EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 March 2022
EMA/205600/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Evusheld

International non-proprietary name or common name: tixagevimab + cilgavimab

Procedure No. EMEA/H/C/005788/0000

Note

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

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List of abbreviations

%CV	Percent coefficient of variation
%gCV	Geometric coefficient of variation
ACE2	Angiotensin converting enzyme 2
ADA	Antidrug antibodies
ADCC	Antibody-dependent cellular cytotoxicity
ADCD	Antibody-dependent complement deposition
ADCP	Antibody-dependent cellular phagocytosis
ADE	Antibody-dependent enhancement of disease
ADEI	Antibody-dependent enhancement of infection
ADNKA	Antibody-dependent NK activation
AE	Adverse event
AESI	Adverse event of special interest
AUC	Area under the plasma concentration-time curve
AUC(0-150)	Area under the serum concentration-time curve from time zero to time 150 days
AUC(0-91)	Area under the serum concentration-time curve from time zero to time 91 days
AUCinf	Area under the serum concentration versus time curve extrapolated to infinity
AUClast	Area under the serum concentration-time curve from zero to the last quantifiable concentration
AZD1061	cilgavimab
AZD7442	Evusheld, combination of tixagevimab and cilgavimab
AZD8895	tixagevimab
BAL	Bronchoalveolar lavage
C1q	Complement component 1q
C0	Back-extrapolated concentration at time 0
CDC	Complement-dependent cytotoxicity
CI	Confidence interval
CL	Clearance
Cmax	Maximum plasma concentration
CoV	Coronavirus
COVID-19	Coronavirus disease 2019
CRF	Case report form
CSP	Clinical Study Protocol

CSR	Clinical Study Report
D8850C00001	Phase I first-time-in-human study
D8850C00002	PROVENT Phase III study
D8850C00003	STORM CHASER Phase III study
DCO	Data cut-off
DP	Drug product
ECG	Electrocardiogram
ELF	Endothelial lining fluid
ELISA	Enzyme-linked immunosorbent assay
EOHSA	Excess over highest single agent
Fab	Antibody-binding fragment
Fc	Fraction crystallisable
FcRn	Neonatal Fc receptor
FcγR	Fc gamma receptor
FTIH	First-time-in-human
GISAID	Global Initiative on Sharing Avian Influenza Data
GLP	Good Laboratory Practice
gRNA	Genomic RNA
H&E	Hematoxylin and eosin
HIV	Human Immunodeficiency Virus
huFcγR	Human Fc gamma receptor(s)
huFcRn	Human neonatal Fc receptor
IC50	Half-maximal inhibitory concentration
IC80	80% maximal inhibitory concentration
IFNγ	Interferon gamma
IgG	Immunoglobulin G
IL-2	Interleukin 2
IM	Intramuscular
IN	Intranasal
IL-D	Illness Visit Day
IMP	Investigational medicinal product
IQR	Interquartile range
IV	Intravenous

IP	Intraperitoneal
IT	Intratracheal
IU	Infectious units
IV	Intravenous
KA	First-order absorption rate constant
KD	Equilibrium dissociation constant
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LLOQ	Lower limit of quantification
LOD	Limited of detection
mAb	Monoclonal antibody
MERS	Middle East Respiratory Syndrome
MIP-1α	Macrophage inflammatory protein 1 alpha
nAb	Neutralising antibody
ND	Not determined
Neut50	Half-maximal neutralising antibody titre
NGS	Next generation sequencing
NLF	Nasal lining fluid
NHP	Non-human primate
NK	Natural killer cell
NOAEL	No observed adverse effect level
PBMC	Peripheral blood mononuclear cell
pfu	Plaque forming units
PK	Pharmacokinetics
PRNT50	Median plaque reduction neutralisation test titre
qRT-PCR	Quantitative reverse transcription polymerase chain reaction
RBD	Receptor binding domain
RNA	Ribonucleic acid
RRR	Relative risk reduction
RSV	Respiratory syncytial virus
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse events
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome associated coronavirus 2

SD	Standard deviation
sgmRNA	Subgenomic ribonucleic acid
t1/2	Terminal half-life
TCID50	Median tissue culture infectious dose
TCR	Tissue cross-reactivity
Tg	Transgenic
TK	Toxicokinetics
TM	L234F/L235E/P331S substitutions in the immunoglobulin heavy chain to reduce Fcγ receptor and C1q binding
Tmax	Time to maximum plasma concentration
TNF	Tumour necrosis factor
ULOQ	Upper limit of quantitation
VDM	Viral dynamic model
vp	vector particles
Vss	Volume of distribution at steady state
VSV	Vesicular stomatitis virus
VSV-SARS-CoV-2	Vesicular stomatitis virus severe acute respiratory coronavirus 2
WT	Wild type
YTE	M252Y/S254T/T256E substitutions in the immunoglobulin heavy chain to increase FcRn affinity that results in the increased half-life of an antibody

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 14 March 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Evusheld, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 12 October 2020.

A combination pack request was submitted to the Agency on 3rd December 2020. In accordance with Eudralex, Notice to Applicants, Volume 2A, Chapter 1, Section 5.5, "In very exceptional circumstances, which must be considered on a case-by-case basis, the marketing of distinct medicinal products in the same package may be indispensable for public health reasons. Such reasons cannot be related to convenience or commercial purposes". Further to consultation with ETF on 19th December 2020, the CHMP endorsed via written procedure, the outcome of the review process that the proposed combination pack was considered indispensable for public health, in order to facilitate patient access to the medicinal product in the current pandemic situation. The European Commission has been informed of this outcome and endorsed the acceptance of the combination pack in the context of the COVID-19 emergency situation, stressing that the studies to support co-formulation shall be accelerated, and the progress of these ongoing studies must be reported to the EMA.

The applicant applied for the following indication: Evusheld is indicated for the prophylaxis of COVID-19 in adults 18 years of age and older.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0235/2021 and P/0236/2021 on the agreement of a paediatric investigation plan (PIPs).

At the time of submission of the application, the PIP P/0235/2021 and P/0236/2021 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request for consideration

1.5.1. Conditional marketing authorisation

Not applicable.

1.5.2. New active Substance status

The applicant requested the active substance tixagevimab / cilgavimab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

25 September 2020	EMEA/H/SA/4661/1/2020/III	*Adriana Andric, Rosalia Ruano Camps, Mair Powell, Jens Reinhardt and Dr Joerg Zinserling*
20 November 2020	EMA/SA/0000046190	*Brigitte Schwarzer-Daum and Elena Wolff-Holz*

The scientific advice pertained to the following *quality, non-clinical, and clinical* aspects:

Summary of questions raised/ issues discussed in the Scientific Advice*

The applicant received scientific advice on the development of AZD7442 for pre-exposure prophylaxis and treatment of COVID-19 from the CHMP on 25 September 2020 (EMEA/H/SA/4661/1/2020/III). The scientific advice pertained to the following quality/non-clinical/clinical aspects:

Proposal to validate in use stability of multidose product presentation

- *Strategy regarding column and membrane re-use for manufacturing AZD8895 and AZD1061*
- *Manufacturing Process Validation*
- *Changes in cell lines and approach to demonstrate comparability*
- *Platform knowledge to identify critical quality attributes and acceptable ranges and/or specification*
- *Acceptability of the preclinical toxicology and pharmacology package for MAA*
- *Design of the prophylaxis study and statistical analysis*
- *Indication statement*
- *Clinical virology plan*
- *Clinical pharmacokinetic assessments and timelines for submission of POP PK report*
- *Immunogenicity assessments*

• *Options for compassionate use programme and MAA*

• *Timelines for PIP submission*

The applicant received scientific advice on the development of AZD1061, AZD8895 for the treatment of COVID-19 from the CHMP on 20/11/2020 (EMA/SA/0000046190).

The scientific advice pertained to the following clinical aspects:

• study design, study population, interventions, duration of follow-up, primary and key secondary endpoints, proposed statistical methods and interim analyses as well as adequacy of the proposed single pivotal phase 3 study

COVID-19 EMA pandemic Task Force (COVID-ETF)

In line with their mandate as per the EMA Emerging Health Threats Plan, the ETF undertook the following activities in the context of this marketing authorisation application: The ETF endorsed the scientific advice letter, confirmed eligibility to the rolling review procedure based on the information provided by the applicant and agreed the start of the rolling review procedure. Furthermore, the ETF discussed the (Co-)Rapporteur's assessment reports overviews and provided their recommendation to the CHMP.

For the exact steps taken at ETF, please refer to section 1.7.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Christophe Focke

CHMP Peer reviewer(s): N/A

The Rapporteur appointed by the PRAC was PRAC Rapporteur: Kimmo Jaakkola

Evusheld was evaluated as part of 'OPEN', an initiative started in December 2020 with the aim of increasing international collaboration in the EU review of COVID-19 vaccines and therapeutics. More information can be found on the EMA website.

The CHMP confirmed eligibility to the centralised procedure on	12 October 2020
The ETF recommended to start the rolling review procedure on	7 October 2021
The procedure (Rolling Review 1) started on	14 October 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP, Peer Reviewer and ETF on	7 January 2022
The Rapporteurs circulated updated Joint Assessment reports to all CHMP, Peer Reviewer and ETF on	17 January 2022
ETF discussions took place on	20 January 2022
Adoption of first LOQ (Rolling Review 1)	27 January 2022
The applicant submitted documentation as part of a rolling review to support the marketing authorisation application	31 January 2022

The procedure (Rolling Review 2) started on	1 February 2022
ETF discussion on the possibility of inviting the company to submit the marketing authorization application and discussion of questions followed by CHMP written consultation	1 and 4 March 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	2 March 2022
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	10 March 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 March 2022
The CHMP Rapporteur's first Assessment Report was circulated to all BWP, CHMP and PRAC members on	11 March 2022
The application for the marketing authorisation was formally received by the EMA on	14 March 2022
The procedure started on	15 March 2022
BWP discussions took place on	15 March 2022
The CHMP Rapporteur's first Assessment Report was circulated to all BWP, CHMP and PRAC members on	18 March 2022
ETF discussion took place	18 March 2022
The updated PRAC/CHMP Rapporteur's Assessment Report was circulated to all CHMP and PRAC members on	18 and 23 March 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Evusheld on	24 March 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	24 March 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

In December 2019, the World Health Organization (WHO) was informed about a cluster of cases of viral pneumonia of unknown cause in Wuhan, China. In mid-January 2020, the pathogen causing this atypical pneumonia was identified as a novel coronavirus, severe acute respiratory coronavirus 2 (SARS-CoV-2) and genome sequence data were published. Since then, the virus has spread globally on

30 January 2020 the WHO declared the outbreak a Public Health Emergency of International Concern and on 11 March 2020 a pandemic.

According to European Centre for Disease Prevention and Control (ECDC), histologic findings from the lungs include diffuse alveolar damage similar to lung injury caused by other respiratory viruses, such as MERS-CoV and influenza virus. A distinctive characteristic of SARS-CoV-2 infection is vascular damage, with severe endothelial injury, widespread thrombosis, microangiopathy and angiogenesis.

In addition, COVID-19 is a zoonosis and some animals as cats seems to be susceptible to the virus (Shi et al., 2020).

2.1.2. Epidemiology and risk factors

As of 18 March 2022, there have been 464,809,377 confirmed cases of SARS-CoV-2 infection globally with approximately 6,062,536 deaths resulting from infection and subsequent coronavirus disease (COVID-19) as registered by WHO (https://covid19.who.int/ last accessed on 20/3/2022), however, the majority of infections result in asymptomatic or mild disease with full recovery. By region, 191,842,819 cases have been confirmed in Europe.

Underlying health conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, immune compromised status, cancer and obesity are considered risk factors for developing severe COVID-19. Increasing age is another risk factor for severe disease and death due to COVID-19.

2.1.3. Aetiology and pathogenesis

Coronaviruses (CoV) are enveloped RNA viruses and are important human and animal pathogens. Two coronaviruses have previously been identified as zoonotic infections which have adapted to humans and caused severe respiratory illnesses with high fatality: Severe Acute Respiratory Syndrome coronavirus 1 (SARS-CoV-1) and Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV).

SARS-CoV-2 spike glycoprotein (S protein) is a class I transmembrane envelope protein that forms a homo-trimer and mediates binding, fusion, and viral entry into host cells. The spike protein contains a polybasic cleavage site, a characteristic known to increase pathogenicity and transmissibility in other viruses. As referred the Spike is responsible for allowing the virus to attach to and fuse with the membrane of a host cell. The S1 subunit catalyses attachment to the angiotensin converting enzyme 2 (ACE-2) receptor present on cells of the respiratory tract, while the S2 subunit facilitates fusion with the cell membrane. The spike protein is considered a relevant antigen for vaccine development because it was shown that antibodies directed against it neutralise the virus and it elicits an immune response that prevents infection in animals.

It is believed that SARS-CoV-2 has zoonotic origins, and it has close genetic similarity to bat coronaviruses. Its gene sequence was published mid-January 2020 and the virus belongs to the beta-coronaviruses.

Human-to-human transmission of SARS-CoV-2 was confirmed in January 2020. Transmission occurs primarily via respiratory droplets from coughs and sneezes and through aerosols.

Finally, novel coronavirus can evolve under relatively strict selective pressure (Lv et al,2020). Different variants have been identified so far as Alpha, Beta, Gamma, Zeta, Delta, Lambda, Omicron, etc. The Delta variant of the virus spreads faster and infects more cells because it catalyzes the fusion process between virus particles and human cell membranes, allowing them to enter cells more efficiently

(Zhang et al., 2021b). The Omicron variant of the virus can escape from human immunity, though fortunately this escape is not complete (Wang et al., 2022).

2.1.4. Clinical presentation, diagnosis

The human disease caused by SARS-CoV-2 has been designated COVID-19. In most (~80%) cases, COVID-19 presents as a mild-to-moderately severe, self-limited acute respiratory illness with fever, cough, and shortness of breath. Symptoms are thought to appear 2 to 14 days after exposure. COVID-19 can be severe, resulting in pneumonia, severe acute respiratory syndrome, hypercoagulation, kidney failure, and death.

Studies among hospitalised patients have found that high SARS-CoV-2 viral load is associated with worse outcomes, including increased mortality rates (Magleby, 2020) (Westblade, 2020). Community-based studies in non-hospitalised patients show symptomatic patients have higher viral load across both adults and children compared to asymptomatic individuals (Chung, 2021).

Patients with severe and critical COVID-19, even prior to the appearance of acute respiratory distress syndrome, exhibit lymphocytopenia and suffer from T-cell exhaustion, which may lead to viral sepsis and an increased mortality rate.

The gold standard method of testing for presence of SARS-CoV-2 is the reverse transcription polymerase chain reaction (RT-PCR), which detects the presence of viral RNA fragments. As this test detects RNA but not infectious virus, its ability to determine duration of infectivity of patients is limited. The test is typically done on respiratory samples obtained by a nasopharyngeal swab, a nasal swab or sputum sample. In addition, serological assays measure antibody responses and determine seroconversion although they are not well suited to detect acute infections.

2.1.5. Management

The management of COVID-19 cases has developed during 2020, and includes supportive care, which may include fluid therapy, oxygen support, and supporting other affected vital organs.

Treatment of hospitalised patients encompass anti-inflammatory agents such as dexamethasone, targeted immunomodulatory agents and anticoagulants as well as antiviral therapy (e.g. Veklury (EMEA/H/C/005622)), antibodies administered from convalescent plasma and hyperimmune immunoglobulins. Tocilizumab (EMEA/H/C/000955/II/0101) was also approved for its use in adults with COVID-19 who are receiving treatment with corticosteroid medicines and require extra oxygen or mechanical ventilation as well as Anakinra (EMEA/H/C/000363/II/0086) for the treatment of coronavirus disease 2019 (COVID-19) in adult patients with pneumonia who are at risk of developing severe respiratory failure. Recently, three monoclonal antibodies Ronapreve (casirivimab/imdevimab, EMEA/H/C/005814) Xevudy (sotrovimab, EMEA/H/C/005676) and Regkirona (regdanvimab, EMEA/H/C/005854) have been authorised for the treatment of COVID-19 disease in adults and, in the case of Ronapreve and Xevudy also adolescents (from 12 years of age and weighing at least 40 kilograms), who do not require supplemental oxygen and who are at increased risk of their disease becoming severe are also included. In addition, Veklury (EMEA/H/C/005622/II/0016) also extended its indication to include treatment of adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

Ronapreve is also approved for prevention of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kilograms.

Additionally, there are 5 approved vaccines for active immunisation against SARS-CoV-2 aiming to prevent COVID-19 disease, these are Comirnaty (EMEA/H/C/005735), Spikevax (EMEA/H/C/005791), Vaxzevria (EMEA/H/C/005675), COVID-19 vaccine Janssen (EMEA/H/C/005737) and Nuvaxovid (EMEA/H/C/005808).

Finally, an oral treatment for adults who do not require supplemental oxygen and who are at increased risk for progressing to severe COVID-19 was approved in January 2022 (Paxlovid, EMEA/H/C/005973)

While care for individuals with COVID-19 has improved with clinical experience, the need for vaccines and therapeutics able to prevent, mitigate and treat COVID-19 infections during the ongoing pandemic still remains. Especially protection of vulnerable groups and mitigating the effects of the pandemic on a population level are desired. In addition, some studies have shown that patients might experience potential sequelae, including chronic fatigue, thrombotic events post infection, non-reversible lung disease, etc, although these aspects have not been fully determined yet.

2.2. About the product

Evusheld (AZD7442) is a medicinal product consisting of two components: tixagevimab (AZD8895) and cilgavimab (AZD1061), i.e., two SARS-CoV-2-specific monoclonal antibodies that bind to non-overlapping epitopes on the receptor-binding domain of the S protein and block its interaction with the hACE2 host cellular receptor, resulting in a blockade of virus entry.

The applicant is seeking marketing authorisation for the following indication and associated posology for Evusheld:

EVUSHELD is indicated for the prophylaxis of COVID-19 in adult and pediatric individuals (12 years of age and older and weighing at least 40 kg).

The recommended posology for Evusheld in adult patients and in adolescent patients 12 years of age and older weighing at least 40 kg is 300 mg of Evusheld, as 150 mg of tixagevimab and 150 mg of cilgavimab administered as separate sequential intramuscular injections.

2.3. Quality aspects

2.3.1. Introduction

Evusheld (AZD7442) is a combination of two monoclonal antibodies (tixagevimab and cilgavimab, also known as AZD8895 and AZD1061, respectively) as active substances, presented as a combination pack, which are directed against two distinct, non-overlapping epitopes on the receptor binding domain (RBD) of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike protein. The antibodies were derived from the B cells of individuals who previously recovered from SARS-CoV-2. The monoclonal antibodies (mAbs) have been engineered with YTE and triple mutation (TM) substitutions to extend the mAb half-life and reduce effector function through reduced binding to FcγRs and C1q. When bound to the SARS-CoV-2 spike RBD, the mAbs prevent its interaction with the human angiotensin-converting enzyme 2 (hACE2) host cellular receptor and neutralise the virus by blocking its entry and replication. Tixagevimab and cilgavimab are produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

The finished product is presented as solution for injection containing 150 mg of tixagevimab and as solution for injection containing 150 mg of cilgavimab as active substance.

Other ingredients are histidine, histidine hydrochloride monohydrate, sucrose, polysorbate 80, and water for injections.

Both tixagevimab and cilgavimab finished products, contained in Evusheld combination pack, are available in separate clear glass vials closed by a chlorobutyl elastomeric stopper sealed with a dark-grey aluminium flip-off top (1 vial each per carton).

2.3.2. Active Substance

2.3.2.1. General information

Cilgavimab and tixagevimab are human IgG1κ mAb composed of two identical heavy chains and two identical light chains directed against the receptor binding domain in spike (S) protein of SARS-CoV-2. Both mAbs harbour two distinct mutations (TM and YTE) in the Fc part. The TM substitutions include: a leucine to a phenylalanine at residue 248 or 240, a leucine to a glutamic acid at residue 249 or 241, and a proline to a serine at residue 345 or 337, respectively. The YTE substitutions include: a methionine to a tyrosine at residue 266 or 256, a serine to a threonine at residue 268 or 260, and a threonine to a glutamic acid at residue 270 or 262, respectively. The modifications are well known for other mAbs and are sufficiently described. TM reduces Fc-effector functions, whereas YTE extends serum half-life by enhancing affinity to FcRn. The mode of action of cilgavimab is blocking of SARS-CoV-2 binding to hACE2. The potency of cilgavimab is determined by a binding ELISA. Cilgavimab has a molecular mass of approximately 152 kDa (including glycosylation), and tixagevimab has a molecular mass of approximately 149 kDa (including glycosylation).

The biological and physico-chemical properties have been described in detail.

2.3.2.2. Manufacture, characterisation and process controls

Description of manufacturing process and process controls

Sufficient GMP documentation is provided for the active substance manufacturing sites Samsung Biologics and Lonza biologics, including an acceptable QP declaration.

The cilgavimab and tixagevimab active substance manufacturing processes have been adequately described.

The upstream manufacturing process of the cilgavimab and tixagevimab active substance includes several cell culturing steps. Medium and feed preparation has been described and is sufficiently controlled. After thawing of the working cell bank (WCB) the cells are expanded in shake flasks and rocker bags. The cells are further expanded in seed bioreactors of increasing size and transferred to the final production bioreactor. The in-process controls (IPCs) and other controls of the different steps are sufficiently described, and adequate ranges/limits have been defined. The unprocessed bulk (UPB) is tested for bioburden, mycoplasma, and adventitious viruses, which is acceptable. The active substance is harvested by a continuous flow centrifuge followed by a membrane filtration operation. The protein is then purified using a series of packed bed chromatographic and membrane filtration techniques. Finally, dilution and excipient solutions are added to prepare the active substances. Finally, the formulated bulk is 0.2 micron filtered and filled directly into active substance containers and designated active substance.

The IPCs and other controls of the different steps are sufficiently described and adequate ranges/limits have been defined. Protein concentration (titre) is controlled at the production bioreactor, with an action limit. Cell viability and viable cell density are controlled process attributes throughout cell

culture expansion; pH, conductivity, bioburden, endotoxin and step yield are tested at harvest. Duration of each step is determined. Limit of duration and condition of hold time at harvest is determined. Step yield, bioburden and endotoxin are also tested throughout the purification process. Also, acceptable range/acceptance criteria are defined for each operating parameter/IPC for the downstream process. Preparation, filtration, and storage conditions for media and feeds are described. IPCs, critical process parameters (CPPs), non-CPPs and performance attributes for inoculum and production media are determined. Media and feeds are filtered through 0.2 micron filters, their storage conditions and acceptable ranges are determined. Overall, the process is considered adequately described and the selected operating parameters and in-process/microbial controls are considered sufficient to ensure consistent manufacturing and safety of the cilgavimab and tixagevimab active substances.

The cleaning and storage regimen for the columns is provided in the dossier. Resin lifetime will be validated according to the provided protocol. Results of laboratory scale studies are also provided.

Reprocessing is permitted in case of technical, operational, or automation issues for the virus filtration and filtration of the formulated bulk. The procedure is limited to re-filtrations and adequately described. The batch numbering systems, using unique numerical digits, have been sufficiently described. For the filtration operations at several manufacturing steps, in line filters are used. It has been stated that different filters might be used, and equivalent alternatives are allowed.

Control of materials

An overview of the raw materials used for cell culture, harvest, and purification is provided. Compendial materials are tested according to compendial methods. Non-compendial materials are tested in accordance with in-house specifications. Water for injections (WFI) that is used in the preparation of media and buffers is produced by the manufacturing site and complies with the requirements stated in the Ph. Eur. The chromatography resins have been described in sufficient detail (specific names of resins). Dialysed foetal bovine serum (FBS) and the CHO cell line have been stated as the only animal derived materials used in the manufacturing process. Materials of other biological origin used have been sufficiently described.

The binding sequence for the SARS-CoV-2 spike was obtained from memory B cells from two SARS-CoV-2 patients. The DNA-sequence of the variable domains were sub-cloned into an expression plasmid. The construction of the expression plasmid is sufficiently described. The host cell line for cilgavimab and tixagevimab expression is a CHO-K1-derived cell line adapted to serum free expansion and designated CAT-S. The development of the cell line and the generation of the cilgavimab production cell line is described in sufficient detail. The clonality of the cell line was assured by fluorescence activated cell sorting (FACS)-based single-cell sorting, which was verified by two independent observers.

A research cell bank (RCB) was established and sufficiently tested and shown to be free of adventitious agents. A two-tiered cell banking system has been established for cilgavimab and tixagevimab, including Master Cell Banks (MCBs) and Working Cell Banks (WCBs). Currently one MCB and one WCB have been produced per mAb; however, during the product lifecycle, further WCB batches can be established by expansion of an MCB vial as per protocol provided in the dossier. Furthermore, an End-of-Production (EOPCB) and Limit-of-In-Vitro-Cell-Age (LIVCA) Cell Bank was manufactured for each product. All cell banks were sufficiently tested for identity, safety, and purity including sterility, mycoplasma, mycobacteria, adventitious and endogenous viruses, and species identification. In addition, the MCB, EOPCB, and LIVCA bank are tested for infectious retroviruses. The cell bank testing was performed in line with the relevant guidance (ICH Q5A, Q5B, Q5D, etc.) with all specifications met. The cell line stability has been sufficiently demonstrated. The genetic stability was investigated by

cDNA verification, gene copy number determination and Southern Blotting of the MCB, EOPCB and LIVCA. All cell banks showed comparable results.

Control of critical steps and intermediates

Critical steps and intermediates have been defined individually for each manufacturing site (i.e. Samsung Biologics and Lonza Biologics). In this section, microbial controls and intermediate hold times are defined. CPPs and IPCs have been included and summarised in the dossier, which is considered acceptable. The assigned limits for the microbial control are adequate. The hold times are currently based on microbial control study results are adequate.

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the cilgavimab and tixagevimab active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified.

Nonetheless, biochemical hold time stability studies are still on-going at both manufacturing sites for the cilgavimab intermediates. In the Rolling Review 2 (RR2) response document, the applicant provided a final date by when results will be submitted, and this point is put forward as quality recommendation **(Quality REC 1).**

Process validation

Process validation was performed individually at the two proposed active substance manufacturing sites. The validation of the cilgavimab and tixagevimab formulated active substance manufacturing process included process performance qualification (PPQ) batches, extended hold times validation, limit of *in vitro* cell age, column and filter (lifetime, cleaning and storage) validation, medium, feed and buffer validation. Consecutive PPQ batches were manufactured and extended holds were performed for all PPQ batches. Process parameters selected for the validation studies are appropriate. All three categories of process outputs: IPCs, microbial controls, and performance attributes (PAs), were included in process validation. Process control terminology and tested parameters are identical for cilgavimab and tixagevimab between the Samsung and Lonza Biologics active substance manufacturing sites. All validation criteria were met, with minor deviations not impacting the overall validation. Extended hold times during manufacturing steps were validated.

The same chromatography resins are used for the manufacturing of cilgavimab and tixagevimab, which is considered adequate given the co-administration of both mAbs. Due to the reduced timeline required by the pandemic, commercial-scale runs were initiated prior to the completion of the small-scale studies. Small-scale studies have been stated to be in progress; however, no data are currently available. The applicant is recommended to provide respective data as soon as they become available to set a preliminary maximum number of cycles. This recommendation applies to both active substances. (Quality REC 2). Clearance of process-related impurities is demonstrated. Results confirm that the downstream manufacturing process is capable to decrease the impurity levels consistently well below the acceptable exposure limits. A number of validation studies are still ongoing. These include small scale process intermediate hold validation study based on biochemical stability at both manufacturing sites (only for cilgavimab; this study is completed for tixagevimab), small and commercial scale resin lifetime and carryover studies at both manufacturing sites (both active substances), ultrafiltration membrane lifetime study (both active substances), and small scale validation studies for reprocessing (both active substances). For the aforementioned studies, the applicant provided a date by when the results could be submitted. Microbial challenge results for the resin sanitisation and storage solutions are summarised in the dossier and confirm that the recommended exposure time to the solutions ensures robust inactivation. Validation of resin lifetime

and carryover has been performed in a ”mixed” manner, where both cilgavimab and tixagevimab intermediate batches were used. This approach is acceptable due to prior platform knowledge of the applicant. The UF/DF membrane lifetime and carryover study is being conducted at commercial-scale; the maximum planned number of cycles for the UFDF membrane is not registered in the dossier, and the applicant plans to change the filter when acceptance criteria are exceeded. Studies for reprocessed virus filtration and final filtration are ongoing at small scale applying the same controls as the routine manufacturing process. The currently available data do not show significant effects on resin materials and product carryover. Therefore, due to the pandemic situation and given the monitoring programme at commercial scale, it is acceptable to use the resins without a defined maximum resin lifetime from the small-scale models. The same set of ultrafiltration/diafiltration membranes are used for the manufacturing of cilgavimab and tixagevimab, which is considered adequate given the co-administration of both mAbs. The lifetime studies were performed at commercial scale at Samsung Biologics and Lonza Biologics. Sufficiently detailed information/summaries for the shipping validation are provided and cover the ground route needed. Reprocessing of the virus filtration and 0.2 micron filtration steps are currently evaluated at small-scale. The results of the studies are pending and the applicant is recommended to provide them as soon as they become available **(Quality REC 3).** AstraZeneca commits to provide the results of the reprocessing of the virus filtration and 0.2 micron filtration studies when they become available. At Samsung Biologics, a batch was reprocessed at the viral filtration step. The applicant provided available results from the reprocessed batch which met all validation acceptance criteria.

