6, 97.6) in all subjects regardless of prior evidence of SARS CoV-2 infection (primary endpoint). This outcome met the pre-specified success criteria.

The efficacy of the vaccine (BNT162b2, 2 doses of 30 µg, separated by 21 days) to prevent COVID-19 in the adolescents aged 12- 15 years either without or with and without evidence of prior SARS-CoV-2 infection, occurring at least 7 days after the second dose, was 100.0% (95%CI 75.3; 100 and 95%CI 78.1; 100, respectively).

In addition, Comirnaty was shown to elicit non-inferior immune responses in subjects 12-15 years of age without previous COVID-19 compared to subjects 16-25 years in terms of geometric mean titres of neutralising antibodies one-month post dose 2.

The efficacy of the vaccine (BNT162b2, 2 doses of 10 µg, separated by 21 days) to prevent COVID-19 in children aged 5 - 11 years either without or with and without evidence of prior SARS-CoV-2 infection, occurring at least 7 days after the second dose, was 90.7 % (95%CI: 67.7; 98.3 and 95% CI: 67.4%, 98.3%, respectively).

In addition, Comirnaty was shown to elicit non-inferior immune responses in subjects 5-11 years of age without previous COVID-19 compared to subjects 16-25 years in terms of geometric mean titres of neutralising antibodies one-month post dose 2.

The efficacy of a homologous booster dose was demonstrated in terms of relative efficacy compared to 'unboosted' subjects. The relative vaccine efficacy information for participants 16 years of age and older without prior evidence of SARS-CoV-2 infection was 95.3% (95% CI: 89.5; 98.3%).

The efficacy of heterologous booster was inferred from immunogenicity data demonstrating 36, 12, and 20 GMR-fold rise in neutralising titres following the Janssen, Moderna, and Comirnaty primary doses, respectively.

Uncertainties and limitations about favourable effects

Remaining uncertainties mainly relate to use in immunocompromised subjects, long-term efficacy and safety, and e.g. efficacy against transmission. Uncertainties are described in previous variation assessment reports.

Unfavourable effects

The safety of Comirnaty was evaluated in participants 16 years of age and older in 2 clinical studies (BNT162-01 and C4591001) that included 21,744 participants that have received at least one dose of Comirnaty in the initial approval application. Overall, the safety profile of Comirnaty is considered

acceptable. The product information has been updated since approval as new data has emerged. All data have been assessed in other procedures such as monthly safety updates, periodic safety updates, signal assessments and variations.

Uncertainties and limitations about unfavourable effects

The uncertainties and limitations of unfavourable effects have been discussed in other procedures. The principal uncertainties are related to long-term effects, and effects in specific risk groups.

Benefit-risk assessment and discussion

The benefits of Comirnaty in terms of protection against COVID-19 clearly outweigh the identified risks, and no new information has emerged during this renewal period that has changed the balance.

All quality related SOBs are considered fulfilled.

The clinical SOBs 006 and 007 will be reclassified as category 3 studies in the RMP and deleted from Annex II, with the final CSRs to be submitted at a later stage as supportive data.

Importance of favourable and unfavourable effects

Not Applicable.

Balance of benefits and risks

Based on the cumulative evidence in terms of favourable and unfavourable effects, the benefit-risk balance of Comirnaty remains positive.

Scientific grounds for recommending the granting of a marketing authorisation not subject to specific obligations

The MAH believes that as of now, comprehensive data are available from multiple sources, including but not limited to clinical trials, exhaustively informing about the safety, reactogenicity, immunogenicity and efficacy of Comirnaty and supporting the favourable benefit/risk profile of in all approved populations.

The MAH has therefore requested to take the opportunity of the present renewal of Comirnaty's conditional marketing authorisation to remove the submission of the final Clinical Study Reports of studies C4591001 and C4591007 from the list of specific obligations and to adopt an opinion recommending the granting of a marketing authorisation in accordance with Article 14(1) of Regulation (EC) No 726/2004 ('marketing authorisation not subject to specific obligations').

The MAH's justification for the request above has been assessed in the post authorisation measure procedures EMEA/H/C/005735/SOB/043, SOB/044.

Considering the vaccination of a large proportion of the control arm patients in study C4591001, which was unavoidable, it is agreed that the continued follow-up would no longer be informative on the safety and efficacy profile of Comirnaty. Thus, the MAH's justification for early termination of study C4591001 is considered justified. Similarly, due to further interventions after the primary series, is not expected that the remaining outstanding data from study C4591007 will alter the benefit-risk profile of Comirnaty for the presently approved use in paediatric subjects.

Therefore, the justification for removal of study C4591001 and study C4591007 from the list of specific obligations is considered acceptable by the Committee.

In summary, it is not expected that the remaining outstanding data from study C4591001 and study C4591007 will bring substantial additional confirmatory evidence impacting the benefit-risk profile of Comirnaty in the respective age groups. The remaining clinical SOBs may therefore be reclassified as category 3 studies in the RMP, with the final CSRs to be submitted at a later stage as supportive data, notwithstanding the premature closure of the dedicated studies. As part of this annual renewal the CHMP is of the opinion that SOBs 006 and 007 can therefore be deleted from Annex II. The conditional marketing authorisation can therefore be converted into a standard marketing authorisation not subject to Specific Obligations.

7. Recommendations

Based on the review of the available information on the status of the fulfilment of Specific Obligations, the benefit-risk balance for Comirnaty in its approved indication (please refer to the Summary of Product Characteristics) continues to be favourable. As all Specific Obligations have either been fulfilled or reclassified as category 3 studies in the RMP, there are no remaining grounds for the marketing authorisation to remain conditional and the CHMP therefore recommends the granting of a standard marketing authorisation not subject to Specific Obligations for Comirnaty.

Amendments to the marketing authorisation

In view of the data submitted with the annual renewal, amendments to Annexes I, II and IIIB to the current marketing authorisation are recommended.

The CHMP is of the opinion that the comprehensive existing data package for this vaccine warrants conversion of the current conditional approval into a standard marketing authorisation not subject to Specific Obligations. As a result, it is recommended that the final study reports for the clinical SOBs are reclassified as category 3 studies in the RMP and therefore deleted from the Annex II to this opinion.

Conditions of the marketing authorisation

The marketing authorisation is subject to the following conditions:

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.