Manufacturing process development

The development and characterisation of the active substance manufacturing process is adequately described in several sub-sections. For the identification of critical quality attributes (CQA) a Failure mode and effects analysis (FMEA) based severity assessment has been performed. The approach employs a numerical scoring system based on impact and uncertainty. The system is sufficiently described. All Quality attributes (QA) are assessed and the results are provided in a tabular format including rationales for each decision. QAs with severity scores ≥9 are defined as critical.

The cilgavimab and tixagevimab manufacturing process was initially developed at a 500 L scale and up-scaled to support preclinical studies and clinical development.

In order to increase the production capacity for late-stage clinical supply, the formulated active substance manufacturing processes for cilgavimab and tixagevimab were transferred and scaled up. This process uses the clonal cell line at clinical scale. The manufacturing process follows the same overall process flow. A comparison of the formulated active substances manufacturing processes is provided in the dossier. The changes implemented are generally considered related to the cell line change and is called Process 2.

For commercial manufacturing Process 2 was transferred and up-scaled to 15 kL at Samsung Biologics, Incheon, Republic of Korea and 6kL at Lonza Biologics, Portsmouth, USA. Due to the up-scale, facility-specific changes were made to the seed train and viral filter but are otherwise the same as the clinical process. The changes were sufficiently described in the dossier.

A comprehensive comparability programme has been performed for both mAbs, which followed the recommendations laid down in ICH Q5E. Based on the results of batch release and characterisation studies as well as degradation profiles, active substances manufactured using either the clinical or commercial process are considered comparable. The applicant is also recommended to provide degradation profiles for the ongoing comparability study for the LB Process 2 material as they become available. This recommendation applies to both active substances. **(Quality REC 4).** In summary, the development of the manufacturing process is sufficiently described. Despite minor differences affecting non-CQAs the materials from the different processes are considered comparable.

The process characterisation is based on risk assessments of each step to conclude whether dedicated characterisation studies are needed. In the provided risk assessment conclusions to not evaluate certain process parameters are mostly based on prior knowledge with other mAbs or experience with the cell culturing process. This is in general acceptable. The characterisation studies were performed as multivariate or univariate studies. Process parameters (PP) that impact at least one CQA are classified as CPPs, while process parameters that do not impact any CQAs are classified as non-CPPs (NCPPs). The final conclusion of a PP as critical was done by calculating an Impact Ratio. The Impact Ratio is calculated as the Impact (impact on CQA at PP target and upper or lower limit) divided by the Tolerable Impact (CQA limits). A parameter is classified as a CPP when the Impact Ratio for at least one CQA exceeds a predefined threshold. Process parameters with Impact Ratios below this threshold are classified as NCPP. The approach is considered adequate, and the results (defined for most CPP/NCPP) are acceptable. The risk of extractables and leachables originating from the manufacturing process materials was evaluated using a three-step safety risk assessment strategy. The approach is sufficiently described and uses questionnaire-based evaluation of the product contact materials followed by a detailed risk assessment (including contact duration, temperature, material surface to product volume ratio, and proximity to active substance in the process sequence). Materials with a defined medium or high risk are finally assessed taking into consideration the process step where the material is used, contact area (relative to the overall process volume), and expected clearance capability of leachables in subsequent process steps. If a potential concern remains, the safety risk is estimated using relevant in-house, supplier, and toxicological data. As they are used in the upstream part of the manufacturing process this is considered adequate as sufficient clearance of small molecules during the downstream process is expected.

Characterisation

The cilgavimab and tixagevimab active substances have been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a human IgG1-type antibody. The analytical results are consistent with the proposed structure.

The Reference Standards were used in the characterisation analysis and elucidation of structure tests. Characterisation was performed extensively with a broad range of analytical techniques. Primary structure was confirmed and post-translational modifications like heavy chain glycosylation, galactosylation, C-terminal Lys removal, asparagine deamidation, N-terminal cyclisation, and methionine oxidation were analysed. Disulfide bond structure was confirmed by peptide-mapping of non-reduced mAbs. The theoretically expected amino acid sequence of both the mAbs was confirmed by LC/MS peptide mapping (using trypsin, 100% sequence coverage) and mass analysis of deglycosylated samples. The disulfide bridges corresponding to the known IgG1 structure have been identified by comparing non-reduced and peptide maps to those obtained upon reduction of the proteolysate. In both mAbs, the predominant glycoforms are G0F, G1F and G2F (complex, biantennary structures with core fucosylation). High mannose was detected in low amounts. Human IgGs contain one conserved N-linked glycosylation site located in the CH2 domain in the heavy chain. For cilgavimab, the N-linked glycosylation site is Asn-311. For tixagevimab, the N-linked glycosylation site is Asn-303. No other N-glycosylation or O-glycosylation sites were detected. Immunogenic carbohydrates, namely NGNA and gal-(α 1-3)-galactose were not identified in either mAb. Charge isoforms were analysed by adequate techniques, and the acidic and basic fractions were qualitatively correlated with post-translational modifications. Low amounts of high and of low molecular weight variants have been detected using HPSEC, analytical ultracentrifugation and capillary SDS-electrophoresis. Sedimentation analysis confirm the relative amount of HMW component. Disulfide bond structure of both mAbs was determined and the disulfide bonds expected for IgG1 type immunoglobulins were confirmed. Far- and near UV CD spectra were compatible with the known

immunoglobulin fold. Regrettably, no experimental data reflecting on the overall molecular size and shape (e.g. sedimentation velocity figures, hydrodynamic radius) of the two mAbs was provided; nevertheless, assuming that cilgavimab and tixagevimab are similar to the known IgG1 type IgGs, this seems reasonable. For both cilgavimab and tixagevimab, the product-related substances not classified as CQA by the risk assessment procedure are discussed in the relevant section of the dossier. For tixagevimab, methionine oxidation in the variable region was also identified. Assessment of potential impact on biological activity, PK, immunogenicity and safety revealed a low risk of these variants. Glycation was found in both cilgavimab and tixagevimab batches. Forced glycation studies, however, indicated that not even very high degrees of glycation exert a negative influence on potency or FcRn binding. Overall, the non-CQA classification of the product-related substances is considered justified for both cilgavimab and tixagevimab.

Furthermore, binding activity to the SARS-CoV-2 Spike protein was determined, and the ability of cilgavimab and tixagevimab to block SARS-CoV-2 Spike protein from binding to the hACE2 receptor on the target cell was measured with a pseudovirus as well as a SARS-CoV-2 neutralisation assay. Cilgavimab and tixagevimab are IgG1s and harbor two mutations (TM and YTE) in the Fc-domain. The TM mutation was included to reduce Fc-effector functions. Binding of FcγRIIIa showed a reduced binding capacity in comparison to a positive control IgG1 mAb. Based on these data and the well-known TM mutation, it is considered acceptable to omit further Fc-effector function analyses (e.g. ADCC, CDC assays, etc.). Furthermore, cilgavimab and tixagevimab harbor the also well-known YTE mutation in the Fc-part, to enhance binding to FcRn and, thereby, prolong the serum half-life of the mAb. This enhanced binding property was confirmed by an AlphaLISA binding assay. The characterisation of the structural aspects and biological activities, including potency, is considered 'state of the art' and does not raise any issues.

The impurities of cilgavimab and tixagevimab were divided into process- and product-related impurities. This is considered acceptable. Process-related impurities with high criticality scores consist of Host cell DNA, Host Cell protein, and Protein A. Potential impurities, like small molecules or synthetic macromolecules, were assessed for safety. All potential impurities were shown to bear minimal acceptable risks for patients with sufficiently high impurity safety factors.

In summary, the characterisation is considered appropriate for this type of molecule.

2.3.2.3. Specification

Specifications for the cilgavimab and tixagevimab active substances are defined in accordance with ICH Q6B. The proposed tests and limits are considered adequate.

A correlation between target antigen binding and virus neutralisation capacity to examine whether the potency test reflects on the therapeutic goal of the product has been adequately shown.

Where acceptable limits were established in pharmacopoeia, regulatory guidance, or relevant scientific publications, these have been adopted. These tests are endotoxin, bioburden, host cell DNA and host cell proteins. In the response document, the applicant agreed with revising the limit on the basis of batch results (Quality REC 8).

In the response document the applicant agreed with revising the acceptance limits when results of additional batches will be available. This recommendation applies to both active substances **(Quality REC 5).**

Analytical methods

The analytical procedures for cilgavimab and tixagevimab are identical. All compendial and non-compendial assay have been adequately described and verified or validated in accordance with ICH, as applicable. References to the compendial analytical methods have been included into the specifications tables for both active substance and finished product for both mAbs. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines. The potency of active substance and finished product is determined by target binding ELISA. The intervals will be recalculated, and the specifications reassessed when additional active substance batches are available for each molecule. This point is put forward as Quality **REC 6**.

All compendial and non-compendial assay have been adequately described and verified or validated, as applicable. References to the compendial analytical methods have been included into the specifications tables for both active substance and finished product for both mAbs. However, the reference IDs of the in-house method should as well be included in the documents in Sections 3.2.S.4.1 and 3.2.P.5.1. **(Quality REC 11)** The tests were transferred to Lonza Biologics as an alternative testing site for release and stability. Transfer validation was demonstrated. As the robustness study was conducted during method development and not with the analytical validation, the applicant will not incorporate the robustness data into the validation section. This does not stand in contradiction to the guidance of ICHQ2. However, robustness study data are recommended to be inserted into an appropriate section of the dossier, e.g. S.2.6. This point is put forward as recommendation and applies to both active substances **(Quality REC 10).**

Batch analysis

Batch information and release data on multiple lots are provided for both mAbs using the manufacturing processes. The results are within the specifications and confirm consistency of the manufacturing process. Batch release data are provided for cilgavimab and tixagevimab active substances manufactured by the commercial process P2 and the previous P1 process. The results from both sites (Samsung Biologics and Lonza Biologics) are comparable. All test results met the pre-defined acceptance criteria.

Reference materials

A two-tiered system with a primary and working reference standards (RS) has been established for cilgavimab and tixagevimab. Qualification data demonstrated their suitability as primary RS. The qualification and stability acceptance criteria for future primary and working standards have been provided.

Container closure system

The container closure system of cilgavimab and tixagevimab active substance is adequately described. Stability studies demonstrate consistent active substance product quality over long-term storage, including no observed precipitation or adsorption (no change in protein concentration) to date. Extractable and leachable studies were performed. No compound was detected above threshold of toxicological concern (TTC) of 20 µg/day in line with ICH M7 (R1).

For the simulated leachables study on the active substance container, results beyond those provided for the 2–8°C and 23–27°C conditions are recommended to be submitted as soon as they are available. This recommendation applies to both active substances and is put forward as recommendation (Quality REC 12).

2.3.2.4. Stability

The stability results indicate that the active substances are sufficiently stable and justify the proposed shelf life when stored at 2-8°C in the proposed container.

Overall, the analytical methods used are considered sufficiently sensitive and able to detect the main degradation pathways of cilgavimab and tixagevimab active substance. Taken together, it can be concluded that the used analytical methods are sufficiently stability-indicating. An adequate post-approval stability protocol has been provided.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

The cilgavimab and tixagevimab finished products are available as sterile, preservative-free, liquid dosage form in a vial. The finished product is a clear to opalescent, colourless to slightly yellow, pH 6.0 solution. Commonly used and compendial compliant excipients are used. It is formulated at 150 mg of cilgavimab or tixagevimab per vial with a 1.5 mL label-claim volume. It is formulated at 100 mg/mL cilgavimab or tixagevimab in L-histidine/L-histidine hydrochloride monohydrate, sucrose, and polysorbate 80, pH 6.0.

All excipients used for the manufacture of the finished product are of compendial grade. No excipients of human or animal origin or novel excipients are used.

During development, the formulation of cilgavimab and tixagevimab was changed from an initial lyophilised to a liquid formulation. The concentration and excipient formulation did not change during the entire development. Minor changes were made to the vial and stopper used. Adequate univariate and multivariate formulation characterisation studies have been performed. The data support the use of the formulation.

The finished product does not include overages. An overfill is used to guarantee the withdrawal of the required dose. The finished product was initially developed as a lyophilised formulation and subsequently changed into a liquid formulation. The process was finally transferred to Samsung Biologics and up-scaled to Process 2 Commercial.

An ICH Q5E compliant comparability study was performed to assess the potential impact of process, scale, and site changes on the quality attributes of cilgavimab. Additional characterisation and stress stability analyses showed comparable results. Taken together, material manufactured at Samsung Biologics Process 2 Commercial is considered comparable to the materials used during development and clinical trials.

Process characterisation studies were performed to evaluate product quality impacts of process parameters, resulting in their classification as either CPPs or NCPPs. The impact of process parameters on process performance was also determined. A process failure mode evaluation analyses (pFMEA) was used and each manufacturing step investigated. Acceptable ranges were defined for NCPPs.

The finished product cannot be finally sterilised by heat and does not include preservatives. Therefore, sterility is ensured by sterile filtration, release testing for sterility and endotoxins and container closure integrity (CCI). The control strategy has been sufficiently described. Furthermore, Rabbit Pyrogen Tests have been performed demonstrating that cilgavimab and tixagevimab are not pyrogenic.

Cilgavimab and tixagevimab are intended to be administered by intramuscular injection. Compatibility studies were performed using 3 mL polypropylene (PP) syringe as well as a 1 mL polycarbonate (PC)

syringe with a 23G gauge stainless steel needle (syringes provided separately). The in-use compatibility study demonstrates the in-use stability of the finished product in the syringe for IM injection for up to 4 hours at 2-8°C or 4 hours at room temperatures up to 30°C.

The container closure system has been sufficiently described. Extractable and leachable studies revealed no compounds potentially present in the finished product originating from the container closure materials at reasonable concentrations.

The primary packaging is a clear glass vial closed by a chlorobutyl elastomeric stopper sealed with a aluminium flip-off top. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.3.3.2. Manufacture of the product and process controls

The cilgavimab and tixagevimab finished product is manufactured at Samsung Biologics, Republic of Korea, and subsequently labelled and secondary packaged. Sufficient GMP documentation is provided for the finished product manufacturing sites. A QP declaration has been provided for Samsung Biologics and Lonza Biologics. The batch size range for the finished product is defined.

The cilgavimab and tixagevimab manufacturing process at Samsung Biologics is provided in the dossier consists of thawing, pooling, bioburden reduction filtration, mixing, sterile filtration, aseptic filling, stoppering, capping, and 100% inspection of filled vials. The filled vials are transferred to the secondary packaging site where labelling and secondary packaging takes place. Each step has been further described in sufficient detail. Time out of refrigeration (TOR) limits for the active substance and finished product have been indicated. No reprocessing of a manufacturing step is mentioned. The batch numbering systems, using unique numerical digits, have been sufficiently described. CPPs, IPCs, and intermediate hold times were determined during process characterisation and validation studies. The control elements together with their respective acceptance criteria were adequately included into the dossier.

The finished product manufacturing process was validated at Samsung Biologics, Incheon, Republic of Korea. Three process validation runs were conducted for the primary finished product manufacturing process. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate. Additional auxiliary validations to support the manufacturing process were as follows: aseptic process validation, container closure integrity testing, filter validation, and shipping qualification. Information about the area of the sterilising filter should be stated in Module 3.2.P.3.3 of the dossier according to the Guideline on the sterilisation (EMA/CHMP/CVMP/QWP/850374/2015) (Quality REC 13). This recommendation applies to both finished products. Shipping validation was performed as simulated transportation study.

2.3.3.3. Product specification

Finished product specifications are set in accordance with ICH Q6B, with acceptably defined acceptance criteria.

Concerning potential finished product impurities reference is made to corresponding AS section, which is considered adequate as no new impurities are expected.

A risk evaluation concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the

"Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Furthermore, an elemental impurity analysis in line with ICH Q3D is currently ongoing, and the applicant is recommended to provide results of the studies **(Quality REC 7).**

Analytical methods

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines. The methods used for finished product testing are either compendial test methods which do not require validation or are identical to the methods used for cilgavimab and/or tixagevimab active substance testing, with the exception of the lateral flow identity and the container closure integrity assay used for identity and sterility (during stability) testing of the finished product. The assay was sufficiently validated covering specificity, limit of detection, and robustness.

Batch analysis

Batch analysis data on several batches of the finished product were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Reference materials

The reference standard used for finished product and the active substance are the same.

2.3.3.4. Stability of the product

The proposed shelf life of cilgavimab and tixagevimab finished product is 18 months when stored in a refrigerator (2-8°C), in the original package in order to protect from light. The finished product should not be frozen nor shaken. Chemical and physical in-use stability has been demonstrated for 4 hours at 2ºC to 25ºC.

The stability of cilgavimab and tixagevimab finished product was evaluated based on ICH Q5C: Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products. Stability studies are ongoing. However, given the current COVID-19 pandemic situation, the approach of the applicant to define a shelf life for cilgavimab and tixagevimab finished products is considered appropriately justified and, thus, accepted for three Process 2 Commercial finished product batches (Process Validation batches). These batches are considered production batches, based on the definition provided in ICH Q1A(R2). Due to the accelerated development of cilgavimab in response to the COVID-19 pandemic, the usual volume of stability data that would be provided for the proposed commercial finished product are not yet available. In line with ICH Q5C, the batches were tested under long-term (2-8°C), accelerated (23-27°C/55-65% RH) and stress (38-42°C/70-80% RH) conditions. Fifteen (up to 12 for clinical and up to 9 for commercial batches) months are currently available for the development batches under long-term conditions. All acceptance criteria were met.

The initial set shelf-life is set at 18 months under long-term conditions based on extrapolation of 9 months stability data. Extrapolation is normally not acceptable for mAbs at MAA. However, due to the pandemic situation and given that 15 months are available for clinical/development batches and comparability to the commercial batches has been shown, the extrapolation was considered justified.

Any further extension of the shelf-life will be done by submission of a variation and it is expected to be based on real-time data of commercial batches. A confirmatory photostability study is planned that will be conducted in accordance with ICH guidance Q1B using one batch of cilgavimab and tixagevimab finished product to demonstrate that the design of the finished product container/closure in secondary packaging (commercial marketing pack) protects the product from potential light exposure during product storage and transportation activities.

2.3.3.5. Adventitious agents

TSE compliance

No animal-derived material is used during the manufacturing process of cilgavimab and tixagevimab. The MCBs are free from TSE-risk substances. There are no excipients of animal origin. In summary, compliance with the TSE guideline (EMEA/410/01 – rev. 3) has been sufficiently demonstrated.

Virus safety

For viral agents, the capacity of manufacturing procedure to eliminate viral agents has been shown in a satisfactory manner. The viral clearance assessment is considered acceptable. Four purification steps were evaluated for their viral clearance capacity, low pH treatment, AEX chromatography, CEX chromatography and virus filtration. The choice of model viruses (Xenotropic Murine Leukemia, Pseudorabies Virus, Reovirus Type 3 and Minute Virus of Mice) can be approved. Reports from the contract laboratory that have performed the virus titre assays are attached. A concise description of the virus titre determination has been submitted. For the scale-down model, process parameters were compared to those in place at manufacture. In addition, process performance data for the AEX and the CEX steps has been submitted. For endogenous viruses, satisfactory safety factors were reported for both cilgavimab and tixagevimab. Prior process experience with both anion and cation exchange chromatography resins for other AstraZeneca monoclonal antibodies supports effectiveness of virus reduction using re-used resins.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of Evusheld, which has been developed as a combination pack of two active substances, cilgavimab and tixagevimab, and their respective finished products, has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that Evusheld should have a satisfactory and uniform performance in clinical use.

A finished product manufacturing site was included in the dossier although process validation was not complete. The absence of completed process validation data was identified as a major objection during RR2 stage. The applicant has subsequently removed the site from the dossier, which resolved the major objection. At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. These points have been put forward and agreed as recommendations for future quality development (see section 2.3.6).

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of Evusheld is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on viral/TSE safety.

2.3.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant is recommended to provide biochemical hold time stability data for cilgavimab intermediates once the study is completed.
2. The applicant is recommended to provide the results of the chromatography resin lifetime studies once they are available. This recommendation applies to both active substances.
3. The applicant is recommended to provide the results of the reprocessing of the virus filtration and 0.2 micron filtration studies when they become available. This recommendation applies to both active substances.
4. The applicant is recommended to provide degradation profiles for the ongoing comparability study for the LB Process 2 material as they become available. This recommendation applies to both active substances.
5. Regarding the potency assay, the applicant is recommended to recalculate the tolerance intervals used to assess process variability for the Stability Limits Approach and Non-Stability Limits Approach once a sufficient number of batches are available. This recommendation applies to both active substances.
6. The applicant is recommended to recalculate the acceptance criteria for Target Binding Potency Assay once a sufficient number of batches are available. This recommendation applies to both active substances.
7. The applicant is recommended provide the final results of the elemental impurities risk assessment as soon as they become available. This recommendation applies to both active substances.
8. Revision of AS HCP acceptance limits on the basis of batch results is recommended for both cilgavimab and tixagevimab.
9. The applicant is recommended to provide the updated analysis for the multivariate FP formulation characterisation. This recommendation applies to both finished products.
10. As the robustness study was conducted during method development and not with the analytical validation, the applicant will not incorporate the robustness data into the validation section. This does not stand in contradiction to the guidance of ICHQ2. However, robustness study data are recommended to be inserted into an appropriate section of the dossier, e.g. S.2.6. This recommendation applies to both active substances.
11. The applicant is recommended to list the reference IDs of the in-house method documents in Sections 3.2.S.4.1 and 3.2.P.5.1.
12. For the simulated leachables study on the active substance container, results beyond that presented for the 2–8°C and 23–27°C conditions are recommended to be submitted as soon as they are available.
13. Information about the area of the sterilising filter should be stated in Module 3.2.P.3.3 of the dossier according to the Guideline on the sterilisation (EMA/CHMP/CVMP/QWP/850374/2015). This recommendation applies to both finished products.

2.4. Non-clinical aspects

2.4.1. Introduction

2.4.2. Pharmacology

AZD7442 (Evusheld) is a combination product of two IgG1 mAbs, (tixagevimab and cilgavimab, also known as AZD8895 and AZD1061), targeting the SARS-CoV-2 spike protein. Both antibodies are derived from the B cells of individuals who previously recovered from SARS-CoV-2 infection and have been engineered with YTE and TM substitutions in the Fc region, to extend mAb half-life and reduce Fc effector function.

2.4.2.1. Primary pharmacodynamic studies

In vitro studies

AZD8895, AZD1061 and AZD7442 were shown to bind with picomolar affinity to the SARS-CoV-2 spike protein trimer ectodomain (KD: 2.76 pM, 13.0 pM and 13.7 pM respectively), and with nanomolar affinity to the spike-RBD. Importantly, the mAb combination AZD7442 bound with approx. 3000x higher affinity (KD: 13.7pM) to the spike trimer than the cellular receptor hACE2 (43 nM).

Co-crystal structures and cryo-electron microscopy (cryo-EM) analysis confirmed that the two antibodies bind simultaneously to the RBD and recognize two unique, non-overlapping epitopes. The structures identified key AZD8895 interactions with RBD residue F486 and AZD1061 interactions with residues K444 and R346. The structures also support human ACE2 (hACE2) blocking as the mechanism of action for AZD8895 and AZD1061, as their epitopes and binding sites overlap with the hACE2 interface.

Functionally, AZD8895, AZD1061 and the combination AZD7442 blocked the interaction of the RBD and hACE2 with comparable IC50 values of 318 pM, 531 pM and 433 pM, respectively. Consistently, AZD8895, AZD1061 and AZD7442 neutralised the USA-WA1/2020 strain of SARS-CoV-2 on Vero E6 cells, with calculated IC50 values of 9, 32 and 10 ng/mL, respectively. Across different assay formats, AZD8895 was slightly more potent than AZD1061, which is in line with its higher affinity for the spike RBD.

In a dose-response neutralisation test using wild-type SARS-CoV-2 and Vero E6 cells the combination of AZD8895 and AZD1061 demonstrated synergistic neutralisation. Similarly, in a dose-response neutralisation matrix using spike-pseudotyped lentivirus, the majority of combination doses of the two mAbs were found to show synergy. In both experiments, synergistic neutralisation was best demonstrated at suboptimal mono-mAb concentrations.

In vivo studies

The *in vivo* efficacy of single doses of AZD7442 has been assessed for the treatment and prevention of SARS-CoV-2 infection in two non-human primate (NHP) studies (MCBS7442-0006 and MCBS7442-0013) and two Syrian golden hamster studies (MCBS7442-0008 and MCBS7442-0011).

Monkeys and hamsters are both models for COVID-19 and have also been used for non-clinical evaluation of SARS-CoV-2 vaccines. The development of clinical symptoms of infection like loss of body weight and pulmonary pathology are more pronounced in hamsters compared to monkeys, possibly making the hamster a more suitable model to evaluate the effect of AZD7442.

AZD7442 was evaluated in two separate NHP models of SARS-CoV-2 infection; one in rhesus macaques and one in cynomolgus macaques. For each study, 3-4 NHPs were administered either an isotype control antibody or AZD7442 at a dose ranging from 40 to 0.04 mg/kg by IV infusion 3 days prior to virus challenge (prophylaxis analysis) or a 40 mg/kg dose of AZD7442, 24 hours after virus challenge (therapeutic analysis). To evaluate contributions of Fc effector function in viral clearance, one group from each study received AZD7442-YTE (mAb with YTE but not TM substitution) as either prophylaxis (4 mg/kg, rhesus macaque study) or treatment (40 mg/kg, cynomolgus macaque study).

Rhesus macaques and cynomolgus macaques were challenged with 100,000 pfu or 100,000 TCID50, respectively with the total virus inoculum split between IN and IT administrations. The viral strain used in the challenges is SARS-CoV-2 strain USA-WA1/2020 (GenBank MN985325.1) which is close to the strain used to build the antibodies.

In both studies, AZD7442 serum levels increased rapidly in a dose-dependent manner following administration and animals that received AZD7442 in treatment showed near maximal serum concentrations within 1 day of dosing. The 4 mg/kg dose resulted in serum AZD7442 concentrations comparable to those observed in humans following 300 mg AZD7442 administration.

Only limited histopathology results are presented. There are no upper respiratory tract slides presented. As the infectious dose is low and NHPs only recapitulate mild disease, the protection of AZD7442 is not apparent in histopathology. The protection is best seen by a comparison of viral loads in the treated vs. control groups and is not very apparent in the treatment setting. The duration of protection is not addressed but will be based on clinical data.

Prophylactic AZD7442 administration demonstrated dose-dependent reduction of SARS-CoV-2 burden in BAL and nasal swab samples compared with control antibody. AZD7442 administration post-exposure resulted in only a modest reduction of SARS-CoV-2 burden. In both experiments AZD7442 showed a similar efficacy as the TM-less AZD7442-YTE at equivalent dose, indicating that antibody effector function is not required for AZD7442 elimination of SARS-CoV-2.

In hamsters, studies were conducted with AZD7442-TM, which incorporates TM but not YTE substitutions. For the prophylaxis study, hamsters were administered 2 mg of an isotype control antibody or AZD7442-TM IP at doses ranging from 0.002 to 2 mg one day prior to SARS-CoV-2 infection. For the treatment study, hamsters were administered 5 mg of the isotype control antibody or AZD7442-TM IP at doses ranging from 0.5 to 5 mg at either 24 or 48 hours after virus challenge. Hamsters were weighed daily after being challenged IN with 100,000 pfu of the USA-WA1/2020 strain of SARS-CoV-2, and euthanised on Day 3 or Day 7 post-infection for virological and histologic assessments.

Prophylactic AZD7442-TM administration protected hamsters against loss of body weight.

AZD7442-TM additionally decreased the viral load in the lungs in a dose-dependent manner; hamsters from the 2 mg dose group showed infectious virus titres below level of detection by Day 3 post-infection. In the treatment study, hamsters that received isotype control antibody showed approximately 5% loss in body weight during the week following SARS-CoV-2 infection.

In contrast, AZD7442-TM treatment at either 24 or 48 hours post-infection, protected hamsters against weight loss and also showed some reduction in viral burden which becomes more apparent at day 7 compared to day 3.

Histologic analyses of hamster lung sections confirmed the viral load results and also showed that prophylactic AZD7442-TM administration resulted in dose-dependent reduction of inflammation and pathologic lesions in the lungs whereas in the therapeutic setting, the administration of ADZ7442 showed a more modest efficacy, although a trend for a faster resolution of the infection was noted on

day 7 post infection compared to the scores at day 3. In both hamster studies, results on viral loads or histopathology in the upper respiratory tracts were not provided and the resulting transmissibility is unknown but considered as likely.

In both NHP and hamster models the *in vivo* efficacy of AZD7442 appears more clearly in the prophylactic setting compared to therapeutic setting even when higher doses are administered shortly after infection. The applicant does however not claim for a therapeutic indication at this point.

Anti-viral resistance studies

The binding sites of AZD8895 and AZD1061 on the spike receptor binding domain were identified based on crystallography data. AZD8895 recognises 17 residues (AA 455-456, 458, 475-480, 483-489, 493), F486 being identified as a key residue. AZD1061 recognises 19 residues (AA 345-346, 439-441, 443-447, 449-450, 452, 484, 490, 492-494, 499), with R346 and K444 found to be critical for the mAb-RBD interaction. In line with these structural data, pseudovirus expressing spike with the substitution F486A was not neutralised by AZD8895, and pseudovirus expressing the substitution K444A was not neutralised by AZD1061. Importantly, the mAb combination AZD7442 was able to neutralise the variants escaping individual mAbs.

Different methodologies were used to select for SARS-CoV-2 virus showing reduced susceptibility to the individual mAbs (AZD8895 or AZD1061), and/or to the AZD7442 combination *in vitro*. Virus variants that escape mAb neutralisation were isolated following serially passaging of SARS-CoV-2 strain USA/WA-1/2020 or replication competent recombinant VSV expressing SARS-CoV-2 spike protein in the presence of increasing concentrations of AZD8895, AZD1061 or AZD7442 or the parental mAb, respectively. In both experiments, the selected escape variants showed reduced susceptibility to AZD1061 alone, but not to AZD8895 alone or to the AZD7442 combination when compared to reference virus. This suggest that the combination of two mAbs may provide a higher threshold for development of escape variants.

AZD1061 selected for viruses with amino acid substitutions at spike residues 74, 364, 444 and 686. AZD1061 was found to bind with much lower affinity to spike protein with individual amino acid substitutions R346I, K444E and K444R; moreover, pseudovirus encoding spike with these amino acid substitutions were less susceptible to AZD1061-mediated neutralisation. These data are consistent with the structural analysis, which identified residues R346 and K444 as critical residues for the interaction with AZD1061.

In additional studies the applicant assessed how conserved the residues recognised by AZD7442 are in circulating SARS-CoV-2 strains. Fourteen of 17 residues bound by AZD8895 and 16 of 19 residues bound by AZD1061 were conserved in > 99% of SARS-CoV-2 genome sequences (n= 2,620,237, analysis through 02 Sept. 2021). The remaining positions were conserved in 67.17% to 97.85% of the sequences. More recent SARS-CoV-2 variant strains harbour characteristic RBD substitutions such as E484K (Beta, Gamma, Eta and Mu variants) or T478K (e.g. Delta variant). Nevertheless, in SARS-CoV-2 viruses circulating from May to August 2021 (n= 586,022) the E484 residue was present to 94.4 %, while the T478 variant was present to only 30.4%.

The applicant has further evaluated to what extent AZD7442 and the individual mAbs are capable of neutralising variants with identified modifications in the spike protein. Neutralisation tests with pseudo-viruses harbouring individual amino acid substitutions in the spike identified the F486S and F486V variants with greatly reduced susceptibility to AZD8895 (> 600x and approx. 150x, respectively). The R346I, K444E, K444Q, K444R, V445A variants were identified as variants with greatly reduced susceptibility to AZD1061 (> 200-fold). Variants with reduced susceptibility to AZD7442 were also observed (E484L, Q493R, E990A, T1009I), however, the level of reduction of susceptibility to the combination was low (up to 5-fold).

Importantly, the applicant also evaluated the potency of AZD7442 and the individual mAbs against authentic circulating SARS-CoV-2 variants including variants of concern. The combination AZD7442 was able of neutralising the identified variants of concern circulating up to Sept. 2021, i.e. Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1) and Delta (B-1-617.2). The so far dominant Delta variant of concern was inhibited with a similar IC50 as the initial SARS-CoV-2 variant.

The evaluation, to what extent AZD1061, AZD8895 and AZD7442 maintain neutralising capacity against the newly detected variant of concern Omicron (B.1.1.529) is ongoing and updated information was provided by the applicant (Feb. 2022). Based on experiments conducted by different, third-party laboratories, AZD7442 maintained neutralising capacity against the Omicron variant, albeit at reduced efficacy with IC50 values ranging from 171 to 277 ng/ml. Compared to the inhibition of the original strain of SARS-CoV-2, the inhibitory activity of AZD7442 was reduced by 12 to 30-fold in assays using authentic virus and by 132 to 183-fold in pseudotype virus neutralisation assays. Additional *in vitro* data submitted by the applicant using pseudovirus neutralisation assays confirmed the reduced potency of AZD7442 against Omicron B.1.1.529/BA.1 and Omicron + R346K variants as compared to the original strain.

The *in vivo* potency of AZD7442 against the Omicron variant was also studied in a K18-hACE2 transgenic mouse model (data from 3rd party) where the prophylactic efficacy of AZD7442 against SARS-CoV-2 strains D614G, B.1.1.529 and B.1.1.529+R346K was compared. AZD7442 reduced viral load in lungs for all the strains tested, with a greater effect for the D614G strain, a lower reduction for B.1.1.529 and even lower for B.1.1.529+R346K. There is no data provided in the treatment setting in that experiment.

The applicant finally referred to a treatment study in Syrian golden hamster (Uraki et al,) which is not peer-reviewed. Animals were treated one day after infection with either D614G or Omicron NC928. Despite some limitations, this *in vivo* data confirms the results in mice and the *in vitro* findings, i.e. a significantly reduced potency of AZD7442 against the Omicron variant.

The clinical relevance of that reduced neutralising activity of AZD7442 against the Omicron variant noted *in vitro* and *in vivo* remains unknown.

2.4.2.2. Secondary pharmacodynamic studies

Secondary pharmacology in vitro

The Fc regions of both AZD8895 and AZD1061 incorporate amino acid residue substitutions to extend their half-life (YTE substitutions) and to reduce Fc effector function (TM substitutions). This change in Fc functionality (compared to wt IgG1) was adequately confirmed by *in vitro* studies.

As shown by surface plasmon resonance binding experiments, incorporation of the YTE substitutions in AZD8895 and AZD1061 increased their affinity to FcRn at low pH (by approx. 8.5x for human FcRn; approx. 6x for cynomolgus FcRn). According to published literature [Dall'Aqua et al., 2006; Robbie et al., 2013] the increase in binding affinity to FcRn at low pH can be expected to translate to a longer half-life *in vivo* in non-human primates and in humans.

Incorporation of the TM substitutions was shown to reduce binding of AZD8895 and AZD1061 to FcγRs and C1q. At concentrations ranging from 50 µg/mL to 450 µg/mL AZD8895, AZD1061 and AZD7442 demonstrated limited or no binding to FcγRs and complement C1q. These mAb concentrations lie in the range of serum concentrations observed in a phase I study in healthy volunteers (study D8850C00001). For AZD7442 administered at 300 mg IM, Cmax was 31.8 µg/ml, at the 3000 mg IV dose Cmax was up to 971 µg/ml. The functional impact of the TM modification in the Fc part was confirmed in cell-based assays. AZD8895 and AZD1061 did not mediate Fc-dependent effector

functions, such as Ab-dependent phagocytosis, cellular cytotoxicity, NK-cell activation and complement deposition. Furthermore, AZD8895, AZD1061 and AZD7442 did not mediate uptake of spike-pseudotyped virus particles by cells that express FcγRs and not ACE2, indicating that the antibodies do not support antibody-dependent enhancement of infection (ADEI) of cells that lack ACE2 receptor expression. This extensive panel of *in vitro* functional tests addresses relevant Fc-mediated effector functions which could contribute to Ab-dependent enhancement of disease (ADE). Based on the results from the *in vitro* studies, the risk that AZD8895 and AZD1061 mediate ADE can be considered low.

Secondary pharmacology in vivo

Additional studies were conducted to evaluate to what extent the presence of AZD7442 would impact the development of vaccine-elicited immune responses. AZD7442 was administered prior to vaccination to enable maximum circulating concentrations of AZD7442. The vaccine used is AZD122, the Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein (ChAdOx1-S). Studies were performed in mice and NHPs where the vaccine-induced humoral and cellular responses were evaluated after 2 immunisations.

AZD1222-immunised BALB/c mice demonstrated comparable levels of antibodies to spike or RBD and comparable levels of spike-specific T cell responses regardless of whether they were given prior administrations of AZD7442-TM or an isotype control antibody. Similarly, AZD1222-immunised cynomolgus macaques demonstrated comparable levels of antibodies to spike or RBD and comparable levels of spike-specific T cell responses regardless of whether they were given prior administrations of AZD7442 or an isotype control antibody.

The applicant claims that pre-administration of AZD7442 did not alter either the humoral or cellular immune responses elicited by AZD1222, and therefore considers that AZD7442 administration is not anticipated to interfere with vaccine-mediated immunity in the clinical setting. However, the justification regarding the drop in AZD7442 exposures noted as of 14 days after the first immunisation compared to the controls is not considered sufficiently robust and the absence of any potential interference cannot be ruled out.

2.4.2.3. Safety pharmacology programme

Safety pharmacology endpoints were assessed as part of the single-dose toxicity study in cynomolgus monkeys. This is acceptable in line with ICH S6 (R1). The study revealed no AZD7442-related effects on the cardiovascular, respiratory and central nervous system.

2.4.2.4. Pharmacodynamic drug interactions

PD drug interaction studies have not been conducted and this is considered acceptable.

2.4.3. Pharmacokinetics

Kinetics of AZD1061 and AZD8895 were evaluated after single IV administration in mice transgenic for human FcRn and in cynomolgus monkeys as part of the single-dose toxicity study after IV and IM administration. This is in line with the intended clinical administration.

Methods

In mice, serum concentrations of AZD8895 and AZD1061 were determined using a qualified ELISA which is based on the detection of human IgG. In cynomolgus monkeys, serum concentrations of AZD8895 and AZD1061 were determined by a validated LC-MS/MS assay. After immuno-affinity

enrichment of the mAbs and proteolytic digestion, characteristic peptides were quantified as surrogates of the individual mAb concentrations. LoQ of the method (9.00 µg/ml) is rather high. However, this is accepted, considering the high doses of AZD8895 and AZD1061 administered in the toxicity study.

Pharmacokinetics in huFcRn transgenic Tg32 mice

HuFcRn transgenic mice (Tg32) are considered a suitable model to assess target-independent kinetics of human IgG molecules since changes to the Fc part affecting the binding to human FcRn will be adequately reflected in these animals. YTE substitutions in the Fc enhance mAb half-life *in vivo*. The TM substitution in the Fc is not expected to affect mAb PK which was confirmed in the present study using two versions of the control Ab MEDI8897. PK of MEDI8897 with and without TM substitution was comparable.

After single IV administration of AZD8895, AZD1061 or control antibodies at 5 mg/kg, Cmax was consistently observed at the first sampling point post-dose (1 hr). Serum concentrations declined in a multi-phasic fashion. For AZD1061, mean volume of distribution was 121 ml/kg and t1/2 was 17.7 days; for AZD8895, mean volume of distribution was 126 ml/kg and t1/2 was 31.7 days. The values for AZD8895 need to be interpreted with caution, since approx. 59% of AUC0-inf for AZD8895 was extrapolated.

The applicant considers the PK of AZD1061 and AZD8895 in Tg32 mice as similar to the PK of MEDI8897 (nirsevimab, an antibody directed against a viral fusion protein and which contains the YTE substitution in the Fc region) and MEDI8897+TM. However, Cmax and AUC0-28 values for AZD8895 and AZD1061 were lower than the respective values for MEDI8897 and MEDI8897+TM. Also the half-life of AZD1061 was shorter, than that of MEDI8897 and MEDI8897+TM. Thus, it remains to be seen if the half-life of AZD7442 in humans will indeed be around 90 days as anticipated by the applicant based on clinical data for MEDI8897.

Toxicokinetics in cynomolgus monkeys

Single-dose TK of AZD7442 over an 8-week period were evaluated in cynomolgus monkeys after IV and IM administration, respectively. Kinetics of the individual mAbs were comparable, regardless of gender.

After IV administration of 600 mg/kg AZD7442 (300 mg/kg for each mAb), Cmax was reached at the first sampling time point post-dose (1 hr) and was 7730 µg/ml for AZD8895 and 7700 for AZD1061. AUC0-56 was 81,400 day*µg/ml for AZD8895 and 97199 day*µg/ml for AZD1061.

After IM administration of 150 mg/kg AZD7442 (75 mg/kg for each mAb), Cmax was reached after 2-3 days and was 948 µg/ml for AZD8895 and 1010 µg/ml for AZD1061. Bioavailability after IM administration was high (F = 1.22 for AZD1061, F = 1.13 for AZD1061). AUC0-56 was 24,900 day*µg/ml for AZD8895 and 27,300 day*µg/ml for AZD1061.

Human efficacious doses for AZD7442 were projected based on *in vitro* functional potency data that account for the potential synergistic effect of 2-mAb combination. Dose levels for FTIH study were selected to ensure exposure in serum and the ELF of the lungs to be above the IC80 of 104 ng/mL for a duration of at least 5 months post-dose. PK simulations and viral dynamic modelling predict that prophylactic and therapeutic benefit can be achieved in the dose range of 300 mg to 3000 mg.

Dedicated studies for distribution, metabolism, excretion and PK drug interactions were not conducted, which is acceptable for monoclonal antibodies.

2.4.4. Toxicology

A limited toxicological programme was conducted for AZD7442, comprising a single-dose toxicity study in cynomolgus monkeys, and tissue cross-reactivity studies with normal human and monkey tissues, and human fetal tissues. Safety pharmacology and local tolerance was assessed as part of the toxicology study. Both the tissue cross-reactivity studies and the single dose toxicology study were conducted in accordance with OECD Test Guidelines and Principles of Good Laboratory Practice (GLP), and according to relevant International Conference on Harmonisation (ICH) guidelines.

The non-clinical safety programme is in line with ICH S6(R1) and takes into account that AZD7442 recognises a foreign target, i.e. viral protein, which is not endogenously expressed in healthy individuals. This programme is acceptable.

2.4.4.1. Single dose toxicity

The safety evaluation consists of a GLP-compliant, single-dose toxicity study in cynomolgus monkeys with an 8-week treatment-free observation period. Selection of cynomolgus as non-clinical species for safety evaluation of AZD7442 is justified, based on the YTE-dependent prolonged half-life of AZD7442 in cynomolgus (as in humans) and considering that the YTE-modification leads to a reduced half-life in rodents. Administration of a single dose is justified based on the intended single-dose treatment in humans; the study adequately covers two possible routes of administration, IV and IM. The study evaluated standard parameters for general toxicity studies; in line with guideline ICH S6 (R1), the study included safety pharmacology endpoints (ECG, blood pressure, heart rate, respiratory rate, neurological examination) as well as local tolerance endpoints (injection site reactions).

In this toxicity study, AZD7442 was well tolerated at doses up to 600 mg/kg IV (300 mg/kg for each Ab) and 150 mg/kg IM (75 mg/kg for each mAb), respectively. The only treatment-related effect was an increase in serum globulins on Day 2, considered non-adverse and related to the administration of high-doses of human IgG. There were no AZD7442-related effects on safety pharmacology endpoints. Due to the lack of findings a longer recovery period (e.g. 5x half-life) is not considered warranted.

A comparison of the AZD7442 exposure in cynomolgus achieved in this study and human exposure in phase I and phase III studies shows an exposure margin of 47 based on Cmax and of 39 based on AUC0-56 days.

2.4.4.2. Repeat dose toxicity

Omission of repeat dose toxicity studies is acceptable, considering that a single-dose administration of AZD7442 is planned in humans.

2.4.4.3. Genotoxicity

In line with ICH S6(R1) omission of genotoxicity studies is acceptable for monoclonal antibodies, as these proteins are not expected to directly interact with DNA or other chromosomal materials.

2.4.4.4. Carcinogenicity

No carcinogenicity studies were conducted for AZD7442. The acute duration of dosing and mechanism of action (binding to viral target) does not suggest any carcinogenic potential. Thus, the lack of studies is acceptable, and in accordance with ICH S6 (R1).

2.4.4.5. Reproductive and developmental toxicity

In line with IHC S6(R1), reproductive and developmental toxicity studies were not conducted, which is acceptable. IgG1 antibodies cross the placenta and may be transferred via milk. In the repeat-dose toxicology study in cynomolgus monkeys there were no drug-related macroscopic or microscopic changes in the testes, epididymides, ovaries, uterus, or vagina. In view of exogenous targets and lack of cross-reactivity with reproductive or fetal tissues in the tissue cross reactivity studies, effects of AZD7442 on developing fetus and breast-fed infants are not expected.

2.4.4.6. Toxicokinetic data

2.4.4.7. Local Tolerance

Assessment of local tolerance to AZD7442 was included in the general toxicity study, this is acceptable. A single IV or IM administration of AZD7442 was well tolerated locally.

2.4.4.8. Other toxicity studies

The potential for off-target binding of AZD7442 and its individual components was assessed in tissue cross-reactivity studies with cynomolgus tissues and human tissues from adult and fetal donors. In these studies, the individual mAbs and the combination stained positive control material, but no binding to any tissue was observed. Thus, the risk of off-target effects in humans is considered low.

The applicant claims that the batches used in the single-dose toxicity study and the tissue cross-reactivity studies (batch number MS00684-83 for the AZD8895 component and MS00684-82 for AZD1061) are representative for the intended marketed products after a comparability assessment was performed for each process change. Reference is made to the comparability conclusions from the quality assessment to confirm that claim.

2.4.5. Ecotoxicity/environmental risk assessment

Both active substances are natural substances (proteins consisting of natural amino acids) not expected to pose a risk to the environment.

2.4.6. Discussion on non-clinical aspects

In summary, the applicant has provided a comprehensive study programme evaluating the pharmacology, kinetics and safety of AZD7442 and its individual components. The dossier is well written; however, inconsistencies between individual documents (e.g. study reports vs. summaries) sometimes hampered the assessment. Therefore, occasional clarification and up-date of documents had been requested.

Pharmacodynamics

AZD8895 and AZD1061 incorporate YTE and TM amino acid substitutions to extend half-life and abrogate Fc effector function, respectively. Similar to published values for other YTE-modified antibodies, *in vitro* AZD8895 and AZD1061 demonstrated higher affinity to FcRn at low pH as compared to antibodies lacking YTE. This is expected to translate to a longer half-life *in vivo* in non-human primates and in humans. *In vitro*, the TM substitutions of AZD8895 and AZD1061 resulted in an expected decrease in binding affinities to Fc gamma receptors (FcγRs) and C1q complement as

compared to the antibodies lacking the TM substitution. The reduced binding occurred at human physiological serum exposure following administration of AZD7442.

AZD8895, AZD1061, and AZD7442 were confirmed to demonstrate reduced or no antibody effector function in assays that measured ADCP, ADCC, ADCD and ADNKA as compared to control antibodies with unmodified Fc regions. AZD8895, AZD1061 and AZD7442 did not mediate uptake of spike-pseudotyped virus particles by cells that express FcγRs and not ACE2, suggesting that the antibodies do not support antibody-dependent enhancement of infection. In addition, studies in NHPs suggest that Fc effector functions are not required for the efficacy of AZD7442.

Co-crystal structures and biochemical assays demonstrated that AZD8895 and AZD1061 do not compete to each other for binding to the RBD and are individually capable of sterically blocking the virus from engaging its cellular receptor ACE2.

The high affinity for binding to spike translates to potent inhibition of SARS-CoV-2 infection *in vitro*, as assessed by micro-neutralisation assay against USA-WA1/2020 strain with calculated IC50 values of 9 ng/mL, 32 ng/mL and 10 ng/mL for AZD8895, AZD1061 and AZD7442, respectively. For the FRNT assay platform, IC50 values of 32 ng/mL, 114 ng/mL and 26 ng/mL, respectively are reported by the applicant. The combination of AZD8895 and AZD1061 further demonstrated synergistic neutralisation of authentic SARS-CoV-2 and spike-pseudotyped virus *in vitro*.

In vivo efficacy

The *in vivo* efficacy of single doses of Evusheld (AZD7442) has been assessed for the treatment and prevention of SARS-CoV-2 infection in 2 NHP studies (MCBS7442-0006 and MCBS7442-0013) and 2 Syrian golden hamster studies (MCBS7442-0008 and MCBS7442-0011).

Monkey and hamster are both models for COVID-19 studies and have also been used for non-clinical evaluation of SARS-CoV-2 vaccines. The development of clinical symptoms of infection like loss of body weight and pulmonary pathology are more pronounced in hamster compared to monkeys, possibly making hamster a more suitable model to evaluate the effect of Evusheld.

Prophylactic AZD7442 administration demonstrated dose-dependent reduction of SARS-CoV-2 burden compared with control antibody in both NHPs and hamsters. AZD7442 administration post-exposure resulted in only a modest reduction of SARS-CoV-2 burden, in both species. In hamsters which are considered as a better model of disease, the therapeutic administration seemed to accelerate the resolution of the infection.

In both models the *in vivo* efficacy of AZD7442 to protect against SARS-CoV-2 infection and virus-induced lung injury appears more clearly when administered prophylactically.

Overall, based on the *in vitro* and *in vivo* studies currently presented the proof-of-concept appears to be established and the data provided support the development of the combinational treatment of tixagevimab (AZD8895) and cilgavimab (AZD1061) for prophylaxis against the SARS-CoV-2 strain USA-WA1/2020 (GenBank MN985325.1).

Secondary pharmacodynamics

Secondary pharmacology studies addressed the impact of the AZD7442 on the immune response generated by subsequent vaccination with AZD1222 - the Chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein (ChAdOx1-S) vaccine. Studies were performed in mice and NHPs where the vaccine-induced humoral and cellular responses were compared after 2 immunisations. The applicant claims that pre-administration of AZD7442 did not alter either the humoral or cellular immune responses elicited by AZD1222, therefore AZD7442 administration is not anticipated to interfere with

vaccine-mediated immunity in the clinical setting. However, a decrease in human IgG exposure seen in immunised mice compared to non-vaccinated animals challenges this view.

Antiviral resistance

In vitro virus passaging with authentic SARS-CoV-2 viruses in Vero E6 cells has been performed in the presence/absence of AZD8895, AZD1061 and AZD7442. Escape variants were isolated in the presence of AZD1061 alone but neither in the presence of AZD8895 alone nor in the presence of the combination (AZD7442). Three amino acid substitutions of the spike protein: N74K (in the N-terminal domain, NTD), R346I (in the receptor-binding domain, RBD) and S686G were identified in those escape variants to AZD1061. Similarly passaging of recombinant VSV expressing SARS-CoV-2 spike identified escape variants for AZD1061 only, with amino acid substitutions K444R and K444E in the RBD of spike.

AZD1061 did not exhibit neutralisation activity against pseudovirus with R346I, K444E or K444R spike at the highest mAb concentrations tested, resulting in increases in calculated IC50 values > 200-fold when compared to the reference pseudovirus.

The frequency of *in vitro* selected AZD1061 resistance-associated substitutions R346I, K444E, and K444R among circulating SARS-CoV-2 variants has been low (<0.01%). However, consistent with the emergence and transmission of variants harbouring characteristic RBD substitutions E484K (e.g., Beta, Gamma, Eta, and Mu) or T478K (e.g., Delta), the conservation of E484 and T478 among recent circulating strains (N=586,022; 16 May 2021 through 16 August 2021, https://www.gisaid.org) has been 94.4% and 30.4%, respectively.

In neutralisation assays using authentic SARS-CoV-2 isolates or pseudoviruses bearing all spike substitutions identified in variants, AZD7442 retained full to nearly full neutralisation activity against Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2) variants of concern, and Eta (B.1.525), Iota (B.1.526), Kappa (B.1.617.1), Lambda (C.37) and Mu (B.1.621) variants of interest. AZD7442 further retained full to nearly full neutralisation activity against Epsilon (B.1.427 / B.1.429), R.1, B.1.1.519, C36.2, B.1.241.2 and B.1.619.1 variants with alerts for further monitoring and P.2, B.1.616, A.23.1, A.27 and AV.1 variants de-escalated from further monitoring. AZD7442 shows potency in neutralising.

The applicant has provided up-dated information regarding the efficacy of AZD7442 against the Omicron (B.1.1.529) variant of concern, that emerged after finalisation of the non-clinical studies. The additional information is based on *in vitro* and *in vivo* studies conducted by 3rd parties and details can be retrieved from publications only. All the results provided suggest that AZD7442 neutralises Omicron (B.1.1.529), but with a clearly reduced efficacy compared to the original SARS-CoV-2 strain. The clinical relevance of that reduced neutralising capacity against the Omicron variant *in vitro* and *in vivo* remains unknown.

Pharmacokinetics

Kinetics of AZD7442 were evaluated in two non-clinical species after single IV and IM administration, respectively. This is in line with the intended clinical route of administration. PK were assessed in mice transgenic for human FcRn. This is endorsed since this model reflects the Fc modifications introduced to prolong the antibodies' half-life *in vivo*. AZD8895 and AZD1061 were administered individually by the IV route. TK were evaluated in cynomolgus monkeys where the combination of AZD8895 and AZD1061 at a 1:1 ratio was administered either IV or IM. Serum concentrations of the individual mAbs were determined based on a LC-MS/MS method; the report demonstrating the validation of the method was missing and therefore requested. The validation report was provided and based on the results from this study, the analytical method is considered adequately validated.

By and large, kinetics of AZD8895 and AZD1061 were comparable and typical for monoclonal antibodies with YTE modification and not recognising an endogenous target. Based on a comparison of the AZD7442 kinetics in these two studies with non-clinical kinetics of MEDI8897, a control mAb bearing the same YTE modification to prolong the half-life, the applicant expects a half-life for AZD7442 in humans of approx. 90 days.

Toxicology

The non-clinical safety programme is in line with ICH S6(R1) and takes into account that AZD7442 recognises a foreign target, i.e. viral protein, which is not endogenously expressed in healthy individuals. The overall safety programme is considered adequate.

The programme consists of a GLP compliant, single-dose toxicity study in cynomolgus monkeys and tissue cross-reactivity studies evaluating potential off-target binding of AZD8895 and AZD1061 in cynomolgus and human tissues. Considering the lack of reproductive and developmental studies, cross-reactivity with human fetal tissues was also evaluated. In the toxicity study, AZD7442 was well tolerated at doses up to 600 mg/kg IV and 150 mg/kg IM, the study revealed no adverse test article-related effects. AZD7442 exposure in cynomolgus achieved in this study provides a safety margin of 39-fold based on AUC(0-56 days) compared to human exposure at the proposed 300 mg dose. The tissue cross-reactivity studies revealed no binding to human tissues; thus, the risk of off-target effects in humans is considered low.
Limited information was provided regarding the relevance of the non-clinical batches for the product intended for commercial use. This will be confirmed by the quality assessment.
The active substances of AZD7442 are natural substances which are not expected to pose a risk to the environment. Thus, the absence of ERA studies is acceptable.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, AZD7442 (tixagevimab (AZD8895) and cilgavimab (AZD1061) is not expected to pose a risk to the environment.

2.4.7. Conclusion on the non-clinical aspects

From a non-clinical point of view, AZD7442 (tixagevimab (AZD8895) and cilgavimab (AZD1061) together) can be recommended for marketing authorisation.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

The efficacy, safety, tolerability, and PK of Evusheld for the prevention of was evaluated in the following ongoing studies:

Two Phase III, randomised, double-blind, placebo-controlled, parallel-group, prophylaxis studies:
- Study D8850C00002 (PROVENT)

- Study D8850C00003 (STORM CHASER)
- Phase I FTIH study (Study D8850C00001).

Table 1: Studies with Evusheld for the prevention indication

Study/Sponsor/Status	Phase	Population	Success Criteria	Dose/Route of EVUSHELD and Number of Participants Exposed[a]	Countries
D8850C00002 (PROVENT)/ AstraZeneca/ Ongoing (recruitment complete)	III	Pre-exposure prophylaxis [b]	Statistically significantly lower incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness for EVUSHELD 300 mg IM than placebo	300 mg IM (N = 3461), placebo (N = 1736)	US, UK, Belgium, France, and Spain
D8850C00003 (STORM CHASER)/ AstraZeneca/ Ongoing (recruitment complete)	III	Post-exposure prophylaxis [c]	Statistically significantly lower incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness for EVUSHELD 300 mg IM than placebo	300 mg IM (N = 749), placebo (N = 372)	US, UK
D8850C00001/ AstraZeneca/ Complete (final CSR in preparation)	I	Healthy volunteers	Safety, tolerability, and pharmacokinetics	300 mg IM (N = 10), 300 mg IV (N = 10), 1000 mg IV (N = 10), 3000 mg IV (N = 10), 3000 mg IV (N = 10) co-administered, placebo (N = 10)	UK

[a] Numbers of participants exposed to the IMP (ie, those in the safety analysis set)

[b] Pre-exposure population: adults ≥ 18 years who were candidates for benefit from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19, based on available risk assessment at time of enrollment (ie, a pre-exposure prophylaxis population). Participants had to be SARS-CoV-2 serology negative at Screening.

[c] Post-exposure population: adults ≥ 18 years of age with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed symptomatic or asymptomatic SARS-CoV-2 infection, and who were therefore at appreciable risk of imminently developing COVID-19, based on available risk assessment at time of enrollment (ie, a post-exposure prophylaxis population). Participants had to be SARS-CoV-2 serology negative at Screening and must not have had COVID-19 symptoms within 10 days of dosing.

COVID-19, coronavirus disease 2019; IM, intramuscular; IV, intravenous; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; UK, United Kingdom; US, United States

Dates of data base lock are provided below:

- **Primary DCO** – data cut-off primary efficacy analysis.
  - PROVENT: 30% of study participants unblinded at this time point.
  - STORM CHASER: 30 days after the 25th primary efficacy event had been reported across the active and placebo groups.
- **June 2021 DCO** – first data cut-off for a minimum of 3 months' safety data on all ongoing participants.
- **August 2021 DCO** – second data cut-off for longer-term safety and efficacy data providing a median duration of follow-up of approximately 6 months, i.e. 5 months key safety and efficacy data of all ongoing participants

2.5.2. Clinical pharmacology

Data including PK, PD (SARS-CoV-2 nAbs), PK/nAbs correlation, immunogenicity, and antiviral resistance of Evusheld are available from 3 clinical studies:

- Study D8850C00001 (Phase I FTIH)
- Study D8850C00002 (PROVENT)
- Study D8850C00003 (STORM CHASER)

In addition, a population PK analysis of pooled Phase I and III data was performed to characterize the PK of Evusheld and to evaluate the impact of covariates such as demographics and renal and liver function tests on the PK exposure. PK data in healthy volunteers (Phase I study [IM and IV arm]) and in participants in the 2 Phase III studies PROVENT and STORM CHASER, and in the treatment Phase III study TACKLE were pooled to develop a population PK model to characterize the PK of Evusheld.

An exposure-response analysis was conducted for PROVENT, and a viral dynamics model was developed to support the dose selection for prophylaxis.

2.5.2.1. Pharmacokinetics

Analytical methods

Serum and nasal lining fluid (NLF) PK samples were analysed for AZD8895 and AZD1061 by an LC-MS/MS method. An immunoaffinity approach using streptavidin magnetic beads coated with biotinylated receptor binding domain (RBD) of SARS-CoV-2 spike protein was used to enrich AZD8895 and AZD1061 (different epitopes) from human serum. Because AZD8895 and AZD1061 are too large for practical direct quantitative analysis using LC-MS/MS technology, the bound proteins were subjected to "onbead" proteolysis with trypsin, following standard protein denaturation, reduction, and alkylation processing steps. As a result of the trypsin digestion, characteristic peptide fragments originating from each antibody were produced by this procedure. Characteristic peptides were quantified as surrogates of the AZD8895 and AZD1061 concentrations.

In serum, the method is applicable to quantitation of AZD8895 and AZD1061 within a nominal range of 0.300 to 30.0 µg/mL. The validations followed the principles laid down in EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2** Guideline on bioanalytical method validation.

For NLF PK assay, calibration curves and quality controls were prepared by fortifying AZD8895 and AZD1061 in surrogate matrix due to the limited nature of blank nasal lining fluid. The method is applicable to quantitation of AZD8895 and AZD1061 within a nominal range of 5.00 to 1500 ng/mL. Assays were qualified but not validated. Concentrations of tixagevimab and cilgavimab in NLF have been determined by collecting nasal fluid via a nasosorption device. The dilution of the nasal fluid introduced by the extraction step was corrected by a multiplication factor calculated from the serum: nasal sample eluate urea concentration ratio.

The live 80% neutralisation assay (PRNT80) was used to test samples from the phase I and phase III studies, which passed validation for all parameters. Study samples were within the validated titer range.

A multi-tiered testing approach, consisting of validated assays for detection (screening assay), specificity (confirmation assay), and semi-quantification (titer assay), was used for the assessment of anti-drug antibody (ADA) responses to Evusheld (tixagevimab and cilgavimab separately). In this assay, samples, positive controls (PCs), and negative control (NC) are pre-incubated with Biotin-AZD8895/AZD1061 and Sulfo-Tag- AZD8895/AZD1061. Any ADA present in the human serum will form a bridge between the Biotin- AZD8895/AZD1061 and Sulfo-Tag- AZD8895/AZD1061 molecules. This complex is bound to a blocked MSD Streptavidin (MSD SA) plate and detected by a chemiluminescent signal that is generated when voltage is applied. The resulting electrochemiluminescent signal (ECL or relative light units, RLU) is directly proportional to the amount of ADA present in the human serum. Validation revealed that the assays met the acceptance criteria of the EMA guidance (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**) for relevant parameters and may be suitable for its intended purpose.

Pharmacokinetic data analysis

Non-compartmental analysis (NCA) was conducted to evaluate Phase I and Phase III data, descriptive statistical summaries have been provided for PK variables.

Population pharmacokinetics

A population PK analysis of pooled Phase I and III data was performed to characterize the PK of Evusheld and to evaluate the impact of covariates. PK data in healthy volunteers (Phase I study [IM and IV arm]), in participants in the 2 Phase III studies PROVENT and STORM CHASER, and in the treatment Phase III study TACKLE were pooled to develop a population PK model to characterize the PK of Evusheld.

The final pooled dataset for analysis included 2527 participants with a total of 7375 Evusheld PK measurements. An IM dose of 300 mg was used in the 2 prophylaxis studies (PROVENT and STORM CHASER), and 600 mg IM in the treatment study (TACKLE). The Phase I study investigated the PK of Evusheld in healthy volunteers with doses ranging from 300 mg IV to 3000 mg IV and 300 mg IM.

The final parameter estimates are presented in the table below.

Table 2

Parameter Estimates (95% Confidence Interval) for EVUSHELD, Tixagevimab, and Cilgavimab PK Model Based on Phase I and Phase III Studies Accounting for Covariate Effects

Parameter	Units	Cilgavimab	Tixagevimab	EVUSHELD
Half-life median[a] (5th and 95th percentiles)	Days	84.4179 (70.61759-146.48903)	88.8277 (72.99582-157.33544)	90.6112 (72.46954-151.18043)
CL (RSE%) {95% CI}	L/day	0.0412 (1.23) {0.0402-0.0422}	0.0405 (1.09) {0.0396-0.0414}	0.0443 (1.40) {0.0430-0.0455}
V2 (RSE%) {95% CI}	L	2.48 (4.22) {2.27-2.68}	2.72 (4.33) {2.49-2.96}	3.62 (3.47) {3.37-3.87}
Q (RSE%) {95% CI}	L/day	0.595 (3.03) {0.560-0.630}	0.588 (3.25) {0.550-0.625}	0.614 (2.62) {0.582-0.645}
V3 (RSE%) {95% CI}	L	2.57 (1.40) {2.50-2.64}	2.64 (1.83) {2.55-2.74}	2.60 (1.98) {2.50-2.70}
KA (RSE%) {95% CI}	1/day	0.106 (3.11) {0.0999-0.113}	0.109 (3.59) {0.102-0.117}	0.125 (3.22) {0.117-0.133}
F1 (RSE%) {95% CI}	-	0.593 (0.951) {0.582-0.604}	0.617 (0.327) {0.613-0.621}	0.669 (0.822) {0.659-0.680}
Additive Error {95% CI}	µg/mL	0.359 (8.02) {0.302-0.415}	1.04 (8.92) {0.858-1.22}	3.39 (2.25) {3.24-3.54}
Proportional Error {95% CI}	-	0.153 (2.24) {0.146-0.159}	0.157 (3.81) {0.145-0.169}	0.0968 (4.41) {0.0885-0.105}
SEX on V2 (RSE%) {95% CI}	-	-0.346 (8.91) {-0.286--0.407}	-0.362 (8.56) {-0.302--0.423}	-0.369 (7.07) {-0.318--0.421}
SEX on KA (RSE%) {95% CI}	-	0.481 (11.7) {0.371-0.591}	0.579 (11.7) {0.447-0.712}	0.449 (12.3) {0.341-0.558}
AGE on KA (RSE%) {95% CI}	-	-0.265 (10.5) {-0.211--0.320}	-0.297 (9.79) {-0.240--0.354}	-0.275 (10.1) {-0.220--0.329}
DIAB on V2 (RSE%) {95% CI}	-	0.578 (18.3) {0.371-0.785}	0.399 (22.8) {0.220-0.577}	0.434 (18.6) {0.275-0.593}
DIAB on CL (RSE%) {95% CI}	-	0.283 (14.0) {0.205-0.361}	0.223 (18.9) {0.140-0.305}	0.199 (23.4) {0.107-0.290}
IIV_CL (RSE%) {95% CI}	%CV	29.3 (4.49) {26.7-31.8}	21.3 (4.79) {19.3-23.3}	20.9 (5.67) {18.6-23.2}
IIV CL V2[b] (RSE%) {95% CI}	-	0.885 (2.75) {0.837-0.932}	0.836 (3.70) {0.776-0.897}	0.809 (4.06) {0.744-0.873}
IIV_V2 (RSE%) {95% CI}	%CV	116 (2.90) {109.-122}	100 (3.52) {93.3-107.}	82.3 (3.07) {77.3-87.2}
IIV_V3 (RSE%) {95% CI}	%CV		6.29 (31.8) {2.37-10.2}	10.3 (30.8) {4.09-16.6}
IIV_KA (RSE%) {95% CI}	%CV	54.5 (4.16) {50.1-59.0}	54.9 (5.22) {49.3-60.5}	47.5 (4.81) {43.0-52.0}

[a] Terminal half-life was derived using micro-constants K12, K21, Kel, V2, and V3 and presented as median and 5th and 95th percentiles.
[b] Estimate of the covariance between CL and V2. Correlation (CL-V2) calculated as Covariance (CL-V2) / Square root(Variance (CL)*Variance (V2))*100.

%CV, percent coefficient of variation; CI, confidence interval; CL, clearance; DIAB, diabetes; F1, absolute bioavailability; IIV, inter-individual variability; KA, 1st order absorption rate constant; K12, 1st order distribution rate constant from central to peripheral compartment; K21, 1st order distribution rate constant from peripheral to central compartment; Kel, 1st order elimination rate constant; PK, pharmacokinetic; Q, inter-compartmental clearance; RSE(%), relative standard error; V2, central volume of distribution; V3, peripheral volume of distribution.

Empirical Bayes estimates of Evusheld PK parameters from the final population PK model were used to simulate:

- Evusheld concentration-time profiles over 15 months after a single 300 mg IM dose and to derive percentages of participants above minimum protective concentration of 2.2 µg/mL

- PK model-based simulations to evaluate the influence of fixed dose versus weight-adjusted dosing on the exposure of Evusheld

- Exposure simulations to support inclusion of the adolescent population (age 12 to < 18 years and body weight of > 40 kg) in the indication. No pharmacokinetic data in the paediatric population are available.

- Influence of Omicron variant on the dose of Evusheld for prophylaxis

Evaluation and qualification of models

A 2-compartmental model with first-order absorption and first-order elimination for tixagevimab, cilgavimab, and Evusheld PK following IV and IM administration was selected as final model to describe the PK data. Weight has been included by fixed allometric scaling exponents (CL: 0.75, V:1.0). Covariates have been selection based on the statistical selection criteria p=0.05 for inclusion and p=0.001 for the backward elimination step.

Diagnostic plots indicate overall a good description of PK data. High variability following a fix dose IM and in Cmax following IM and IV could be detected. The issue of potential correlation bias in the pop PK model regarding weight, sex and diabetes will be followed in updated versions of the popPK model and need to be addressed by considering outstanding bioanalytical data.

Absorption

After a single 300 mg IM dose (150 mg each mAb) in the Phase I study, the mean (%CV) Cmax was 16.52 (35.56%) and 15.27 (38.53%) µg/mL for tixagevimab and cilgavimab, respectively, which was reached at a median tmax of 14 days.

The population PK model-based absorption rates (KA; 1/day) were similar for tixagevimab (0.109 1/day) and cilgavimab (0.106 1/day). Based on PK modeling, the time to achieve the minimum protective serum concentration (2.2 µg/mL) of Evusheld is estimated to be 6 hours (IQR of 3.4 to 11.7 hours) following 300 mg IM administration, while for the Omicron variant (minimum protective serum concentration of 3.3 µg/mL) it is estimated to be 10.5 hours (IQR 5 to 21 hours).

Bioavailability

In the Phase I study, the estimated absolute bioavailability after a single 150 mg IM dose was 68.54% for tixagevimab and 65.79% for cilgavimab. The population PK model-based bioavailability of Evusheld was 66.9%.

Bioequivalence

The PROVENT and STORM CHASER studies were initiated with cell pools material. Once clonal cell line material (the proposed commercial material) became available, this was used in an additional cohort in PROVENT to obtain PK and safety data in the prophylaxis setting. A preliminary comparability assessment of clonal cell line material was performed. This comparability analysis was not initially planned when the study was designed. Based on the measured PK variability in Phase I, it was calculated that PK data were required from at least 70 participants dosed with cell pools material and 70 participants dosed with the clonal cell line material to be able to demonstrate that the 90% CI interval of the ratio of the geometric mean AUC0-91 or Cmax is between 80 to 125%. PK data were available for 68 participants who were dosed with AZD7442 clonal cell line material and had PK results for both AZD8895 and AZD1061 at all sampling time points (Day 8, Day 29, Day 58, and Day 92). Corresponding data are available for 67 participants who were dosed with cell pools material. For some participants from whom the Day 92 samples were collected early, the parameter AUC0-91 could not be calculated by extrapolation and AUClast was used instead.

Figure 1: Geometric Mean Serum Concentrations of AZD7442 (AZD1061+AZD8895) Following Single IM Dose of 300 mg AZD7442, linear scale

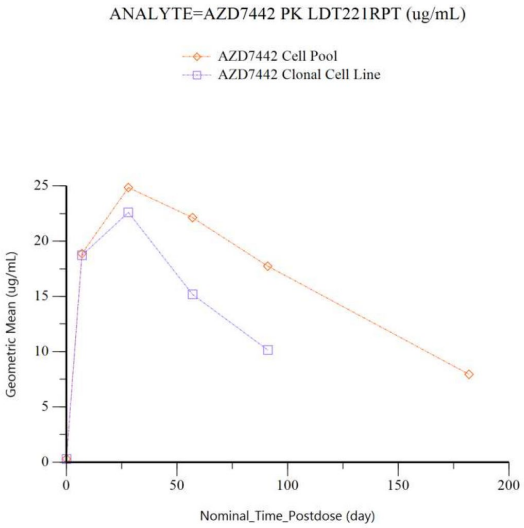


Table 3: Statistical Comparison of Pharmacokinetic Exposure Parameters Between Clonal Cell Line and Cell Pools Materials - PK Analysis Set

Analyte	Parameter (Units)	Treatment	N	GLSM	90% CI	Material Comparison (Clonal Cell Line vs Cell Pool)	
						GMR (%)	90% CI
Cilgavimab	$AUC_{0\text{-}91}$ (day·µg/mL)	Cell Pools (Reference)	67	916	(840, 999)	80.5	(71.3, 90.9)
		Clonal Cell Line (Test)	68	737	(677, 803)		
	C_{max} (µg/mL)	Cell Pools (Reference)	67	12.8	(11.7, 13.9)	94.4	(83.4, 107)
		Clonal Cell Line (Test)	68	12.0	(11.0, 13.1)		
Tixagevimab	$AUC_{0\text{-}91}$ (day·µg/mL)	Cell Pools (Reference)	67	949	(873, 1030)	87.7	(78.0, 98.6)
		Clonal Cell Line (Test)	68	833	(767, 904)		
	C_{max} (µg/mL)	Cell Pools (Reference)	67	13.3	(12.2, 14.4)	102	(90.4, 114)
		Clonal Cell Line (Test)	68	13.5	(12.4, 14.6)		
EVUSHELD	$AUC_{0\text{-}91}$ (day·µg/mL)	Cell Pools (Reference)	67	1880	(1740, 2040)	83.8	(74.8, 93.8)
		Clonal Cell Line (Test)	68	1580	(1460, 1710)		
	C_{max} (µg/mL)	Cell Pools (Reference)	67	26.1	(24.1, 28.3)	97.1	(86.8, 109)
		Clonal Cell Line (Test)	68	25.4	(23.5, 27.5)		

AUC0-91, area under the concentration-time curve from time zero to time 91 days; CI, confidence interval; Cmax, maximum serum concentration; DCO, data cut-off; GLSM, geometric least squares mean; GMR, geometric mean ratio; N, number of participants for whom data were available in each category; PK, pharmacokinetic.

No differences in the safety profiles were noted for participants who received cell pools material versus clonal cell line material (although the proportion of participants who received clonal cell line material was relatively small). Due to the small number of events in PROVENT, a specific analysis of efficacy in cell pools material versus clonal cell line material was not carried out. The geometric mean serum neutralising antibody titre at days 8 and 29 was notably higher in subjects receiving intended

commercial material (779.5 and 881.3) compared to subjects receiving study material (472.4 and 663.2). However, individual nAb titres in the participants that received clonal cell line material fall within the distribution of the overall population and as the cohort receiving commercial material was small (70 subjects), chance findings are possible. Testing material (cell pools vs clonal cell line) as a covariate for clearance in the population PK model supported that material was not a clinically significant covariate and did not reduce the percentage of unidentified inter-subject variability in CL.

Distribution, metabolism and elimination

Volume of distribution was 2.72 L for tixagevimab and 2.48 L for cilgavimab for central compartments and 2.64 L for tixagevimab and 2.57 L for cilgavimab for peripheral compartments, reflecting the limited ability of extravascular distribution.

Tixagevimab and cilgavimab are expected to be degraded into small peptides and component amino acids via catabolic pathways in the same manner as endogenous immunoglobulin G antibodies.

From population PK modelling the estimated typical CL was 0.0405 L/day for tixagevimab and 0.0412 L/day for cilgavimab with between subject variability of 21.3% and 29.3% respectively. CL is lower than known for typical mAbs (ranging between 0.2 – 0.5 L/day) and correlates with the half-life extension of the antibodies.

The estimated population median terminal elimination half-life was 90.6 days for Evusheld, 88.8 days for tixagevimab and 84.4 days for cilgavimab; values confirm successful half-life extension of the antibodies.

Dose proportionality and time dependencies

Based on results from FITH study D8850C00001, the pharmacokinetics of both, tixagevimab and cilgavimab, are linear and dose-proportional between 300 mg and 3 000 mg following a single intravenous administration. Only 1 dose level has been administered via IM route in clinical trials. Thus, dose-dependency of absorption cannot be assessed.

Evusheld is currently planned to be administered as a single dose. No analysis of PK under steady state conditions has been performed; the potential for accumulation has not been investigated.

Variability

In FITH study D8850C00001, between-participant variability (%CV) in tixagevimab AUCinf and Cmax after 300 mg IM administration was 30.22% and 35.56%, respectively, and 31.66% and 38.53%, respectively, for cilgavimab. PK variability up to Day 92 was higher in the PROVENT population compared with the Phase I population of healthy volunteers, with the geometric CV% ranging from 71.5% to 90.3% for Evusheld over the 4 time points sampled (Days 8, 29, 58, and 92).

By popPK modelling, all parameters were estimated with good precision (%RSE for all parameters were below 30%) except IIV of V3 with 30.8% RSE. The extent of the shrinkage of the individual parameter estimates to the typical values was evaluated. The IIV (%CV) of Evusheld for CL was estimated to 20.9%, however, was high for V2 (82.3%) and Ka (47.5%). The IIV on bioavailability (F1) did not show a significant improvement in the population PK model performance and was not included. The IIV for V3 was not included for the cilgavimab population PK model due to no change in OFV.

No intra-individual comparison has been performed in the clinical trials with single dose administration.

PK in healthy volunteers

Complete 1-year PK data for AZD7442 in healthy volunteers are available from the FITH study D8850C00001. This was a Phase I, FTIH, randomised, double-blind, placebo-controlled, dose escalation study evaluating the safety, tolerability, and PK of Evusheld in healthy adult participants 18 to 55 years of age. Participants were randomised 10:2 to receive either Evusheld or placebo administered IV or IM, across 5 fixed dose cohorts as follows:

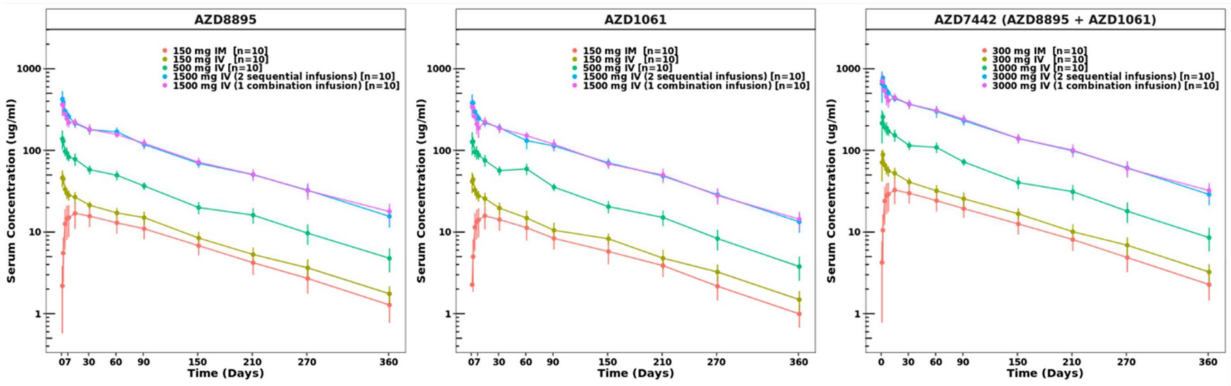
- Cohort 1a (Evusheld 300 mg or placebo IM),
- Cohort 1b (Evusheld 300 mg or placebo IV),
- Cohort 2 (Evusheld 1000 mg or placebo IV),
- Cohort 3 (Evusheld 3000 mg or placebo IV), and
- Cohort 4 (Evusheld 3000 mg with the 2 mAbs co-administered, or placebo IV).

In Cohorts 1a, 1b, 2, and 3, the 2 constituent mAbs of Evusheld were administered as separate injections or infusions; in Cohort 4, the 2 mAbs were co-administered within the same IV infusion.

Overall, 60 participants were enrolled in this study. A total of 10 participants were enrolled and randomised to Evusheld in each cohort, and 10 participants were randomised to pooled placebo. The mean age of Evusheld participants was 39.4 years. Most Evusheld participants were male (32 [64.0%]) and White (34 [68.0%]).

Blood samples for serum PK analysis were collected at predose (baseline), mid-infusion (IV), end of dosing (IV), 8 hours post-dose, Day 2 (discharge), and Post-dose Follow-up Days 4, 6, 8, 15, 31 61, 91, 151, 211, 271, and 361.

Figure 2: Arithmetic Mean (± SD) Serum Concentrations of AZD8895, AZD1061, and AZD7442 (AZD8895 + AZD1061) Following Single Dose IM or IV administration to Healthy Participants, Through Day 361 (Phase I, Study D8850C00001; Pharmacokinetic Analysis Set)



AZD7442 concentration = the sum of the AZD8895 and AZD1061 concentrations; Days on the horizontal axis are days post-dose (ie, study Day -1); IM, intramuscular; IV, intravenous; SD, standard deviation

Descriptive statistics were available for PK variables including values up to day 211:

Table 4: Summary of PK Parameters for AZD8895 and AZD1061 Following Single Dose IM or IV Administration of AZD7442 – Day 211 (Pharmacokinetic Analysis Set)

Analyte	Parameter (Units)	300 mg AZD7442 IM [a] (N = 10)	300 mg AZD7442 IV [a] (N = 10)	1000 mg AZD7442 IV [b] (N = 10)	3000 mg AZD7442 IV [c] (N = 10)	3000 mg AZD7442 IV co-administration [c] (N = 10)
AZD8895	AUC_{0-210d} (day·µg/mL)	2010 (28.50)	2936 (12.63)	7858 (10.85) [f]	25300 (9.707)	24990 (10.02)
	AUC_{last} (day·µg/mL)	2196 (28.46)	3191 (12.66)	7859 (10.85) [f]	25280 (9.637)	24980 (10.12)
	AUC_{inf} (day·µg/mL)	2529 (30.22)	3690 (14.40)	9954 (14.17) [f]	31790 (10.73)	31910 (11.65)
	C_{max} (µg/mL)	16.52 (35.56)	52.66 (11.51)	162.2 (11.31)	505.8 (10.54)	447.8 (8.980)
	$C_{avg210d}$ (µg/mL) [d]	9.572 (28.50)	13.98 (12.63)	37.42 (10.85) [f]	120.5 (9.707)	119.0 (10.02)
	t_{max} (day)	13.96 (3.05 – 29.99)	0.04 (0.02 – 0.33)	0.04 (0.02 – 0.05)	0.10 (0.06 – 0.13)	0.05 (0.05 – 0.05)
	$t_{1/2\lambda z}$ (day)	87.93 (13.95)	94.37 (15.61)	89.21 (17.70) [f]	89.64 (12.32)	94.60 (11.75)
	t_{last} (day)	268.12 (261.19 – 271.06)	269.00 (265.01 – 272.18)	210.01 (209.97 – 210.17) [f]	209.94 (205.06 – 210.90)	209.96 (204.97 – 212.39)
	CL(/F) (L/day)	0.06175 (0.01884)	0.04101 (0.005568)	0.05069 (0.007347) [f]	0.04743 (0.005234)	0.04730 (0.005557)
	V_z(/F) (L)	7.656 (1.971)	5.525 (0.8578)	6.412 (0.9317) [f]	6.102 (0.8203)	6.408 (0.7795)
	V_{ss} (L)	NA	5.342 (0.8309)	6.486 (0.9285) [f]	6.113 (0.7148)	6.365 (0.7692)
	F_{210d} (%) [e]	68.54	NA	NA	NA	NA
AZD1061	AUC_{0-210d} (day·µg/mL)	1721 (30.51)	2580 (14.53)	8049 (10.53) [f]	24110 (11.24)	24310 (10.64)
	AUC_{last} (day·µg/mL)	1881 (30.73)	2810 (14.02)	8050 (10.53) [f]	24100 (10.65)	24300 (10.72)
	AUC_{inf} (day·µg/mL)	2133 (31.66)	3242 (14.40)	9964 (13.80) [f]	30440 (11.24)	30870 (12.85)
	C_{max} (µg/mL)	15.27 (38.53)	50.10 (15.31)	154.3 (14.66)	465.5 (11.09)	419.3 (11.62)
	$C_{avg210d}$ (µg/mL) [d]	8.197 (30.51)	12.29 (14.53)	38.33 (10.53) [f]	114.8 (10.70)	115.7 (10.64)
	t_{max} (day)	13.98 (3.05 – 60.23)	0.02 (0.02 – 0.96)	0.02 (0.02 – 0.34)	0.06 (0.06 – 0.33)	0.05 (0.05 – 0.33)
	$t_{1/2\lambda z}$ (day)	82.90 (12.26)	91.04 (17.97)	86.85 (21.64) [f]	91.24 (12.05)	91.04 (12.15)
	t_{last} (day)	268.12 (261.19 – 271.06)	269.00 (265.01 – 272.18)	210.01 (209.97 – 210.17) [f]	209.94 (205.06 – 210.90)	209.96 (204.97 – 212.39)
	CL(/F) (L/day)	0.07386 (0.02814)	0.04668 (0.006247)	0.05061 (0.007113) [f]	0.04956 (0.005617)	0.04896 (0.006405)
	V_z(/F) (L)	8.684 (2.735)	6.086 (1.334)	6.214 (1.074) [f]	6.502 (1.035)	6.369 (0.8170)
	V_{ss} (L)	NA	6.034 (1.270)	6.190 (0.9476) [f]	6.479 (0.8004)	6.458 (0.8214)
	F_{210d} (%) [e]	65.79	NA	NA	NA	NA

a 300 mg AZD7442 (150 mg AZD8895 and 150 mg AZD1061).

b 1000 mg AZD7442 (500 mg AZD8895 and 500 mg AZD1061).

c 3000 mg AZD7442 (1500 mg AZD8895 and 1500 mg AZD1061).

d Average concentration over 210 days post-dose, calculated as AUC0 - 210d/210 days.

e Calculated as the single ratio of geometric mean AUCinf after IM to IV, thus no %CV.

f n = 9, participant E0001070 had no samples beyond 1440 hours post-dose due to early termination; this participant's AUC0 - 210d and Cavg210d were calculated via extrapolation.

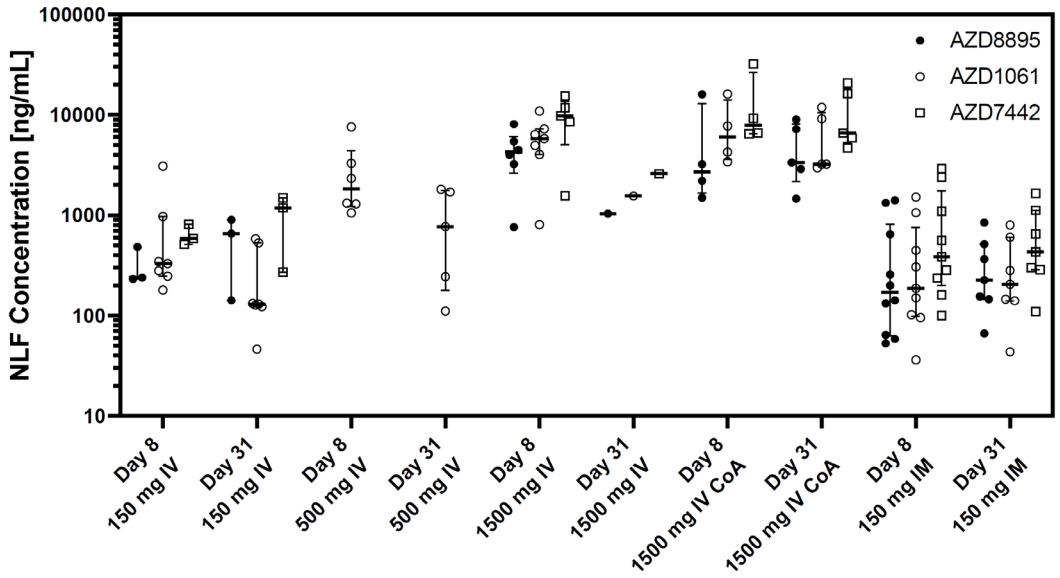
Data are presented as geometric mean (geometric CV), except for tmax and tlast as median (min – max), and t1/2λz, CL(/F), Vz(/F), and Vss as arithmetic mean (SD).

AUC0-210d, area under the serum concentration-time curve from time zero to Day 211; AUClast, area under the serum concentration-time curve from time zero to the last measurable

time point; AUCinf, area under the serum concentration-time curve from time zero to infinity; Cavg210d, average serum concentration over 210 days post-dose; Cmax, maximum serum concentration; CL, total body clearance of drug from serum after intravascular administration; CL(/F), apparent total body clearance of drug from serum after extravascular administration; %CV, percent coefficient of variation; F210d, bioavailability at Day 211; IM, intramuscular; IV, intravenous; NA, not applicable; t1/2λz, half-life associated with terminal slope of a semi-logarithmic concentration-time curve; tlast, time to last serum concentration measurement; tmax, time to maximum serum concentration; Vss, volume of distribution at steady state from an IV dose; Vz, volume of distribution following iv administration (based on terminal phase); Vz(/F), volume of distribution (apparent) following extravascular administration (based on terminal phase). Source: Table 14.2.4.1 and Table 14.2.4.2.

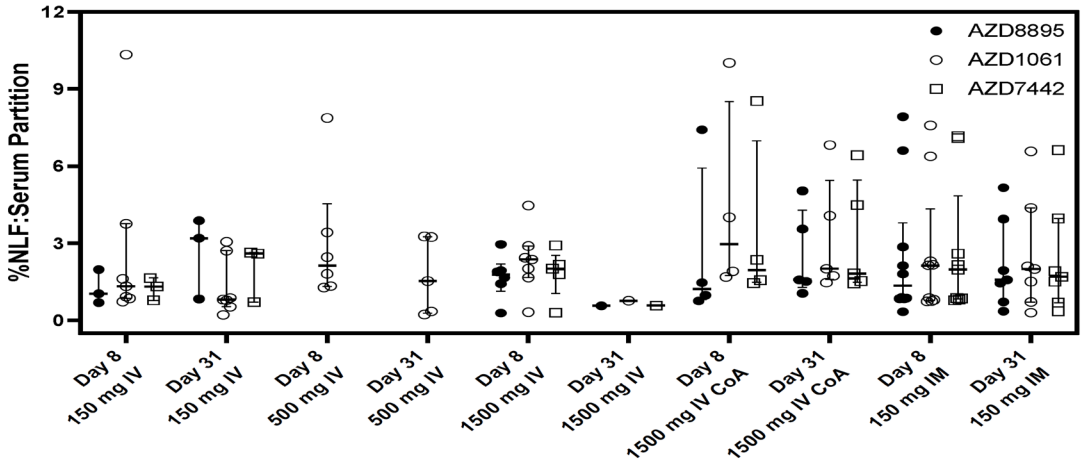
Nasosorption samples for NLF PK analysis were collected at baseline (predose), Days 8, 31, 91, and 151. Data are available for baseline, Day 8, and Day 31 in all cohorts. NLF concentration data were used to determine the partition ratio.

Figure 3: Concentrations of AZD8895, AZD1061, and AZD7442 in Nasal Lining Fluid After a Single AZD7442 Dose (Pharmacokinetic Analysis Set)



Error bars correspond to Q1 and Q3 of results; CoA, co-administered; IM, intramuscular; IV, intravenous; NLF, nasal lining fluid; Q1, first quartile; Q3, third quartile; Source: Figure 14.2.6.1

Figure 4: NLF:Serum partition ratio of AZD8895, AZD1061, and AZD7442 After a Single AZD7442 Dose (Pharmacokinetic Analysis Set)



Error bars correspond to Q1 and Q3 of results; CoA, co-administered; IM, intramuscular; IV, intravenous; NLF, nasal lining fluid; Q1, first quartile; Q3, third quartile; Source: Figure 14.2.6.2

Pharmacokinetics in target population

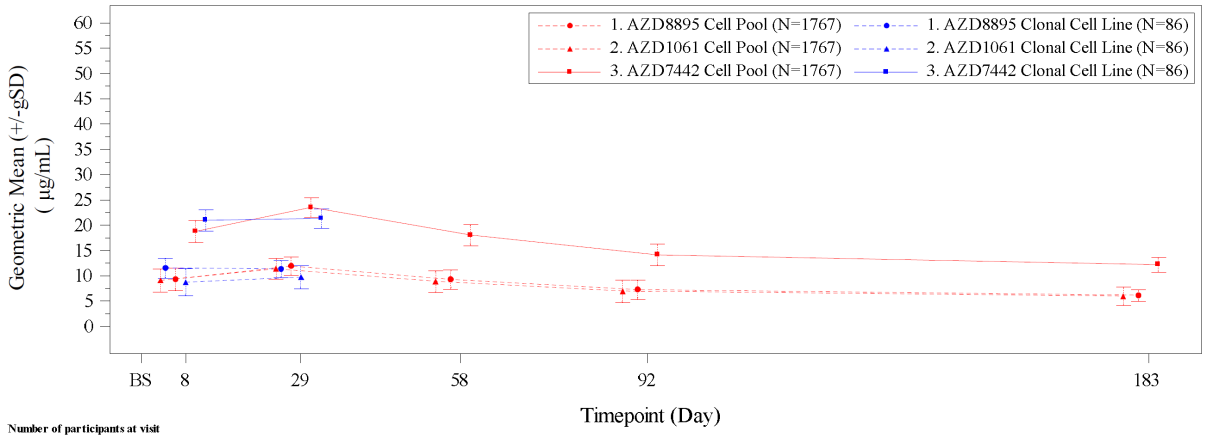
PROVENT

Blood samples for serum PK analysis are scheduled for collection at pre-dose (baseline), and at Study Days 8, 29, 58, 92, 183, 366, and 457. Serum tixagevimab and cilgavimab concentration data are available for Day 8 (n = 1545 and 1545, respectively), Day 29 (n = 1222 and 1222), Day 58 (n = 1025 and 1022), Day 92 (n = 633 and 632), and Day 183 (n = 2 and 2) after a 150 mg IM dose of each antibody (total Evusheld dose of 300 mg IM) in the gluteal muscle on Day 1. In addition, serum

tixagevimab and cilgavimab concentration data were available for 4 COVID-19 positive participants on Illness Visits IL-D1, IL-D14, IL-D21, and IL-D28 in 4, 1, 1, and 1 participants, respectively.

Quantifiable amounts of either AZD8895 or AZD1061 were not detected in any baseline samples. The nominal geometric mean (%gCV) AZD8895 concentrations on Study Days 8, 29, 58, 92, and 183 were 9.41 (93.3%), 11.9 (65.3%), 9.27 (72.5%), 7.26 (71.0%), and 6.11 (13.6%) µg/mL, respectively. The nominal geometric mean (%gCV) AZD1061 concentrations at Study Days 8, 29, 58, 92, and 183 were numerically similar to AZD8895 at 9.04 (101%), 11.3 (83.5%), 8.84 (87.0%), 6.93 (93.3%), and 5.92 (66.9%) µg/mL, respectively. The nominal geometric mean (%gCV) AZD7442 concentrations at Study Days 8, 29, 58, 92, and 183 were 18.9 (90.3%), 23.4 (71.5%), 18.0 (84.5%), 14.1 (86.2%), and 12.2 (38.1%) µg/mL, respectively.

Figure 5: Geometric Mean (+/-gSD) of Serum Drug Concentration (µg/mL) versus Time, Linear Line Plot by Analyte, Main Study Visits, PK Analysis Set, Primary Analysis DCO, PROVENT



Number of participants at visit						
AZD8895 Cell Pool	1583	1466	1143	1025	633	2
AZD8895 Clonal Cell Line	80	79	79	0	0	0
AZD1061 Cell Pool	1583	1466	1143	1022	632	2
AZD1061 Clonal Cell Line	80	79	79	0	0	0
AZD7442 Cell Pool	1583	1466	1143	1025	633	2
AZD7442 Clonal Cell Line	80	79	79	0	0	0

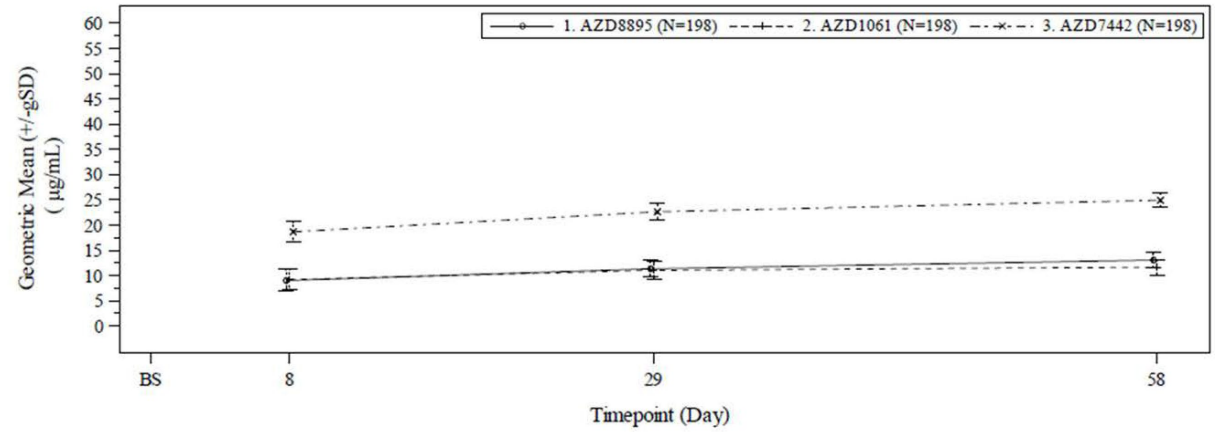
BS: Baseline PK concentration is non-quantifiable. BS, baseline; DCO, data cut-off; gSD, geometric standard deviation; N, number in analysis set; PK, pharmacokinetic. Source: Figure 14.2.4.2.3 (DCO: 05 May 2021)

STORM CHASER

Blood samples for serum PK analysis are scheduled for collection at pre-dose (baseline), and at Study Days 8, 29, 58, 92, 183, 366, and 457. Serum concentration data for tixagevimab and cilgavimab are available for baseline, and for Study Days 8, 29, and 58 in 176, 104, 126, and 12 participants, respectively, after a 150 mg IM dose of each antibody (total Evusheld dose of 300 mg IM). In addition, serum concentration data for tixagevimab and cilgavimab are available for IL-D1, IL-D14, and IL-D28 in 9, 6, and 2 participants, respectively, out of 23 participants receiving Evusheld who had confirmed COVID-19.

A quantifiable amount of either AZD8895 or AZD1016 was not detected in any baseline samples. The geometric mean (%gCV) AZD8895 concentrations for nominal time points at Study Days 8, 29, and 58 were 9.023 (90.638%), 11.341 (53.875%), and 13.064 (39.088%) µg/mL, respectively. The geometric mean (%gCV) AZD1061 concentrations at Day 8, Day 29, and Day 58 were numerically similar to AZD8895 at 9.206 (85.700%), 11.056 (57.298%), and 11.663 (44.052%) µg/mL, respectively.

Figure 6: Geometric Arithmetic Mean (+/- GSD) of Drug Serum Concentration (µg/mL) Versus Time, Linear Line Plot by Analyte - PK Analysis Set, Primary Analysis, Main Study Visits; STORM CHASER



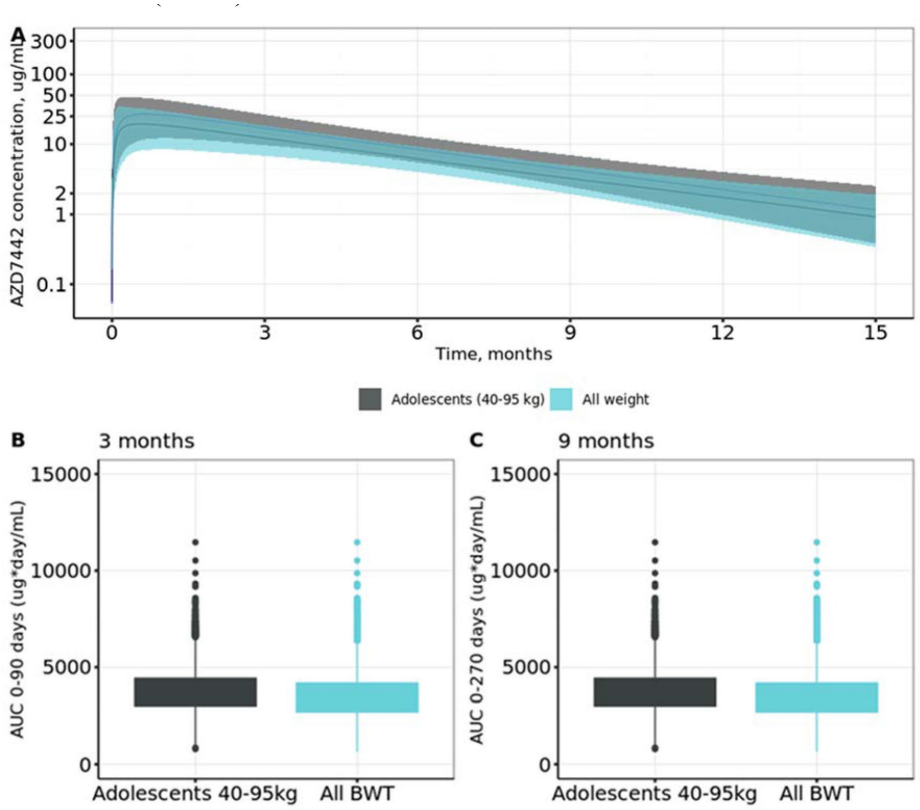
Number of participant at visit				
AZD8895	176	104	126	12
AZD1061	176	104	126	12
AZD7442	176	104	126	12

Baseline PK concentration was non-quantifiable. BS, baseline; N, number in analysis set; PK, pharmacokinetic; GSD, geometric standard deviation. Source: Figure 14.2.5.2.3 (Data cut-off, 07 April 2021).

Paediatric target population

Simulations using the population PK model were performed to support dosing of Evusheld for the prophylaxis of COVID-19 in adolescents aged ≥ 12 years weighing at least 40 kg. The median and 90% percentiles of AUC ratio (adolescents 40 to 95 kg /all weight 36 to 177 kg) at 3 months is 1.09 (1.04 to 1.15) and at 9 months it is 1.08 (1.04 to 1.16), which falls within the boundary of 0.8 to 1.25 equivalence criteria. This predicted minimal increase in exposure in the average adolescent population compared with the average adult population in combination with the favourable safety profile of Evusheld at the 300 mg IM dose with exposures that are ~12-fold lower than the exposures associated with the highest IV dose tested in Phase I, justifies the use of Evusheld in the untested adolescent population.

Figure 7: Comparison of the PK Profiles with Body Weight of 40 to 95 kg (Adolescents) or 36 to 177 kg (Adults)



AUC, area under the serum concentration-time curve; AZD7442, Evusheld; BWT, body weight. Source: Figure 10, Population PK report, Module 5.3.3.5.

Special populations

Sex and age were statistically significant covariates on KA, sex and diabetes on V2, and diabetes on CL. These covariates were not considered clinically significant as these covariates reduced the IIV of KA by only 7.0%, V2 by 15.7%, V3 by 0.3% and CL by just 1% relative to the base population PK model with fixed allometric exponents on clearance and volume of distribution. Vaccination status is not indicated to have a relevant impact on PK.

The issue of potential correlation bias in the pop PK model regarding weight, sex and diabetes will be followed in updated versions of the popPK model.

In general, monoclonal antibodies are not expected to be eliminated via renal excretion due to their high molecular weight of about 150 kDa. Thus, no formal studies have been conducted to investigate the effect of renal impairment on Evusheld. Based on population PK analysis, there is no difference in the clearance of tixagevimab and cilgavimab in participants with mild (n = 978) or moderate (n = 174) renal function compared with participants with normal renal function. In the population PK model, there were insufficient participants with severe impairment or complete renal failure (0.8%; n = 21) to draw conclusions regarding the impact of severe renal impairment on the PK of tixagevimab and cilgavimab. Evusheld is predominantly cleared via catalysis by cells of the reticulo-endothelial system. Therefore, dialysis is not expected to impact the clearance of Evusheld as supported by the limited PK data available in participants on dialysis (n = 11).

Tixagevimab and cilgavimab are expected to be primarily metabolised via proteolysis at the cellular level, so that impairment of hepatic clearance is not expected to lead to increased drug exposure. Thus, no specific studies have been conducted to examine the effects of hepatic impairment on the PK

of Evusheld. In the population PK model, the effect of hepatic function on CL using either aspartate aminotransferase, alanine aminotransferase, or bilirubin baseline concentrations as a covariate was not statistically significant. This exploratory analysis was limited by the fact that there were only 56 hepatically impaired participants (2.2%) in the Phase III PK analysis data set.

PK data on 1220 (47.7%) female participants included in the population PK analysis suggest that sex is not a clinically significant covariate for Evusheld PK with comparable weight-adjusted CL in females and males. The population PK covariate model suggests that male participants have a faster absorption rate (45%) and lower central volume of distribution (37%) and thus slightly lower exposure of Evusheld compared with female participants.

Based on the population PK analysis, race and ethnicity did not have a statistically significant effect on CL of Evusheld based on data from Hispanic/Latino (n = 531) vs non- Hispanic/non-Latino participants (n = 1875) and based on Black (n = 269) vs White (1939), vs other participants (n = 352).

Body mass index as a categorical covariate (< 30 vs ≥ 30 kg/m2) on KA in the population PK model did not test as statistically significant and therefore the dose of Evusheld does not need to be adjusted for BMI based on the BMI range of 21 to 41 kg/m² in Phase III studies. PK model simulations were conducted with the final population PK model to compare exposure for fixed dose versus weight-adjusted dose in the studied population with body weight ranging from 36 to 177 kg. Allometric exponents for scaling CL and V were set to 0.75 and 1 in the base and final model. The results showed that the predicted AUC over the first 6 months after dosing mostly overlapped between the 2 regimens.

All clearance or blood flow parameters (CL, Q) were scaled by body weight to the 0.75 power, and all distribution/tissue size parameters (V2 and V3) were scaled linearly by body weight with a power exponent of 1. Mean body weight in the population PK analysis dataset was 83.5 kg (90% percentiles: 56 to 120 kg). Body weight on CL reduced the CL % IIV from 32.1% to 21.9%, body weight on V2 reduced the V2 % IIV from 107% to 98%, and body weight on V3 reduced the V3 % IIV from 24% to 10.6%. Assuming no other covariate effect, the CL of Evusheld is predicted to be 50% higher for a participant with body weight of 120 kg (95th percentile), while CL is predicted to be 15% lower for a participant with body weight of 56 kg (5th percentile).

PK data on 790 (30.9%) participants with cardiovascular disease were included in the population PK covariate analysis to evaluate its effect on CL and V2. Results suggest that cardiovascular disease is not a statistically significant covariate for Evusheld PK.

Population PK analysis in which age is included as a categorical covariate (< 65 years or ≥ 65 years of age) suggest that Evusheld PK is not clinically affected by age and does not warrant dose adjustment. There were no observed differences in safety and/or effectiveness in older participants compared with younger adult participants. Participants aged ≥ 65 years showed slightly lower absorption.

Table 5: Tabular Summary of Participants Stratified Based on Age

	Age 65-74 (Older subjects number /total number)	**Age 75-84** (Older subjects number /total number)	**Age 85+** (Older subjects number /total number)
Study D8850C00001	0/50	0/50	0/50
PROVENT	413/1870	71/1870	2/1870
STROM CHASER	27/198	8/198	1/198
TACKLE	38/442	21/442	0/442

a Data from the TACKLE study are presented here as they were included in the population PK model

Pharmacokinetic interaction studies

No interaction studies have been conducted. Evusheld is not renally excreted or metabolised by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

Based on PK modelling, vaccination following Evusheld administration had no clinically relevant impact on the clearance of Evusheld.

2.5.2.2. Pharmacodynamics

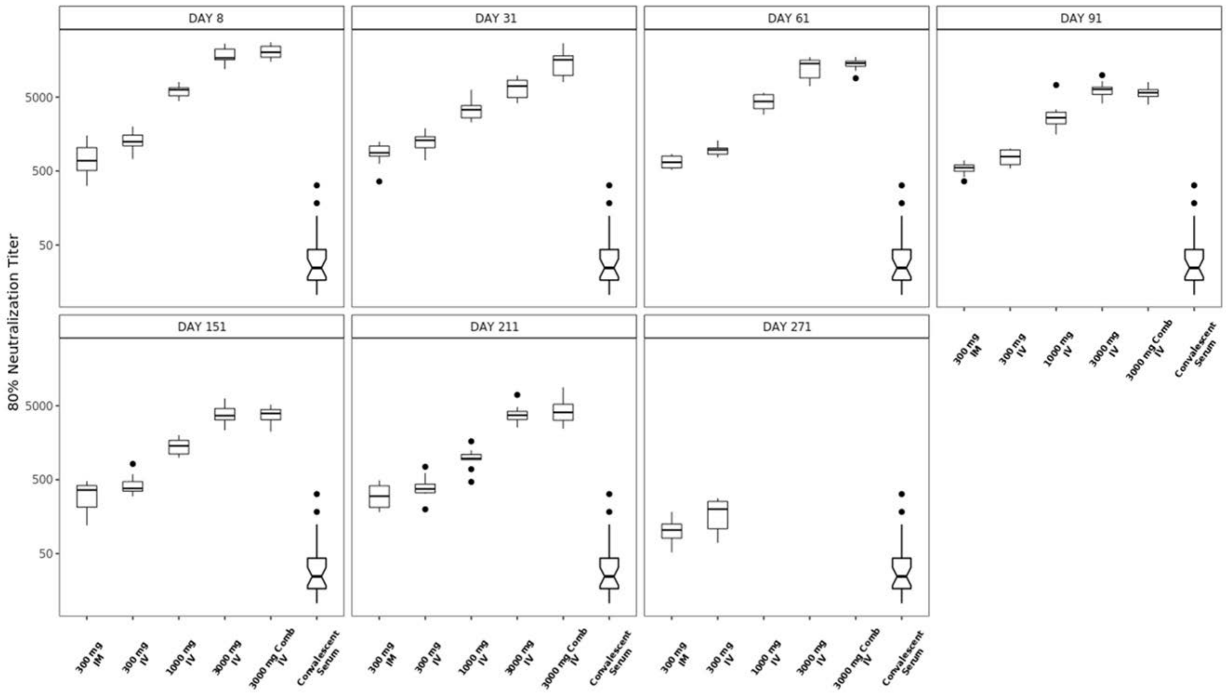
Mechanism of action

AZD8895 and AZD1061 simultaneously bind to non-overlapping regions of the RBD of SARS-CoV-2 spike protein. AZD8895 and AZD1061 and AZD7442 as combination product bind to spike protein with equilibrium dissociation constants of KD = 2.76 pM, 13.0 pM and 13.7 pM, respectively, blocking its interaction with the human ACE2 receptor, resulting in a blockade of virus entry and neutralisation of the SARS-CoV-2 virus. AZD8895 and AZD1061 and AZD7442 as combination product blocked RBD binding to the human ACE2 receptor with IC50 values of 47.7 ng/mL, 79.6 ng/mL, and 65.0 ng/mL, respectively. The virus-neutralising activity of AZD7442 and the two mAbs that comprise it were assessed against SARS-CoV-2 strain USA-WA1/2020. AZD7442 had a calculated IC50 value of 10 ng/mL. Data demonstrate that AZD8895 and AZD1061 can independently, or in combination (AZD7442), potently neutralize SARS-CoV-2 *in vitro*.

Primary pharmacology: Analysis of neutralising antibodies against SARS-CoV-2

In FITH study D8850C00001, 80% neutralising antibody titres against SARS-CoV-2 were measured at baseline (Day 1), 7 days (Day 8), 30 days (Day 31), 60 days (Day 61), 90 days (Day 91), 150 days (Day 151), 210 days (Day 211), and 270 days (Day 271) after administration of Evusheld in a validated live neutralisation assay (PRNT80). No participants had detectable nAbs prior to receiving Evusheld. Values below LLOQ were assigned a value half of LLOQ (ie, 10) for the purposes of calculating fold-change values post-treatment. At all post-dose time points evaluated after single dose administration of Evusheld, the geometric mean titres (GMTs) in participants receiving placebo were below the LLOQ of the assay. All 50 participants receiving Evusheld exhibited > 4-fold increases in nAb titre compared with baseline at Day 8 and maintained this increase out to Day 211. Participants in the 300 mg cohorts further maintained this > 4-fold increase from baseline in nAb titre out to Day 271.

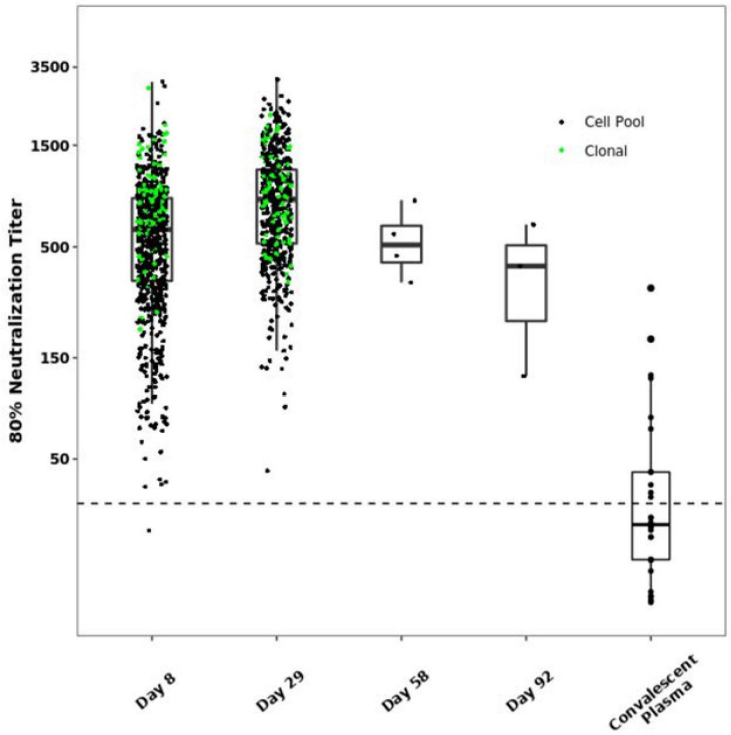
Figure 8: Box Plot of Neutralising Antibody Titers against SARS-CoV-2 on Day 8, Day 31, Day 61, Day 91, Day 151, Day 211, and Day 271 in Comparison with Convalescent Plasma (Safety Analysis Set); FITH study D8850C00001



IM, intramuscular; IV, intravenous, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. Source: Table 14.2.7.1 (AZD7442 data), Loo et al 2021 submitted (convalescent plasma data)

In study PROVENT, neutralising antibody titres against SARS-CoV-2 were measured after administration of Evusheld in the same validated live 80% neutralisation assay used to test samples from the Phase I study. Neutralising antibody titres against SARS-CoV-2 were evaluated predose (baseline), and at Days 8, 29, 58, 92, 183, 366, and 457 and at illness visits. Up to the DCO, data were available from Day 1 through Day 92 after administration of IMP. For participants who developed COVID-19, nAb data are available on Day 1 (IL-D1), Day 14 (IL-D14), Day 21 (IL-D21), and Day 28 (IL-D28) after symptom onset. Results indicate that SARS-CoV2 nAb titres in participants in the PROVENT population are similar to those observed in participants from the Phase I study at similar post-treatment timepoints. At all timepoints evaluated, the GMT in participants who received Evusheld in PROVENT exhibited > 4-fold increases in titre compared with baseline.

Figure 9: Box Plot of Neutralising Antibody Titers against SARS-CoV-2 on Day 8 and Day 29 in Comparison with Convalescent Plasma for 300 mg IM in PROVENT



IM, intramuscular; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. Horizontal line represents GMT measured in plasma samples from convalescing COVID-19 patients (n = 28). Green symbols represent nAb titres measured in participants that received clonal cell line material. Source: Figure 3, Exposure-Response Memo, Module 5.3.4.2 (DCO: 05 May 2021)

At IL-D1, IL-D14, IL-D21, and IL-D28 after symptom onset, participants who developed a case of COVID-19 after receiving Evusheld (n = 5) had 12.8, 6.7, 4.4, and 4.8-fold higher GMT than the GMT in samples from patients recovering from a SARS-CoV-2 infection, which are similar to the fold changes observed in participants receiving Evusheld who did not develop COVID-19.

In study STORM CHASER, neutralising antibody titres against SARS-CoV-2 were evaluated at 7 days (Day 8), 28 days (Day 29), 57 days (Day 58), and 91 days (Day 92) after administration of Evusheld or placebo. For participants that developed COVID-19, nAb data were also available on Day 1 (IL-D1), Day 14 (IL-D14), and Day 28 (IL-D28) after symptom onset. The GMT of participants in this study who received Evusheld increased > 4-fold compared with baseline, at all timepoints evaluated. At IL-D1, IL-D14, and IL-D28 after symptom onset, participants who developed a case of COVID-19 after receiving Evusheld (n = 14) had 16.6, 22.4, and 28.4-fold higher GMT than the GMT in plasma samples from convalescing COVID-19 patients, which are similar to the fold changes observed in participants receiving Evusheld who did not develop COVID-19.

Pharmacodynamic interactions

No human interaction studies have been conducted. There is a theoretical risk for PD interaction with COVID-19 vaccines (impaired cellular or humoral immune response).

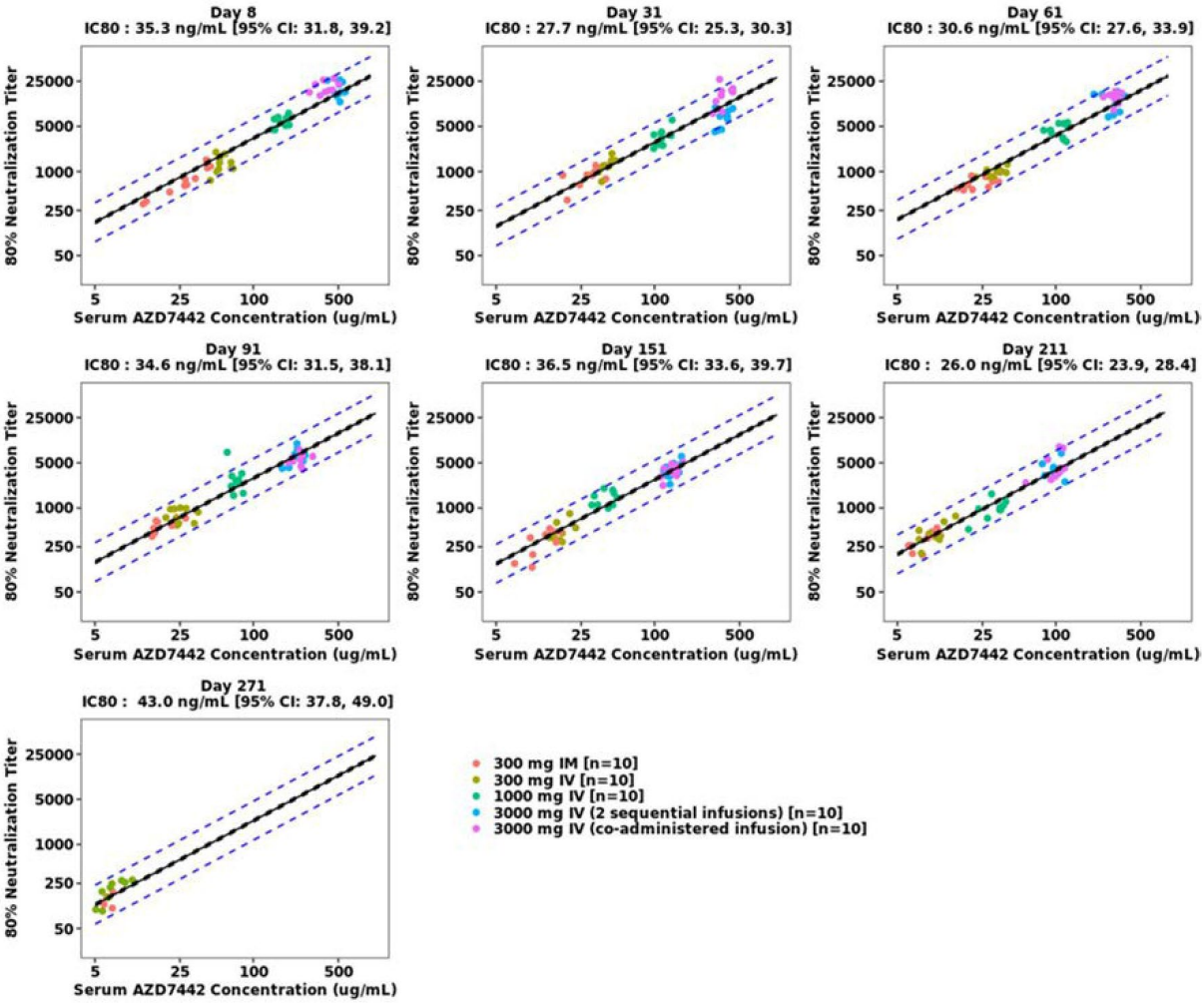
Relationship between plasma concentration and effect

The correlation between PK and Neutralising Antibodies was investigated with data from FITH study D8850C00001.

Linear regression model ("lm" function after adjusting the intercept to 1) was used in R studio to fit the correlation between 80% neutralisation titre and serum concentration. The correlation line was best described as "Regressor", as opposed to linear regression line. To accommodate the large dynamic range of the data with a constant coefficient of variation across the data from low to high dose, the regression was performed on log-transformed nAb titre and Evusheld concentration data.

The analyses show that there is a strong linear relationship between drug concentration and nAb titre that is maintained over time. For each Study Day, the upper bound of the 95% CI of the estimated IC80 is below the IC80 derived in the *in vitro* SARSCoV- 2 microneutralisation assay for Evusheld (4 × IC50 of 10 ng/mL is 40 ng/mL, assuming a Hill coefficient of 1). The mean IC80 estimates are 35.3 ng/mL, 27.7 ng/mL, 30.6 ng/mL, 34.6 ng/mL and 36.5 ng/mL, 26.0 ng/mL, and 43.0 ng/mL (based on partial data) on Days 8, 31, 61, 91, 151, 211, and 271, respectively. The consistency of the IC80 estimates over time support that the potency of Evusheld is not compromised over time.

Figure 10: Correlation Between the Serum Evusheld Concentrations and the Neutralising Antibody Titre on Day 8, Day 31, Day 61, Day 91, Day 151, Day 211, and Day 271, Study D8850C00001 (Phase I)

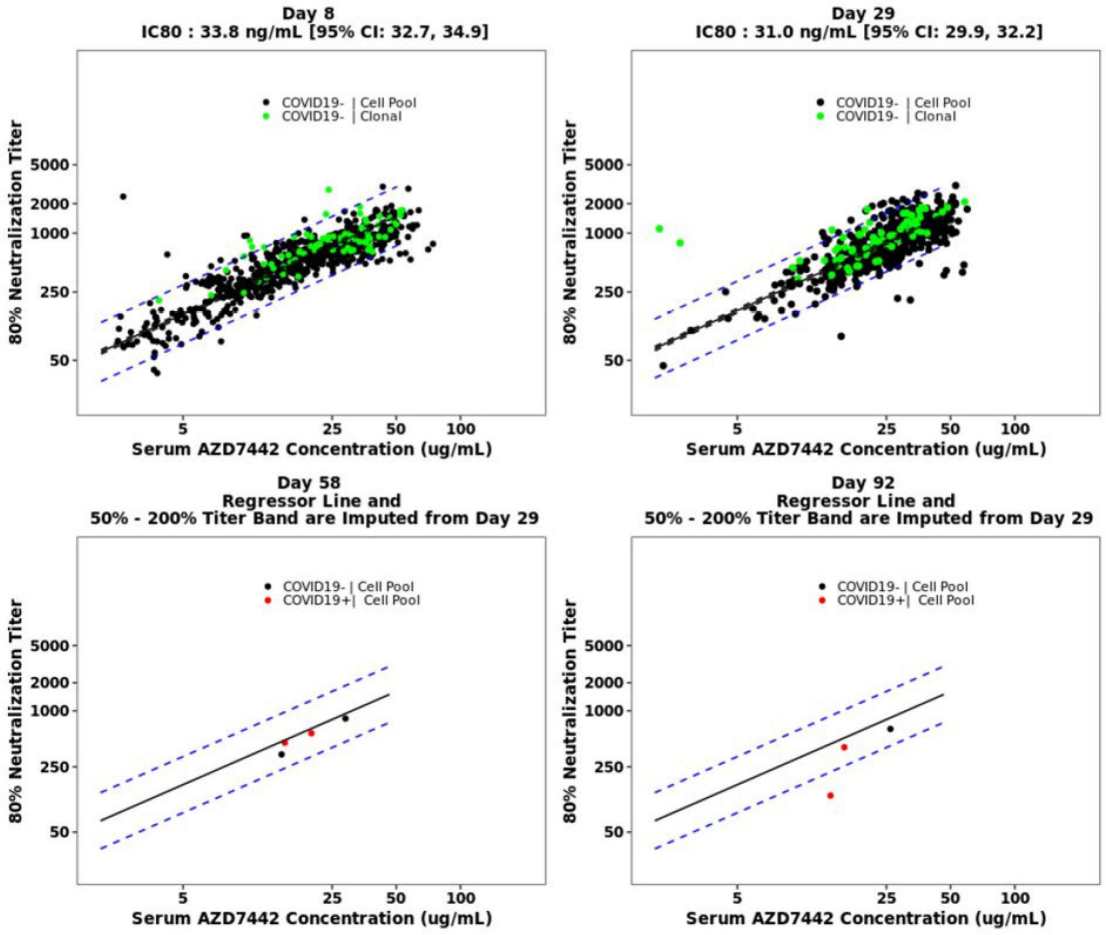


Area within blue dashed lines reflects acceptable live virus nAb assay accuracy of measured titre which is within one log2-dilution step, ie, 50% - 200% of the nominal neutralisation titer. AZD7442, Evusheld; CI, confidence interval;

DCO, data cut-off; IC80, 80% SARS-CoV-2 neutralisation concentration; IM, intramuscular; IV, intravenous Source: Figure 1, Exposure-Response Memo, Module 5.3.4.2 (DCO: 06 June 2021).

In PROVENT samples were scheduled to be collected on Days 8, 29, 58, 92,169, 366, and 457. Data are available so far mostly on Day 8 and Day 29. Similar to the Phase I data, the Evusheld concentration is strongly correlated to the nAb titre and is maintained over the first month. The inverse of the slope, which reflects the IC80 of Evusheld, was estimated as 33.8 ng/mL and 31.0 ng/mL on Days 8 and 29, respectively, and in the same range as those derived in Phase I.

Figure 11: Correlation Between the Serum Evusheld Concentrations and the Neutralising Antibody Titre on Day 8, and Day 29 for Dose 300 mg IM in PROVENT (Phase III)



Area within blue dashed lines reflects acceptable live virus nAb assay accuracy of measured titre which is within one log2-dilution step, ie, 50% - 200% of the nominal neutralisation titre; IC80, 80% SARS-CoV-2 neutralisation concentration; Green symbols represent nAb titres measured in participants that received clonal cell line material. CI, confidence interval; COVID-19, coronavirus disease 2019; DCO, data cut-off; IM, intramuscular; IC80, 80% maximal inhibitory concentration; nAb, neutralising antibodies; SARS-CoV-2, Severe acute respiratory syndrome-coronavirus 2. Source: Figure 2, Exposure-Response Memo, Module 5.3.4.2 (DCO: 05 May 2021).

The exposure response relationship of Evusheld for the efficacy endpoint of incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness that occurs within 150 days after a 300 mg IM dose of Evusheld (ie, by Day 151) was evaluated for PROVENT. The data used for this exposure-response analysis consisted of 663 actively treated participants out of 1637 participants (active and placebo) in the of the time-to-event dataset that met both criteria of having available COVID-19 status records and PK data over time. In this time-to-event data set, there were 7 COVID-19 positive participants for the treatment arm (out of 663 actively treated participants), while there was a total of 18 COVID-19

positive cases in the 1637 active plus placebo participants. For the exposure-response analysis, the population PK model individual predicted AUC(0-150) parameter divided in 4 quartiles was correlated to the incidence of SARS-CoV-2 RTPCR- positive symptomatic illness that occurs by Day 151 after a 300 mg IM dose of Evusheld. Based on the 5-month exposure-response data set, there was no exposure-response relationship.

No exposure-response analysis for safety has been conducted

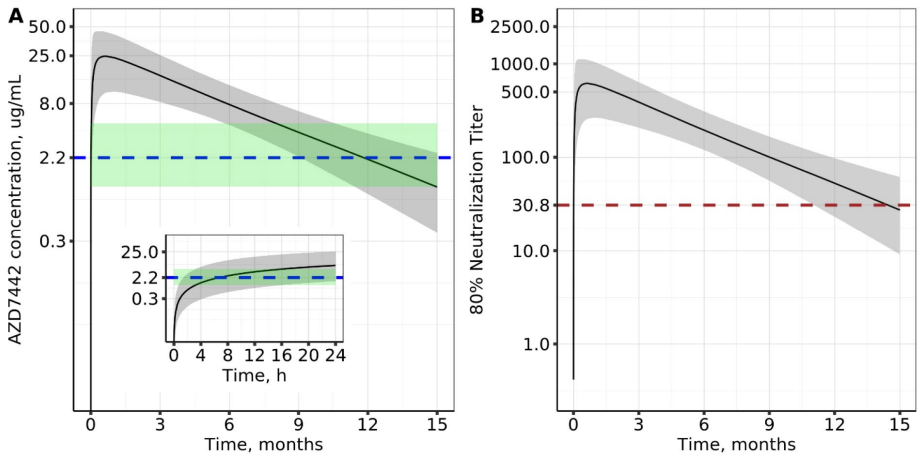
Dose justification

The justification of the Evusheld dose of 300 mg IM for prophylaxis was based on integrating the following information:

1. The *in vitro* IC50 of Evusheld for neutralisation of the original SARS-CoV-2 strain measured in the microneutralisation SARS-CoV-2 assay at 10 ng/mL.
2. Using the upper respiratory tract as the site of interest to prevent any viral load increase and therefore any symptoms.
3. A VDM-derived minimal required inhibition of viral cell entry of 80% required for prophylaxis efficacy.
4. The *ex vivo* derived IC80 of Evusheld by correlating PK and nAb titres measured in the live virus SARS-CoV-2 assay in Phase I and Phase III in support of the authentic microneutralisation SARSCoV-2 assay results.
5. The calculated median serum to NLF partition ratio of 1.81% in the 300 mg IM cohort in the Phase I study.
6. The Evusheld PK in Phase I and in Phase III that were well characterised by a population PK model and supported an extended half-life of ~ 90 days.

Integrating the information in components 1 to 5 allowed for the derivation of a predicted minimum protective serum Evusheld concentration of 2.2 µg/mL. Considering the predictable linear PK of Evusheld, the development of a population PK model allowed for long-term prediction of the serum Evusheld concentration. This allowed the derivation of the duration of protection by assessing how many months the serum Evusheld concentration would remain above the minimum protective concentration of 2.2 µg/mL. The PK predictions support that a dose of 300 mg IM will provide protection for at least 6 months and that the target serum concentration of 2.2 µg/mL was reached within 6 hours in the typical participant and by 28 hours in 90% of participants in the PROVENT and STORM CHASER population. In addition, a 2.2 µg/mL concentration was predicted to be exceeded in 50% of the PROVENT and STORM CHASER participants 12 months after the single 300 mg IM dose.

Figure 12: PK Model Predicted Median (90% Prediction Intervals) Serum Evusheld Concentration and Translated Anti-SARS-CoV-2 80% Neutralising Antibody Titres Following Administration of 300 mg IM Evusheld, Over 15 Months Based on PK Modelling Using Pooled Data of Phase I and Phase III Studies

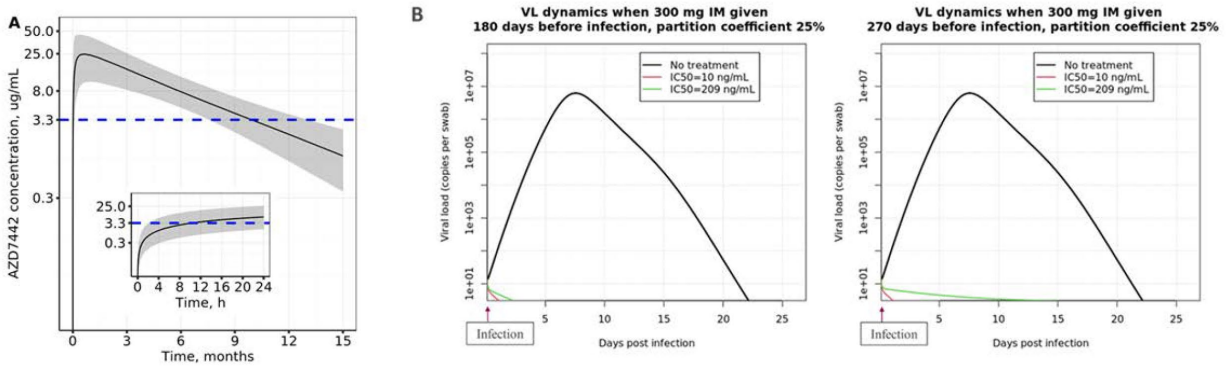


Blue horizontal line represents minimum protective concentration of 2.2 µg/mL in serum which with a 1.81% NLF:Serum partition ratio will result in the 40 ng/mL (IC80) in the upper respiratory tract (for Wuhan Variant). Green shaded area represents 25th (0.8%) and 75th (3.6%) percentile of NLF:Serum partition ratio. Brown horizontal line represents the geometric mean of the nAb titre (30.8) measured in 28 individual convalescent plasma samples. IC80, concentration of Evusheld at which the viral cell entry is inhibited by 80%; IM, intramuscular; nAB, neutralising antibody; NLF, nasal lining fluid; PK, pharmacokinetic; SARS-CoV-2, severe acute respiratory syndrome coronavirus

To assess the impact of the lower potency or higher IC50 on the duration of protection by Evusheld against the Omicron variant, the geometric mean IC50 of 209 ng/mL across 4 available different IC50 values (FNIH 2022, Dejnirattisai et al 2021, VanBlargan et al 2021) was used. The potency loss of Evusheld against the Omicron variant (ie, the duration of protection against Omicron to prevent symptomatic COVID-19 or upper respiratory tract infections) is likely to be shorter compared with that against the original SARS-CoV-2 strain. However, the duration of protection against Omicron is still expected to be maintained if the target site is the lower respiratory tract and the clinical endpoint is prevention of severe COVID-19 or death. This prediction is based on the assumption based on available data with other biologics that the serum to lower respiratory tract transfer is ~25% and VDM modelling.

Using the IC50 of 209 ng/mL, a required minimal inhibition of 80%, and a partition into lung of 25%, an updated target minimum protective serum concentration value was derived to be 3.3 µg/mL. The 3.3 µg/mL concentration is predicted to be reached in 50% of the participants within 10.5 hours (IQR 5 to 21 hours) and in 80% of the participants within 24 hours. The viral dynamic model prediction using the 25% partition ratio into the lower respiratory tract and the IC50 of 209 ng/mL confirms the PK prediction in that a single 300 mg IM dose would still result in protection from severe symptoms if the exposure to the Omicron variant occurs 6 months post-dose.

Figure 13: Predicted Duration of Protection Against Omicron SARS-CoV-2 Strain Post a Single Dose of 300 mg IM A) PK B) Viral Load Dynamics for Original and Omicron Variant IC50 Values



A) Blue horizontal line represents minimum protective concentration of 3.3 µg/mL in serum which with a 25% Lung:Serum partition ratio will result in the 209 ng/mL (IC80) in the lower respiratory tract (for Omicron variant). B) Viral load dynamics when 300 mg IM AZD7442 given 6 months (180 days; left plot) and 9 months (270 days; right plot) before infection occurs, using potency of IC50 = 10 ng/mL (original SARS-CoV-2 strain) and IC50 = 209 ng/mL (geometric mean IC50 against Omicron variant) and a serum to lower respiratory tract partition of 25%. The viral load clears rapidly for 300 mg IM using IC50 = 10 ng/mL (red line) and at reduced potency of IC50 = 209 ng/mL (green line) at day 0 when infection occurs. AZD7442, Evusheld; h, hour; IC50, 50% inhibitory concentration; IM, intramuscular; PK, pharmacokinetic; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Immunogenicity

From study PROVENT, ADA data to AZD8895, AZD1061, and Evusheld up to Study Day 183 are available on a subset of ADA-evaluable participants in the Evusheld and placebo groups.

Table 6: Summary of ADA Responses to AZD8895 and AZD1061 Following Administration of 300 mg IM Evusheld Over 182 Days (ADA Evaluable Analysis Set), PROVENT

ADA Category	Statistics	AZD8895[a]		AZD1061[b]		EVUSHELD[c]	
		Treatment (N = 716)	Placebo (N = 382)	Treatment (N = 644)	Placebo (N = 339)	Treatment (N = 743)	Placebo (N = 393)
ADA positive at any visit (ADA prevalence)	n (%)	25 (3.5)	10 (2.6)	22 (3.4)	8 (2.4)	37 (5.0)	14 (3.6)
	Median of maximum titer	160.0	240.0	80.0	160.0	80.0	160.0
	(min, max)	(80, 5120)	(160, 1280)	(40, 5120)	(40, 640)	(40, 5120)	(40, 1280)
TE-ADA positive[d] (ADA prevalence)	n (%)	6 (0.8)	3 (0.8)	7 (1.1)	2 (0.6)	10 (1.3)	3 (0.8)
	Median of maximum titer	160.0	320.0	80.0	240.0	160.0	320.0
	(min, max)	(160, 1280)	(160, 320)	(80, 320)	(160, 320)	(80, 1280)	(160, 320)

a Lowest reportable titre = 80

b Lowest reportable titre = 40 a

c ADA positive to Evusheld is defined as ADA positive to AZD8895 and/or AZD1061; TE-ADA positive to Evusheld is defined as TE-ADA positive to AZD8895 and/or AZD1061.

d Either ADA negative at baseline and ADA positive at ≥ 1 post-baseline assessments with ADA titre ≥ 2 times the MRD of the respective mAb, or baseline positive ADA titre that was boosted to ≥ 4-fold during the study period.

ADA, anti-drug antibody; min, minimum; max, maximum; TE-ADA, treatment-emergent ADA. Source: Appendix B, PROVENT Tables 14.2.4.5B, 14.2.4.6B and 14.2.4.7B

From study STORM CHASER, ADA data to AZD8895, AZD1061, and Evusheld up to Study Day 92 are available on a subset of ADA-evaluable participants in the Evusheld and placebo groups.

Table 7: Summary of ADA Responses to AZD8895 and AZD1061 Following Administration of 300 mg IM Evusheld Over 92 Days (ADA Evaluable Analysis Set), STORM CHASER

ADA Category	Statistics	AZD8895[a]		AZD1061[b]		EVUSHELD [c]	
		Treatment (N = 196)	Placebo (N = 105)	Treatment (N = 200)	Placebo (N = 102)	Treatment (N = 246)	Placebo (N = 125)
ADA positive at any visit (ADA prevalence)	n (%)	2 (1.0)	3 (2.9)	8 (4.0)	6 (5.9)	9 (3.7)	8 (6.4)
	Median of maximum titer	160.0	80.0	80.0	40.0	160.0	60.0
	(min, max)	(160, 160)	(80, 160)	(40, 10240)	(40, 80)	(40, 10240)	(40, 160)
TE-ADA positive[d] (ADA prevalence)	n (%)	1 (0.5)	0	3 (1.5)	0	3 (1.2)	0
	Median of maximum titer	160.0	NA	80.0	NA	160.0	NA
	(min, max)	(160, 160)	NA	(80, 160)	NA	(80, 160)	NA

a Lowest reportable titre = 80

b Lowest reportable titre = 40 a

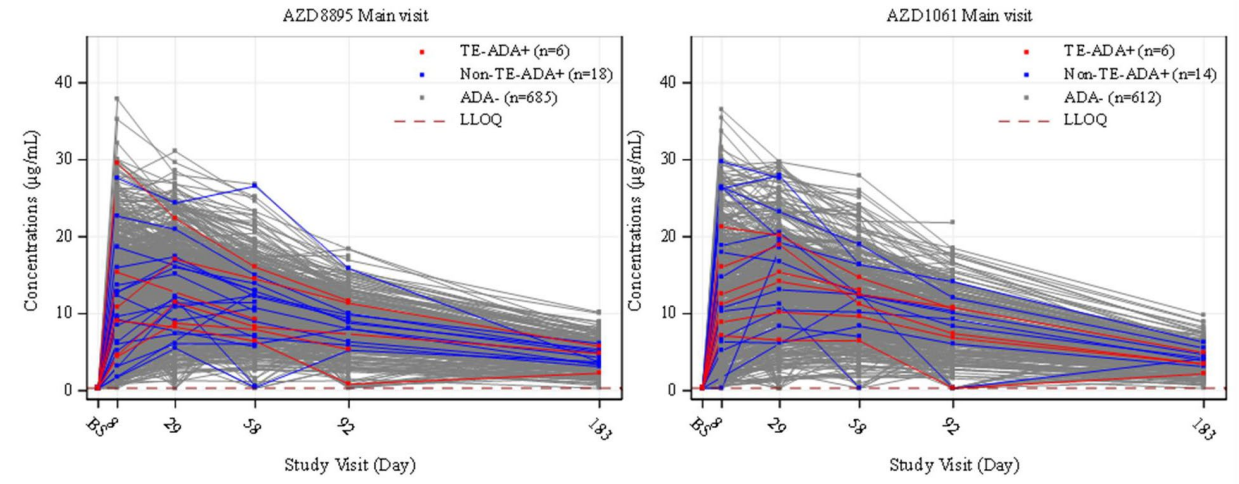
c ADA positive to Evusheld is defined as ADA positive to AZD8895 and/or AZD1061; TE-ADA positive to Evusheld is defined as TE-ADA positive to AZD8895 and/or AZD1061.

d Either ADA negative at baseline and ADA positive at ≥ 1 post-baseline assessments with ADA titre ≥ 2 times the MRD of the respective mAb, or baseline positive ADA titre that was boosted to ≥ 4-fold during the study period.

ADA, anti-drug antibody; min, minimum; max, maximum; TE-ADA, treatment-emergent ADA. Source: Appendix C, STORM CHASER Tables 14.2.5.4B, 14.2.5.5B and 14.2.5.6B

There were few TE ADA+ participants through Day 183 in PROVENT. As such, it was not possible to formally assess the potential impact of ADA on PK. AZD8895 and AZD1061 serum concentration time profiles of TE ADA+ participants were within the range of ADA-negative participants. Overall, there was no apparent effect of ADA on the PK of Evusheld.

Figure 14: Individual Serum Drug Concentrations (µg/mL) versus Time, by ADA Status and mAb Components (PK Analysis Set)



None of the TE ADA+ to Evusheld had reported hypersensitivity/anaphylaxis. Of the 82 participants in the active group who had at least 1 reported case of injection site reaction, only 1 was TE ADA+ to Evusheld. In addition, there is no data indicating that the reported cardiac and non-cardiac thrombotic SAEs were related to the presence of ADA to Evusheld.

Viral resistance

At timing of this report, genotypic and phenotypic testing are ongoing to monitor for SARS-CoV-2 spike variants containing potential tixagevimab, cilgavimab, and Evusheld (tixagevimab and cilgavimab) resistance-associated substitutions in PROVENT and STORM CHASER.

Genotypic analyses of SARS-CoV-2 spike protein sequences were derived from a validated GenoSure SARS-CoV-2 spike NGS assay (Monogram Biosciences, South San Francisco, CA). For participants that developed SARS-CoV-2RT-PCR-positive symptomatic illness, SARS-CoV-2 spike protein sequences are available on Illness Visit Day 1 (IL-D1). Variant frequency tables are generated to depict spike-based Pango lineages and amino acid substitutions that differ from the Wuhan-Hu-1/2019 reference strain. The phenotypic impact of SARS-CoV-2 spike protein sequences changes, including Evusheld binding site substitutions, are evaluated in validated pseudovirus neutralisation susceptibility assays. Key variants of concern/interest circulating at the time of the studies are further evaluated in research-grade authentic live virus neutralisation susceptibility assays.

For activity against variants of concern/interest in research-grade neutralisation assays, see section 2.2 of this report.

In PROVENT, illness visit sequencing data were available for 21 participants with COVID-19 infection (6 Evusheld and 15 placebo). At an allele fraction ≥ 25%, 14/21 participants were infected with variants of concern or variants of interest, including 8 participants with Alpha (B.1.1.7) (8 placebo), 1 participant with Beta (B.1.351) (1 Evusheld), 3 participants with Delta (B.1.617.2) (3 placebo), and 2 participants with Epsilon (B.1.429) (2 Evusheld). Seven (7) additional participants were infected with B.1.375 (1 Evusheld) or the A_1 set of lineages containing a constellation of spike protein substitutions including D614G and P681H or Q677P (3 Evusheld and 3 placebo).

In STORM CHASER, illness visit sequencing data were available for 19 participants with COVID-19 infection (12 of 12 Evusheld and 7 of 7 placebo). At an allele fraction ≥ 25%, 12/19 participants were infected with variants of concern or variants of interest, including 9 participants with Alpha (B.1.1.7) (5 Evusheld and 4 placebo) and 3 participants with Epsilon (B.1.427/B.1.429) (2 Evusheld and 1 placebo). Seven additional participants were infected with B.1.1.519 (1 Evusheld) or the A_1 set of lineages containing a constellation of spike protein substitutions including D614G and D138H, Q675H, Q677H, or V1176F (4 Evusheld and 2 placebo).

None of the variants detected under AZD7442 treatment was associated with susceptibility reduction >10fold in nonclinical pseudovirus assays.

2.5.3. Discussion on clinical pharmacology

Pharmacokinetics

Pharmacokinetic data are available from 3 clinical studies that evaluated Evusheld for the prophylaxis of COVID-19 in adults (18 years of age and older), namely study D8850C00001 (Phase I FTIH) and the phase 3 studies PROVENT and STORM CHASER. In addition, a population PK analysis of pooled Phase I and III data was performed to characterize the PK of Evusheld and to evaluate the impact of covariates such as demographics and renal and liver function tests on the PK exposure.

Analytical methods

An affinity purification extraction followed by LC-MS/MS detection was developed and used for the quantification of both, AZD8895 and AZD1061, concentrations. Method validation revealed that both assays perform with adequate accuracy and precision. The impact of endogenous anti-spike antibodies on method performance is considered to be low. Bioanalytical reports for both methods are outstanding; Summary information on sample storage, dilutions, performance of analytical runs and incurred sample re-analysis for PROVENT and STORM CHASER should be provided when available. **(REC)** For additional detection of AZD8895 and AZD1061 in nasal lining fluid (NLF), the same LC-MS/MS method was applied as used for serum concentrations. Urea was additionally quantified in NLF and serum in order to calculate an extraction efficiency factor for each NLF sample. The method for

AZD8895 and AZD1061 detection in NLF is qualified but not validated. The use of a fit-for-purpose qualified assay can be agreed, as NLF PK was mainly used to determine AZD8895 and AZD1061 partition rate in the upper respiratory tract (exploratory endpoint). The method passed acceptance criteria for within-run accuracy and precision. Experiments on elution from the nasosorption device showed adequate recovery.

For determination of anti-drug antibodies (ADAs) of AZD8895 and AZD1061, a 3-tiered approach comprising a screening assay followed by a confirmatory assay and the analysis of anti-AZD8895 and anti-AZD1061 antibody titre was developed and validated. A bridging ECL assay was applied; relevant assay performance parameters including assay cut point, precision, sensitivity, drug tolerance, selectivity and sample stability were investigated. Method validation revealed that both assays perform with adequate accuracy and precision. Overall, the methods may be suitable for its intended purpose. The use of pAb and anti-YTE Ab in addition to anti-ID mAb as positive controls is endorsed. Using PROVENT clinical samples, it was demonstrated that both AZD8895 and AZD1061 ADA assays could detect low-titre ADA in the presence of drug concentrations as high as 29.740 µg/mL, indicating that these assays have sufficient drug tolerance performance for their intended use. The poor drug tolerance seen with polyclonal anti-AZD8895 and anti-AZD1061 Abs seems to have little or no relevance for detection of ADAs. Confirmed ADA-positive samples are planned to be analysed in a separate ligand-binding assay. As neutralising ADAs have not been investigated so far, the method is not discussed here.

Population PK model

PK data in healthy volunteers (Phase I study [IM and IV arm]) and in participants in the 2 Phase III studies PROVENT and STORM CHASER, and in the treatment Phase III study TACKLE were pooled to develop a population PK model to characterize the PK of Evusheld.

The final pooled dataset for analysis included 2527 participants with a total of 7375 Evusheld PK measurements. An IM dose of 300 mg was used in the 2 prophylaxis studies (PROVENT and STORM CHASER), and 600 mg IM in the treatment study (TACKLE). The Phase I study investigated the PK of Evusheld in healthy volunteers with doses ranging from 300 mg IV to 3000 mg IV and 300 mg IM.

Derivation of the final pop PK dataset is agreed, but deviation from the analysis plan (Appendix D) could be detected. There, it was stated that if more than 10% of all concentrations are below LLOQ, likelihood methods for imputing the missing data may be considered. The number of samples classified as LLOQ that were flagged was N=75, which is less than 10% of total samples, thus the deviation is not deemed to be of concern.

A 2-compartmental model with first-order absorption and first-order elimination for tixagevimab, cilgavimab, and Evusheld PK following IV and IM administration was selected as final model to describe the PK data. Weight has been included by fixed allometric scaling exponents (CL: 0.75, V:1). Upon request, model predictive performances were shown to be comparable using fixed versus estimated allometric exponents for the bodyweight covariate.

Again, deviations in the pre-specified covariates and covariate selection process were detected. Vaccination status was added as potential covariate, which is endorsed. Upon request, a comparison of PK profiles along with number of participants in vaccinated vs unvaccinated group per study were provided, but no comparison of PK metrics. It is agreed from the visual representation, that the vaccination status is not indicated to have a relevant impact on PK. No further exploratory analyses have been provided by the applicant. The numbers per status was overall balanced in PROVENT (Not vaccinated: N=1040, vaccinated: N=813) and would not preclude "vaccination status" to be tested by pop PK analysis.

During the covariate model building, covariates that could be clinically relevant, but for which the applicant considered number of participants to be insufficient to investigate covariate-PK parameter relationship (< 10% of total participants) were not tested. This is not acceptable and should be adequately addressed. It is noted that for some of these covariate the absolute number was sufficiently high for the covariate effect to be detectable using nonlinear mixed effect approach. The applicant was asked to provide the results of covariate testing for CLD, CKD, COPD, Immunocompromised/immunosuppressants, COVID-19 status, CVS, and Study. Only the relevant subset of the dataset can be used for this purpose. From the data provided, CLD, CKD, COPD, Immunocompromised/immunosuppressants, COVID-19 status, CVS, and Study were tested as covariate during model development. None of these covariates were retained in the popPK model since they did not meet both clinically significant effect size (ie, >20%) and meaningful drop in the OFV value (3.84).

With respect to statistical selection criteria, the level of significance criteria set deviated from the analysis plan. Different statistical significance criteria were stated (p=0.01 (or 6.63 of change in OFV with df=1, Appendix) and p=0.05 (or 3.84 of change in OFV) pop PK report). The applicant was asked to clarify and justify the changes in the significance criteria. The applicant admitted that there was a deviation from the analysis plan with respect to the setting of p-values in the covariate selection (change from p=0.01 to p=0.05). This has been justified based on the study population (PROVENT) that included mostly (75%) subjects with high risk for severe COVID-19 with various co-morbidities. Thus, a more lenient p-value was set to more likely identify clinically plausible covariates. The stringent one for the backward elimination step was kept (p=0.001) which is agreed. Nevertheless, overall the selection (including weight) and correlation between covariates are still of concern.

During the covariate exploratory analysis, scatter plots highlighting possible relationships between continuous covariates was shown as well as some box plots displaying possible relationships between selected categorical and continuous covariates. However, the latter was detected to be incomplete. Of particular interest is the correlation between diabetes and bodyweight because the two covariates are retained on the same PK parameter in the final model. The applicant was asked to provide these plots. The box plot provided shows a correlation between diabetes and body weight with higher body weight in diabetes patients compared to non-diabetes. Both, body weight and diabetes, were statistically significant covariates on CL. However no dose adaptations were proposed for diabetes and the allometric exponent was fixed for bodyweight effect on CL. Hence, the inclusion of both body weight and diabetes as covariates on CL is not an issue for the current popPK model.)
In the same line, a correlation between bodyweight, that was incorporated using fix allometry in the base model, and sex was identified. Given this, the applicant was asked to discuss the appropriateness of retaining both sex and bodyweight as covariates on the CL and V in the final model. However, no dose adaptations was proposed for sex and the allometric exponent were fixed for bodyweight effect on CL. Hence, the inclusion of both body weight and sex as covariates on CL and V is not an issue for the current popPK model. The issue will be followed in updated versions of the popPK model. (**REC**)

The goodness of fit was assessed by means of diagnostic plots. It would have been of interest to see the effect on parameter estimation when TACKLE data were neglected. It seems that these data from the treatment study were necessary to stabilize the model structure development and parameter estimation.

The shrinkage and the IIV estimates were very high for V3 and V2, respectively. The applicant thus was asked to discuss the impact on the reliability of these parameters. The applicant argued that this can be contributed to the addition of sparse Phase III PK data that increased the shrinkage towards moderate to high. As expected, sample size has very limited impact on shrinkage of the PK parameters of the two-compartment model. Moreover, the applicant did not use Empirical Bayes Estimates based diagnostics during popPK model decision making process and thus the impact of high shrinkage will be

minimal and will not influence the reliability of estimated PK parameters (V2 and V3), which can be followed.

Overall, plots indicates the high variability in PK following a fix dose IM. The absorption constant Ka is showing a two-peaked distribution and predicted vs observed plots indicate a trend of overprediction of observed values for both antibodies.

From the VPC plots, it is apparent that low PK samples (5th percentile) from PROVENT (300 mg IM) are not captures be the model-predicted exposure range, whereas most observation from TACKLE are captured (600 mg IM). In light of the VPC plots, the applicant was asked to discuss potential sources and characteristics of patients in PROVENT that show low exposure, not captured and explained by the covariates included. Data following 300 mg IM from Phase I and comparison should also be taken into account. The applicant's elaboration on low PK samples following 300 mg IM can be endorsed. However, as no bioanalytical reports were provided so far, any bioanalytical reasons for that finding cannot be assessed for the time being. Upon request, the applicant provided a sensitivity analysis to further elucidate the impact of subjects that showed unexplained "up and down PK profiles" (low concentrations followed by an increase at later time points) from the PROVENT study (n = 107, out of 1870 subjects). As an expected result, the additive error parameter reduced by 2.4-fold (ie, 3.39 to 1.40 µg/mL). On the other hand, IIV of CL, V2, V3 and Ka is increased (model with excluded subjects) compared with the final pop PK model accompanied with some changes in covariate effect parameters. As there are remaining issues to be addressed with updated versions of pop PK modelling, and the bioanalytical final reports from PROVENT are still pending, this issue should also be readdressed with respect to PK data inclusion and final conclusions on covariates, in particular weight effects. (**REC**)

From the plots initially provided, it was not apparent how well Cmax after IM treatment and End-of-infusion is captured. Upon request, the applicant provided VPC plots again but focussing on the very early time span relevant for Cmax following IV and IM treatment. However, the plots still were presented in a truncated way (Phase I data). Although it is agreed that Cmax following 300 mg IM (PROVENT, Phase III) is overall adequately captured and comparable with Cmax following 300 mg IM in Phase I, the presented time course shows no absorption Phase. High variability in PK becomes apparent in both, Cmax following IV and IM mode of administration, regardless of dose.

ADME

In the Phase I study, the estimated absolute bioavailability after a single 150 mg IM dose was 68.54% for tixagevimab and 65.79% for cilgavimab. Due to the chosen route of administration Cmax is reached with lag time (approximately at day 14), which is considered acceptable for a pre-exposure prophylaxis setting. Furthermore, values far lower than Cmax are suggested to suffice for treatment effects. These "minimum protective serum concentrations" are estimated to be reached within few hours. Volume of distribution was 2.72 L for tixagevimab and 2.48 L for cilgavimab for central compartments and 2.64 L for tixagevimab and 2.57 L for cilgavimab for peripheral compartments, reflecting the limited ability of extravascular distribution. Estimated values for population median terminal elimination half-life (90.6 days for Evusheld, 88.8 days for tixagevimab and 84.4 days for cilgavimab) confirm successful half-life extension of the antibodies. Clearance (0.0405 L/day for tixagevimab and 0.0412 L/day for cilgavimab) is lower than known for typical mAbs (ranging between 0.2 – 0.5 L/day) and correlates with the half-life extension of the antibodies.

PK comparability testing

The PROVENT and STORM CHASER studies were initiated with cell pools material. Once clonal cell line material (the proposed commercial material) became available, this was used in an additional cohort in PROVENT to obtain PK and safety data in the prophylaxis setting. A preliminary comparability assessment of clonal cell line material was performed. Bioequivalence criteria were met for Cmax and

AUC0-58d (post hoc provided upon request) for both mAbs, but not for AUC0-91d. PK differences seen with AUC0-91d may be at least partly attributed to wide extrapolations conducted for this endpoint. Furthermore, subject characteristics of this partial population from study PROVENT were not that comparable between both treatment groups as it would have been expected for a classical bioequivalence study investigating inter-subject PK comparability. Thus, interpretation of PK comparability is somewhat impeded by differences in baseline characteristics. The inter-subject variability was high in these subgroups of study PROVENT, with geometric CV% ranging from 71.5% to 90.3% over the 4 time points sampled (Days 8, 29, 58, and 92). Of note, analytical comparability was sufficiently demonstrated, with no difference seen in potency and FcRn-binding assays. Thus, overall it can be assumed that the study was not adequately designed to detect potential differences in material's PK performance. Results on PK comparability for Cmax and AUCd0-58 as well as analytical comparability indicate that actual differences in material performance should be minor (if any). Final comparability analysis is planned to be performed for the final CSR when additional data will be available with serum concentrations data through Day 366.

Dose proportionality and time dependency

Based on results from FITH study D8850C00001, the pharmacokinetics of both, tixagevimab and cilgavimab, are linear and dose-proportional between 300 mg and 3 000 mg following a single intravenous administration. Only 1 dose level has been administered via IM route in clinical trials. Thus, dose-dependency of absorption cannot be assessed. Evusheld is currently planned to be administered as a single dose. No analysis of PK under steady state conditions has been performed; the potential for accumulation has not been investigated.

Intra- and inter-individual variability

Moderate inter-individual variability for AUC and Cmax was determined in healthy volunteers, while in the target population variability was remarkably higher. In the popPK analysis, IIV for CL was estimated to 20.9%, however was high for V2 (82.3%) and Ka (47.5%). No intra-individual comparison has been performed in the clinical trials with single dose administration.

PK in nasal lining fluid

PK data for nasal-lining fluid (NLF) from study D8850C00001 (Phase I FTIH) are so far only available for pre-dose, Day 8 and Day 31. The NLF concentration data show that both AZD8895 and AZD1061 distribute significantly into the upper respiratory tract. NLF concentration data were used to determine the partition ratio. It was shown that partition ratio is dose-independent, mAb-independent, and time-independent with regard to the time points investigated (Day 8 and Day 31). For the intended prophylactic dose of 300 mg IM, the median partition from serum to NLF was calculated as 1.81% for AZD7442. The median value for the %partition ratio for AZD7442 from serum to NLF was considered in calculations for targeted minimum protective level (2.2 µg/mL in serum for original strain). Based on results provided, this approach is deemed appropriate.

PK in target population

Preliminary PK data derived from the PROVENT and STORM CHASER trials were provided as data summary only. Based on results obtained, concentrations remained above the target serum level of 2.2 µg/mL for up to Day 183. As PK sampling was not completed at the time of the data cut-off, the PK profile is not complete. The development of a popPK model allowed for long-term prediction of the serum Evusheld concentration. Furthermore, complete 1-year PK data are available from FITH study D8850C00001 and support reliability of long-term PK predictions made based on popPK model.

PK in paediatric target population

No adolescent PK data are available from AZD7442 clinical trial programme so far. Exposure predictions for adolescents weighing at least 40 kg have been based on pop PK modelling. In general, paediatric dosing of adolescent patients aged 12 years or older and weighing at least 40 kg based on exposure matching with adult exposure can be agreed, as the mode of action and exposure-response is not expected to be different between adolescents and the adult population. Due to the lower body weight, and the fix dose regimen, slightly higher exposure is expected and was predicted for the adolescent subpopulation. Considering the broad safety margins of the 300 mg dose based on preclinical and phase 1 human studies, a slightly higher exposure is assumed not to result in safety problems. Furthermore, the lower weight limit of subjects that provided data for pop PK modelling was 40.8 kg. Overall, the administration of 300 mg AZD7442 IM in adolescents weighing ≥40 kg can be acceptable.

PK in special populations

PK data were obtained for some subjects that became COVID-19 vaccinated in studies PROVENT and STORM CHASER. The PK profiles of subjects who were vaccinated post Evusheld dose overlaps with those for unvaccinated subjects. Thus, it may be assumed that vaccination status is not indicated to have a relevant impact on PK. No further exploratory analyses have been provided by the applicant.

In general, monoclonal antibodies are not expected to be eliminated via renal excretion due to their high molecular weight of about 150 kDa. is expected to be primarily metabolised via proteolysis at the cellular level, so that impairment of hepatic clearance is not expected to lead to increased drug exposure. It is acceptable that no specific PK studies on renal or hepatic impairment are planned. Based on a population PK analyses, the PK profiles were not found to be affected by intrinsic factors including sex, race, or ethnicity. PK data from male and female were balanced; most PK data were collected from non- Hispanic/non-Latino participants and White. Weight was included in the base and final pop PK models assuming fix allometric exponents (0.75 on CL and Q; and 1 on V2 and V3). Mean age in the Evusheld PK analysis dataset was 52 years (5th and 95th percentiles: 24 -73). Age (< 65 years or ≥ 65 years of age) was not found to be a clinically significant covariate. Only very few subjects aged 85 years and older were included in trials (N=2 in PROVENT, N=1 in STORM CHASER) and became part of the popPK data file for analysis.

As it was indicated that the applicant did some update from the submitted pop PK model, the applicantwas requested to provide the results of PTA analysis using the latest updated POPPK model. This model should be based on the most actual PK data considered appropriate in terms of data integrity. In addition, as covariate selection was concerned e.g. with respect to inclusion of weight effect, a sensitivity analysis should be provided assuming fix allometry and estimated allometric exponents. It was clarified that the final model provided for rolling review was used for PTA calculations. Nevertheless, the remaining issues need to be addressed using an updated version of the pop PK model, when outstanding data become available (**REC**)

Pharmacodynamics

Data including PD (SARS-CoV-2 nAbs), PK/nAbs correlation, immunogenicity, and antiviral resistance of Evusheld are available from 3 clinical studies (study D8850C00001 (Phase I FTIH), phase 3 studies PROVENT and STORM CHASER).

The virus-neutralising activity of AZD7442 and the two mAbs that comprise it were assessed against SARS-CoV-2 strain USA-WA1/2020 *in vitro*. AZD7442 had a calculated IC50 value of 10 ng/mL.

SARS-CoV-2 nAbs

In the FITH study D8850C00001, the increase in neutralising antibody titres against SARS-CoV-2 (Strain: BavPat1/2020) was demonstrated to be dose-dependent. Participants receiving AZD7442 at the 300 mg IM dose exhibited > 4-fold increases in nAb titre compared to baseline at Day 8 and maintained this increase out to Day 271. Importantly, across all doses and timepoints evaluated, the levels of nAbs exceeded the mean nAb titres measured in the same assay in SARS-CoV-2 convalescent plasma samples. In the PROVENT and STORM CHASER trials, neutralising antibody titres against SARS-CoV-2 were measured up to Day 92 after administration of AZD7442. Results of phase 3 trials were incomplete with the presented data cut-off, with the majority of subjects not yet analysed (not part of the "nAbs evaluable analysis set") and only very few samples analysed for later time points (days 58 and 92 p.a). At all time points investigated, the geometric mean titre exhibited > 4-fold increases compared with baseline. Samples from some participants who developed a case of COVID-19 after receiving AZD7442 were analysed with the presented data cut-off. With symptom onset, results were similar to the fold changes observed in participants receiving AZD7442 who did not develop COVID-19. Considering this data, the relevance of specific SARS-CoV-2 nAb titre values for development of COVID-19 is questionable. Results from PRNT50 pseudovirus assays development and validation against specific Omicron variants are expected by Q2 2022. In this line, evaluation of relevant clinical trial samples (*ex vivo* neutralisation capacity) should be provided as well. (**REC)**

Pharmacodynamic interactions

As for other mAbs with external target, no PD interaction with concomitant mediation is expected. However, there is a theoretical risk for PD interaction with COVID-19 vaccines (impaired cellular or humoral immune response). No subjects previously vaccinated against COVID-19 were included in the clinical trials. Subjects in phase 3 trials were allowed to receive COVID-19 vaccination after Evusheld administration with study progress. Separate presentation of safety results available so far from these subjects do not raise concern. Recommendations for time intervals between Evusheld administration and subsequent COVID-19 vaccination and *vice versa* cannot be based on clinical data obtained with Evusheld. Thus, decision will need to be based on local/national guidelines. The applicant states that no PD interaction with SARS-CoV-2 vaccines is expected based on animal studies. However, as discussed in non-clinical assessment report, the performed experiments showed some shortcomings and thus, results should be interpreted with caution. Therefore, the lack of clinical information on PD interactions with COVID-19 vaccines is communicated in the statement "No human interaction studies have been performed" in Section 4.5 of the SmPC.

Relationship between plasma concentration and effect

Exposure-response analysis was performed for 80% SARS-CoV-2 neutralising antibody titres from FITH study D8850C00001 and study PROVENT. A good correlation between plasma concentration and 80% SARS-CoV-2 neutralising antibody titres was expected (as kind of concept proof) and is seen with data from both studies. The derived median *ex vivo* IC80 was close to the in *vitro* IC80 value measured in the SARS-CoV-2 original strain. Noteworthy, based on PD results obtained in subjects with symptomatic COVID-19, high neutralising antibody titres are presumed not to be predictive for beneficial clinical outcome.

Exposure-response analysis for the primary endpoint of study PROVENT was conducted, with Evusheld $AUC_{0\text{-}150}$ split into quartiles. With the very low number of events under Evusheld treatment (N=7), no exposure-response was seen.

No exposure-response analysis for safety has been conducted. As Evusheld aims at an exogenous target, no target-related AEs are expected. For safety parameters investigated (e.g. systemic hypersensitivity, SEAs, deaths), incidence was low and exposure-safety analyses are not expected to be robust. Thus, it is deemed acceptable not to perform exposure-safety analyses for safety endpoints.

Dose justification

A viral dynamics model (VDM) has been built in order to describe viral loads during infection. However, the model is only based on viral load data published in literature from a limited number of patients. Upon request, the VDM has been validated by comparing the predicted mean viral load through the VDM to the observed viral dynamics in a human challenge study (Killingly et al 2022). There was a reasonably good concordance between the shape and magnitude of the predicted and observed viral load in the rising and declining phase of the curve. The peak viral load in the challenge study was higher than predicted, because, according to the applicant, the longitudinal samples (used to fit the VDMs) indicated the patients were already in the downward phase of the viral load curve. However, updated VDM with viral load data gathered throughout their clinical programme and correlation of viral dynamics with clinical outcomes, and the effect of Evusheld on viral dynamics/outcomes are pending. The updated VDM and outcomes will be available by June 2022. (**REC**)

The totality of available *in vitro* (microneutralisation SARS-CoV-2 assay with original virus strain) and clinical information (serum and nasal fluid PK, neutralising antibody titres from phase 1 and 3 trials) as well as modelling/simulation (viral dynamic model, popPK) was applied for dose justification. The use of a model-based approach to approximate the target exposure attainment is endorsed in principle. The herby predicted minimum protective serum Evusheld concentration is 2.2 µg/mL. As Evusheld serum concentration decline was considered linear, the popPK model allowed long-term prediction of Evusheld concentrations. The minimum serum protective concentration threshold of 2.2 µg/mL was predicted to be reached for at least 6 months in 100% of participants, 9 months in 96% of participants, and for 12 months in 46% of participants.

After administration of a 300 mg dose IM, maximal concentrations obtained in clinical trials are greatly exceeding (up to approximately 10-fold) predicted minimum serum protective concentration. However, presumably due to the exogenous target, they were not associated with safety problems. Hypersensitivities and application-related reactions are presumed to potentially occur independent of dose. Thus, this kind of "excess dosing" can be acceptable from a safety perspective. Furthermore, a comparable "excess dosing" approach was utilised for other mAbs with exogenous target, including those approved for prophylaxis of COVID-19, however, requiring more frequent dosing. The long-term effect achieved by Evusheld after a single IM dose is considered beneficial in the envisaged pre-exposure prophylaxis indication. The chosen dose of 300 mg IM is deemed appropriate in the prophylaxis setting considering data generated with information from original virus strain. However, dose and dosing interval might need to be re-considered with recent/ potentially upcoming viral variants showing reduced susceptibility *in vitro* (see below), that affects the duration over a minimum protective serum concentration.

Dose justification for omicron variant

External data on *in vitro* IC50 (pseudovirus and authentic virus) were applied to predict protection against the omicron variant. As a geometric mean from results of 4 independent laboratories, an IC50 of 209 ng/mL was applied for variant BA.1; this is approximately 20-fold higher than IC50 seen with original strain (10 ng/mL). Presuming a required minimal inhibition of 80%, and a partition into lung of 25%, an updated target minimum protective serum concentration value was derived to be 3.3 µg/mL. The minimum serum protective concentration threshold of 3.3 µg/mL was predicted to be maintained for at least 6 months in 100% of participants, for 9 months in 72% of participants, and for 12 months in 13% of participants. It has to be noted that, in contrast to modelling for original strain that was basis for dose justification, the low partition rate in the upper respiratory tract (1.81% based on PK results in nasal lining fluid) was not considered for predictions on omicron variant, and there is uncertainty in the lung partition ratio of 25% as there are data supporting even lower ratios (6.5%,

12%) to be equally justified. No data with Evusheld are available in this regard. Thus, the applicant claims prevention of severe COVID-19 or death but not prevention of symptomatic illness (as this would require virus neutralisation also in the upper respiratory tract). However, as in a prophylaxis setting prevention of COVID-19 (of any severity) is claimed, additional simulation was requested. Furthermore, kind of a "worst case scenarios" covering variability in partition rate and IC50 values observed across different *in vitro* experiments (including omicron sub-variants) as well as weight effect on PK were asked to be simulated to elucidate how sensitive the duration over minimum protective serum concentration would change dependent on the assumptions used for model simulations. IC80 and the more stringent IC90 should be considered as *in vivo* PD target for calculation of probability of target attainment (PTA) and simulations of (worst case) scenarios for Omicron variants. Additionally, simulations should cover IC50 values observed across different *in vitro* experiments on Omicron sub variants.

In response, the upper respiratory tract was not taken into account for dose justification facing Omicron variants. The applicant provided sensitivity analyses assuming lung partition coefficients (6,5% and 12%) and mean IC50 (209 ng/mL) and max IC50 (273 ng/mL) of variant BA.1.

Table 8:

Sensitivity Analysis: Population PK Model Predicted % Participants with Concentrations ≥ the Minimum Protective Concentration in Serum for EVUSHELD Against the Omicron BA.1 Variant Following a Single IM Dose of EVUSHELD

	Time (Months)	% of Participants Above Minimum Protective Concentrations			
		Single Dose			
		IC80 (836 ng/ml; VLP+AV; 6.5% LPR) [b] MPC = 12.9 µg/mL	IC80 (1092 ng/mL; AV; 6.5% LPR) [c] MPC = 16.8 µg/mL	IC80 (836 ng/mL; VLP+AV; 12% LPR) [d] MPC = 7 µg/mL	IC80 (1092 ng/ml; AV; 12% LPR) [e] MPC = 9.1 µg/mL
300 mg EVUSHELD[a] IM	3	71	41	99	92
	6	6	0	65	27
600 mg EVUSHELD[a] IM	3	99	95	100	100
	6	73	40	98	97

[a] EVUSHELD concentration = the sum of the tixagevimab and cilgavimab concentrations

[b] The EVUSHELD driven IC80 is 836 ng/mL based on in vitro SARS-CoV-2 Omicron BA.1 variant neutralization assays from both pseudotyped VLP and AV assays. The assays were pooled and the central tendency represented as the geometric mean of the BA.1 values in Table 1. The geometric mean IC80 was then estimated from a concentration-response relationship (4 × IC50 of 208.8 ng/mL is 836 ng/mL, assuming a Hill coefficient of 1). Uses a 6.5% LPR resulting in a MPC of 16.7 µg/mL.

[c] The EVUSHELD driven IC80 is 1092 ng/mL based on an in vitro SARS-CoV-2 Omicron BA.1 variant neutralization assay using AV. The geometric mean IC80 was then estimated from a concentration-response relationship (4 × IC50 of 273 ng/mL is 1092 ng/mL, assuming a Hill coefficient of 1). Uses a 6.5% LPR resulting in a MPC of 21.8 µg/mL.

[d] Same as b, but uses a 12% LPR resulting in a MPC of 7 µg/mL.

[e] Same as c, but uses a 12% LPR resulting in a MPC of 9.1 µg/mL.

AV, authentic live virus; IC80, 80% SARS-CoV-2 cell entry inhibition concentration; IM, intramuscular; LPR, lower respiratory tract penetration ratio; MPC, minimum protective serum concentration; VLP, virus-like particles

No further *in vitro* results were considered for BA.1. *In vivo* anti-viral activity in terms if IC90 PD target was also not considered, although the predictability from the VDM, that was used to derive the IC80 level, has been questioned. Thus, while the proposed limits for LPR and IC50 values are supported, predictions considering a 90% *in vivo* effect should still be considered unless the viral dynamic model is appropriately updated. However, even assuming a PD target of 80%, the simulations indicate that duration over an estimated minimum protective level in serum is highly dependent on the assumptions used for simulations. No such simulations have been provided for Omicron strain BA.1.1 and BA.2. Of note, for BA.1.1 IC50 ranged from 466 (pseudo virus) to 1147 (authentic virus) ng/mL with an up to 424 fold reduction. In turn, duration of protection is expected to be even more reduced for the Omicron variant BA.1.1 compared to BA.1. For variant BA.2, which is increasingly becoming the most important strain in Europe, IC50 from *in vitro* neutralising data for both, pseudovirus (9.8 ng/mL) and authentic virus (35 ng/mL), are indicated to be comparable with those for original strains (10 ng/mL), neutralising activity is expected to be more comparable as well. However no further simulations/predictions including IC90 and assumptions regarding the upper and lower respiratory

tract, have been calculated. No additional data have been provided. Thus, and in absence of confirmatory clinical trial data with BA.1.1 and BA.2 variants, probability of target attainment (PTA) analyses for all three variants were asked to be provided with special focus on subjects at high weight. By considering the results from (worst case) scenarios, the applicant was asked to simulate optimised posology for each of the Omicron strains (BA.1, BA.1.1 and BA.2) that would predict at least 70% of the subjects over the minimum protective serum concentration needed for protection over the duration of 6 months (300 mg IM and 600 mg IM with respective dosing intervals should be opposed). In this line, data from interim analysis on the first 50 participants from a PROVENT sub-study (multiple dosing) available in Q2 2022 should be provided (REC). Simulations provided following the latest request and including IC90 calculations indicate, that alternative dosing in terms of 600 mg IM – as the only additional dose at higher strength with sparse safety data – would not be feasible as a single dose or multiple dose treatment option to ensure an acceptable duration of protection against BA.1 and BA.1.1. Simulations focusing on bodyweight quartiles have not been conducted with the highest MPC (4.8 µg/ml) for the BA.2 strain. Thus, it could not be precluded that the duration of protection patients at high weight (>95 kg) is reduced to a clinically relevant level (also for original strains) (REC).

Immunogenicity

As per data cut-off June 2021, no patients in the FITH were tested positive for ADAs. However, due to limitations seen in the assay, ADA samples may be inconclusive and ADA response might be underestimated for high doses in the phase 1 trial. In the target population (studies PROVENT and STORM CHASER), ADA results from 989 Evusheld ADA-evaluable participants were available. Overall, ADA incidence was low. The majority of ADA-positive participants were classified as non-TE ADA positive. Mean ADA titres were rather low (80-320).

Individual AZD serum concentrations were presented for ADA positive subjects. Concentration vs time curves of ADA positives were within the range seen in overall population. The presence of TE-ADAs was not associated with hypersensitivities or anaphylaxis. However, most TE-ADAs were detected at later timepoints and not in temporal proximity with dosing (were hypersensitivity would be expected). Data for ADA positive subjects prior to treatment (non TE-ADAs) were not presented. Overall, it is agreed that ADA results from 989 Evusheld ADA-evaluable participants may be sufficient in sample size for a statement in the SmPC. The current presentation of ADA results in the SmPC is acceptable.

Viral Resistance

Due to the small number of overall events, post-treatment sequencing data from the prophylaxis studies are very limited. Preliminary data from patients with breakthrough infections under Evusheld treatment do not raise concern. Overall, no conclusion on clinical efficacy in prophylaxis against certain variants can be drawn based on available information. Completed results on PROVENT and STORM CHASER viral resistance analysis are expected with final CSRs. The current presentation of clinical viral resistance data in the SmPC is acceptable.

The applicant's plan to conduct continuous reviews of genomic databases such as GISAID for emerging Variants of Interest and Variants of Concern (and subsequent phenotypic evaluation by use of *in vitro* assays, if appropriate) is supported. Beyond that, the applicant plans to monitor data on breakthrough infections due to emerging variants from all available data sources, including but not limited to: Spontaneous cases reported during emergency/post-authorisation use; Clinical trial data from the applicant; Studies conducted by public health authorities; Literature. As this is part of the RMP under "other forms of routine pharmacovigilance activities for lack of efficacy", timely information of the Authorities will be ensured.

2.5.4. Conclusions on clinical pharmacology

Pharmacokinetics

Data package on pharmacokinetics is overall deemed sufficient to characterize the PK of AZD8895, AZD1061, and Evusheld (combination of both mAbs).

PK data and pop PK data analysis indicate linear and dose proportional PK over the dose ranges studied with regard to both monoclonal antibodies AZD8895 and AZD1061, respectively (300 mg to 3000 mg IV, 300 mg IM). Sampling was sufficient to characterize the time course following a single dose of each mAb administered IM. Obtained PK parameters are in line with what would have been expected for mAbs with exogenous target and half-life extension.

Long-term PK predictions made based on popPK model were confirmed by 1-year PK data from Phase 1 study D8850C00001.

Paediatric dosing of adolescent patients aged 12 years or older and weighing at least 40 kg based on exposure matching with adult exposure can be agreed.

Final PK results from study PROVENT and STORM CHASER are not yet available. Issues identified regarding covariate selection and correlation among covariates should be followed in updated versions of the popPK model based on the most recent PK data set including currently outstanding PK data.

Pharmacodynamics

Clinical data on neutralising SARS-CoV-2 antibody titre indicate that sufficiently high values for a treatment effect against original virus strain will be obtained for up to 6 months. A good correlation between Evusheld plasma concentration and *ex vivo* 80% SARS-CoV-2 neutralising antibody titres was expected (as kind of concept proof) and is seen with clinical data.

The viral dynamics model (VDM) was validated by use of observed viral dynamics in a human challenge study. However, confirmation of the model with own viral load data generated during illness visits in phase 3 studies is still outstanding and so far it has not been established how viral load correlates with clinical outcome.

The totality of available *in vitro* (microneutralisation SARS-CoV-2 assay for original virus strain) and clinical information (serum and nasal fluid PK, neutralising antibody titres from phase 1 and 3 trials) as well as modelling/simulation (viral dynamic model, popPK) was applied for initial dose justification. By that, the minimum serum protective concentration threshold of 2.2 µg/mL against original virus strain was predicted to be maintained for at least 6 months in 100% of participants. However, in order to account for reduced susceptibility seen *in vitro,* additional simulations for omicron and sub-variants should be provided.

Viral sequencing data from the prophylaxis studies are too limited to allow conclusion on clinical efficacy in prophylaxis against certain VOC/VOI. Based on provided simulations regarding the duration over expected protective serum concentrations against Omicron strains, and provided clinical and PK data, however, Evusheld 300 mg IM can be regarded as the appropriate dose to protect the majority of patients against multiple SARS-CoV-2 variants including BA.2, with BA.2 becoming the most dominant strain across Europe. Alternative dosing regimen of Evusheld are considered not feasible for the prevention of COVID-19 resulting from emerging variants including BA.1 and BA.1.1. as there are no safety data to support such high doses or multiple dosing, with potential accumulation due to long half-life, that would be needed to ensure acceptable duration of prevention against these strains.

Whether alternative dosing regimen of Evusheld could be appropriate for the prevention of COVID-19 resulting from emerging variants remains to be determined.

The risk of viral resistance will be addressed post approval by "other forms of routine pharmacovigilance activities for lack of efficacy".

There is a theoretical risk for PD interaction of Evusheld with COVID-19 vaccines (impaired cellular or humoral immune response) that has not been addressed in clinical trials.

Data base for ADA analysis is sufficient for a statement in the SmPC. There was a low number of TE-ADA positive subjects in phase 3 prophylaxis trials.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

Please see list of the recommendations in the appendix at the end of this document.

2.5.5. Clinical efficacy

The efficacy of Evusheld for the prevention of was evaluated in the following studies:

Two Phase III, randomised, double-blind, placebo-controlled, parallel-group, prophylaxis studies:

- Study D8850C00002 (PROVENT)
- Study D8850C00003 (STORM CHASER)

The applicant's clinical development programme was subject to a Scientific Advice procedure with the CHMP.

Key aspects of the pre-Phase III advice and the impact on the PROVENT study:

- The comparability of clinical trial material derived from the cell pools material and material derived from a single clonal cell line should be demonstrated. In addition, clonal cell line material should be utilised in the clinical programme. Analytical comparability of the clonal cell line material versus cell pools material has been demonstrated *in vitro*. A comparison of the PK and safety of drug product derived from clonal cell line material versus cell pools material in PROVENT have been provided by the applicant.
- Details on concomitant COVID-19 vaccination and subsequent monitoring should be provided
- CHMP requested primary endpoint definition in PROVENT to be amended to include all clinically apparent and laboratory-proven cases from the time of administration onwards.
- CHMP recommended 'region' as stratification factor; included as a subgroup analysis. Recruitment was not stratified by region to reduce the risk of the Poisson model failing to converge.

Key aspects of the pre-Phase I advise on Study D8850C00001:

- PEI suggested to identify the epitopes and look at circulating strains and track mutations. Evusheld binding sites have been identified and SARS-CoV-2 variants and binding site substitutions observed in clinical studies are being actively tracked. SARS-CoV-2 spike protein sequences from open-source genomic databases are being monitored.

- US FDA recommended modifying the inclusion criteria to specify a WHO Clinical Progression Scale score > 1, rather than > 0, to avoid confusion. This change was incorporated into the protocol.

2.5.5.1. Dose response studies

The phase I study D8850C00001 was designed to evaluate the safety, tolerability, and pharmacokinetics of AZD7442 in healthy adult participants between 18 and 55 years of age. Dose levels were selected based on available in vitro functional potency data and PK data.

At the time of data cut-off for the interim analysis, 60 participants have been randomised, received the investigational medicinal product (IMP) and 59 are ongoing in the Follow-up Period.

The first participant received their first dose on 21 August 2020. All participants were enrolled at one study center and randomised 10:2 to either AZD7442 or placebo administered intravenous (IV) or intramuscular (IM), across 5 fixed-dose cohorts:

- Cohort 1a: **300 mg of AZD7442** or PBO **IM** injection: 2 sequential starting with 150 mg tixagevimab (AZD8895) / PBO followed by 150 mg cilgavimab (AZD1061) / PBO
- Cohort 1b: **300 mg of AZD7442** or PBO **IV** injection: 2 sequential starting with 150 mg tixagevimab (AZD8895) / PBO followed by 150 mg cilgavimab (AZD1061) / PBO
- Cohort 2: **1000 mg** of AZD7442 or PBO **IV** injection: 2 sequential starting with 500 mg tixagevimab (AZD8895) / PBO followed by 500 mg cilgavimab (AZD1061) / PBO
- Cohort 3: **3000 mg** of AZD7442 or PBO **IV** injection: 2 sequential starting with 1500 mg tixagevimab (AZD8895) / PBO followed by 1500 mg cilgavimab (AZD1061) / PBO
- Cohort 4: **3000 mg** of AZD7442 or PBO **IV** injection: Co-administered IV infusion of tixagevimab and cilgavimab / PBO

Monitoring for TEAEs, SAEs, ADAs is planned up to day 361.

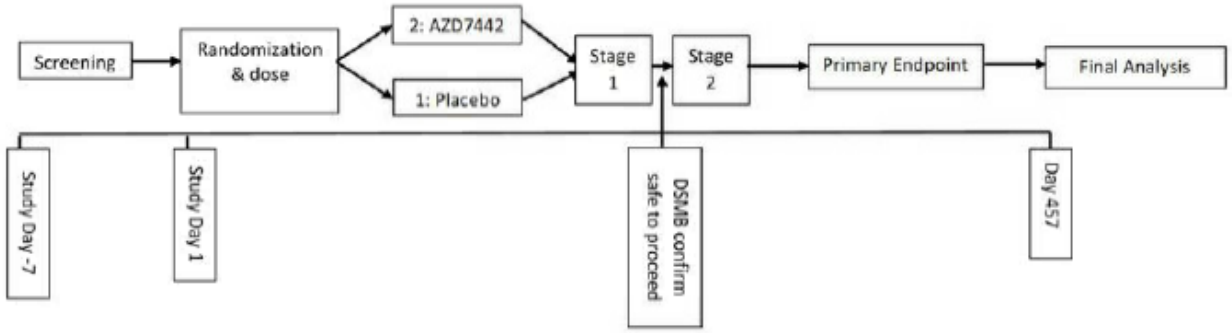
2.5.5.2. Main studies

PROVENT (study code D8850C00002)

Methods

PROVENT is an ongoing Phase III, randomised, double blind, placebo-controlled, multicenter, study assessing the safety and efficacy of a single dose of Evusheld compared to placebo for the prevention of COVID-19. This ongoing study is being conducted in 87 study centers across the United States (US), United Kingdom (UK), Belgium, France, and Spain. Participants were recruited from Europe (including UK) (28.4% of participants in PROVENT and 8.7% of participants in STORM CHASER), and US (71.6% PROVENT, 91.3% STORM CHASER).

Figure 15: Study design PROVENT



Patients were assigned to 2 cohorts:

- Cohort 1: Adults ≥ 60 years of age. All such participants were considered as being at increased risk for inadequate response to active immunisation on the basis of age (presumed immunosenescence). Within this cohort, randomisation was stratified by residence in a long-term care facility (yes/no).
- Cohort 2: Adults < 60 years of age. Within this cohort, randomisation was stratified by risk of exposure to infection with SARS-CoV-2.

Study Participants

Inclusion Criteria

- Participant was ≥ 18 years of age at the time of signing the informed consent.
- Candidate for benefit from passive immunisation with antibodies, defined as:
    - Increased risk for inadequate response to active immunisation (predicted poor responders to vaccines) (Furer et al 2020, Poland et al 2018, Wagner and Weinberger 2020, Zimmermann and Curtis 2019), defined as:
        - Elderly, ie, ≥ 60 years old
        - Obese, ie, BMI ≥ 30
        - Congestive heart failure
        - Chronic obstructive pulmonary disease
        - Chronic kidney disease, ie, GFR < 30 mL/min/1.73 m2 (Lamb et al 2013)
        - Chronic liver disease
        - Immunocompromised state from solid organ transplant, blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of other immunosuppressive medicines
        - Intolerant of vaccine. Defined as previous history of severe adverse event or serious adverse event after receiving any approved vaccine.
    - Increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19, based on available risk assessment at time of enrollment. Examples include:
        - Health care workers, including staff of long-term care facilities (including skilled nursing facilities, assisted living facilities, and independent living facilities for senior adults)
        - Workers in industrial settings shown to have been at high risk for SARS-COV-2 transmission, including but not limited to meatpacking plants o Military personnel residing or working in high-density settings including but not limited to barracks, ships, or close-quarters working environments
        - Students living in dormitory settings
        - Others living in settings of similar close or high-density proximity.
- Medically stable defined as disease not requiring significant change in therapy or hospitalisation

for worsening disease during the one month prior to enrollment, with no acute change in condition at the time of study enrollment as judged by the Investigator).
- Negative result from point of care SARS-CoV-2 serology testing at screening (added in CSP Amendment 2 [see Section 9.9]).
- If able, signed informed consent.
  Able to understand and comply with study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorised representative or equivalent representative as locally defined) based on the assessment of the Investigator.

Exclusion Criteria

- Significant infection or other acute illness, including fever > 100 °F (> 37.8 °C) on the day prior to or day of randomisation.
- History of laboratory-confirmed SARS-CoV-2 infection or any positive SARS-CoV-2 result based on available data at screening.
- History of infection with severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS).
- Known history of allergy or reaction to any component of the study drug formulation.
- Previous hypersensitivity, infusion-related reaction, or severe adverse reaction following administration of a mAb.
- Any prior receipt of investigational or licensed vaccine or other mAb/biologic indicated for the prevention of SARS-CoV-2 or COVID-19 or expected receipt during the period of study follow-up.
- Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture.
- Any other significant disease, disorder, or finding that may significantly increase the risk to the participant because of participation in the study, affect the ability of the participant to participate in the study, or impair interpretation of the study data.
- Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.
- For women only – currently pregnant (confirmed with positive pregnancy test) or breast feeding.
- Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to randomisation.
- Employees of the Sponsor involved in planning, executing, supervising, or reviewing the AZD7442 programme, clinical study site staff, or any other individuals involved with the conduct of the study, or immediate family members of such individuals.
- In nations, states, or other jurisdictions that for legal or ethical reasons bar the enrollment of participants who lack capacity to provide their own informed consent, such participants are excluded.

Treatments

- **Evusheld (AZD7442),** cell pools or clonal cell line material, including 2 separate vials of tixagevimab (AZD8895) and cilgavimab (AZD1061), each as 150 mg colorless to slightly yellow, clear to opalescent solutions for injection.
- **Placebo: 0.9% saline**

Study treatments were sequentially administered as a single, separate IM doses. Participants were allowed to take concomitant medication as prescribed by their primary care provider. Participants who developed COVID-19 after receiving IMP were treated according to local standard of care, including investigational agents outside a clinical trial setting.

Objectives

Primary objectives

- To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19 prior to Day 183
- To assess the safety and tolerability of a single IM dose of AZD7442 compared to placebo

Secondary objectives

- To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of SARS-CoV-2 infection
- To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of severe or critical symptomatic COVID-19
- To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19-related Emergency Department visits
- To assess the PK of AZD7442 administered as a single dose of 300 mg IM
- To evaluate ADA responses to AZD7442 in serum

Exploratory objectives

- To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19 through Day 366
- To evaluate the single dose pharmacokinetic concentrations of AZD7442 in nasal fluid
- To determine anti-SARS-CoV-2 nAb levels in serum following a single IM dose of AZD7442 or placebo
- To quantify SARS-CoV-2 viral loads in infected participants treated with a single IM dose of AZD7442 or placebo (Illness Visits)
- To quantify duration of viral shedding in participants with symptomatic COVID-19 treated with a single IM dose of AZD7442 or placebo (Illness Visits)
- To characterize resistance to AZD7442 (Illness Visits)
- To assess the biometric profiles associated with COVID-19 using a biosensor in participants treated with a single IM dose of AZD7442 or placebo (Illness Visits)
- To assess symptoms associated with COVID-19 using an e-Diary in participants treated with a single IM dose of AZD7442 or placebo (Illness Visits only)
- To assess additional immune responses following a single IM dose of AZD7442 or placebo

Outcomes/endpoints

Table 9: Objectives and Endpoints PROVENT

Primary objectives	**Primary endpoints**
To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19 prior to Day 183	A binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs post dose of IMP prior to Day 183
To assess the safety and tolerability of a single IM dose of AZD7442 compared to placebo	AEs, SAEs, MAAEs, and AESIs post dose of IMP
Key secondary objective	**Key secondary endpoint**
To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of SARS-CoV-2 infection	The incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies
Secondary objectives	**Secondary endpoints**

To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of severe or critical symptomatic COVID-19	The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring after dosing with IMP
To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19-related Emergency Department visits	The incidence of COVID-19-related Emergency Department visits occurring after dosing with IMP.
To assess the PK of AZD7442 administered as a single dose of 300 mg IM	Serum AZD7442 concentrations
To evaluate ADA responses to AZD7442 in serum	Incidence of ADA to AZD7442 in serum

Randomisation and blinding (masking)

All participants were planned to be centrally assigned to a randomised IMP using an IRT. Before the study was initiated, user guides, the log-in information, and directions for the IRT were planned to be provided to each study site. Randomisation was planned to be stratified within each of the 2 cohorts:

- Cohort 1: Adults ≥ 60 years of age. All participants were considered as being at increased risk for inadequate response to active immunisation on the basis of age (presumed immunosenescence). Cohort 1 was capped, not to exceed 80% of total participants randomised. Within this cohort, randomisation was stratified by residence in a long-term care facility or not.
- Cohort 2: Adults < 60 years of age. Cohort 2 was capped, not to exceed 80% of total participants randomised. Within this cohort, randomisation was stratified by risk of exposure to infection with SARS-CoV-2.

In the initial version of the study protocol, the cohorts 1 and 2 were planned to be capped at 65% and 50%, respectively. These caps were changed in protocol version 4 (21 December 2020), in order to allow more flexible recruitment.

Neither the participant nor any of the investigators or sponsor staff who were involved in the treatment or clinical evaluation and monitoring of the participants were aware of the IMP received. Because AZD7442 and placebo were visually distinct prior to dose preparation (due to differences in container closure), IMP was handled by an unblinded pharmacist (or designee, in accordance with local and institutional regulations) at the study site. Syringe masking was required in order to maintain the blind. The IRT provided the investigator(s) or pharmacists a dose tracking number to be allocated to the participant at the dispensing visit. Routines for this were described in the IRT user manual that was provided to each study site.

The randomisation code was not to be broken except in medical emergencies when the appropriate management of the participant required knowledge of the treatment randomisation. The investigator documented and reported the action to the sponsor, without revealing the treatment given to the participant to the sponsor staff.

The sponsor retained the right to break the code for SAEs that are unexpected and are suspected to be causally related to the IMP and that potentially require expedited reporting to regulatory authorities. Randomisation codes were not to be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant had been made and documented.

Statistical methods

The primary efficacy endpoint in PROVENT is a binary response, whereby a participant was defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs post-dose of IMP and prior to Day 183.

The primary analysis was planned after approximately 24 primary endpoint events had been confirmed across the active and control groups or 30% of study participants had become unblinded (at which point the ability to observe primary endpoint events was expected to have diminished), whichever occurred earlier. All primary endpoint events accrued up until the data cut-off were included in the primary analysis. Thirty percent of study participants had become unblinded by 05 May 2021 (primarily due to the participants wanting to be vaccinated against SARSCoV-2) (ie, the DCO for the primary analysis).

The primary efficacy estimate was planned to be calculated as RRR = 100% × (1-relative risk), which is the incidence of infection in the AZD7442 arm relative to the incidence of infection in the control arm, expressed as a percentage. Efficacy summaries were planned to be presented with a 2-sided 95% CI. Statistical significance was planned to be achieved if the two-sided p-value < 0.05.

A Poisson regression model with robust variance (Zou 2004) adjusting for follow-up time, was planned to be used as the primary efficacy analysis model to estimate the risk reduction on the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose of IMP between the AZD7442 and the placebo groups (see Section 16.1.4 of the SAP). The model was planned to contain the planned treatment group and age group at the time of informed consent (ie, ≥ 60 years and < 60 years) as a covariate. The logarithm of the participant's corresponding follow-up time at risk starting from dose up to the study Day 183 visit was planned to be used as an offset variable in the model to adjust for participants having different exposure times during which the events occurred.

The primary estimand was planned to be used for the analysis of the primary efficacy endpoint. It was planned to be based on participants in the full pre-exposure analysis set, defined as all randomised participants who received at least one dose of IMP without having had a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection, analyzed according to their randomised treatment. For participants with multiple events, only the first occurrence was planned to be used for the primary efficacy endpoint analysis. The set of intercurrent events for this estimand was planned to consist of participants who became unblinded to treatment assignment and/or took a COVID-19 vaccine or other COVID-19 preventive product, in both cases prior to having met the primary efficacy endpoint. The intercurrent events were planned to be handled using a while on treatment strategy, where participants who experienced an intercurrent event were planned to be censored at the date of unblinding/receipt of first dose of COVID-19 product, whichever was earlier, within the primary estimand. Absence of data following participants' withdrawal prior to having met the primary efficacy endpoint was planned to be treated as missing and participants were considered as not having the event through the time of last observation. Deaths that were caused by COVID-19 and all hospitalisations due to COVID-19 were planned to be also considered as primary efficacy endpoints.

An estimand using the treatment policy strategy, which included all endpoint events, irrespective of unblinding and/or vaccination, was planned to be used as the first of two key supportive analyses of the primary endpoint and was planned to be included in the multiple testing hierarchy. A second key supportive analysis, in which the endpoint was defined as first case of SARS-CoV-2 RT-PCR-positive symptomatic illness or death from any cause post dose of IMP and prior to Day 183, was planned to be performed and included in the multiple testing hierarchy.
The hierarchical approach was planned to include the below analyses as ordered:

1. the primary estimand, after approximately 24 primary endpoint events have been confirmed or 30% of study participants have become unblinded, whichever occurs earlier.
2. the first key supportive estimand (treatment policy strategy)
3. the second key supportive estimand (including death due to any cause)
4. the key secondary efficacy endpoint (incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies)

Estimand

The primary estimand is not a treatment policy estimand, but a "while-not-vaccinated-or-unblinded" estimand, excluding events that occur after vaccination. It is understood and acknowledged that the applicant made considerations how to best account for unblinding and vaccination. However, a "while-not-vaccinated" estimand is not necessarily the most relevant estimand for a regulatory decision. It is acknowledged that a supportive treatment policy estimand (regardless of vaccination) is provided, and this is endorsed. Consistency of the two estimands is expected to provide some reassurance on the extent that unblinding and vaccination may have affected results.

Analysis set

The primary analysis was done on the so-called full pre-exposure set, comprising all subjects randomised and treated who were not infected with SARS-CoV-2 prior to baseline.

Excluding subjects with evidence of prior infection may be somewhat selective, and does not seem to fully reflect a treatment policy, as these subjects were included and treated in the study. However, they can be considered a subgroup, and accordingly, no bias is expected in the estimation. Still, the selection warrants further discussion:

Initially it was planned to conduct the primary analysis on the full analysis set (FAS) comprising all randomised subjects who were treated at least once, but this was changed in an amendment to the Full Pre-Exposure Analysis Set. Upon request, the applicant provided primary and key secondary results in the FAS and separately in those FAS subjects who were excluded from the Full pre-exposure analysis set.

Variable and analysis model

A binary endpoint is considered adequate, the analysis model using a poisson regression is in principle acceptable, but adjustment of the model may need further discussion.

The primary analysis was planned to be adjusted for age and observation time. It is understood that due to small incidences the possibilities for adjustment or stratification are limited, but it seems that adjustment for the strata of randomisation (residence in a long-term care facility, risk of exposure to infection with SARS-CoV-2) was not discussed. Upon request, the applicant provided further analyses to assess the impact of those variables on results. Results from these analyses did not raise any concern.

Significance level and multiplicity

A two-sided significance level of $\alpha = 0.05$ is acceptable. Whether the level of statistical significance is considered persuasive for a regulatory decision may also depend on the results of supportive studies, as this is currently the only pivotal study.

The hierarchical testing approach is acceptable. The key-secondray endpoint incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies was added rather late, in protocol version 8.

Success criterion

A stricter success criterion was initially planned, but discarded in an early amendment. Prior to version 3 of the study protocol (13 November 2020), success of the study was planned as follows:

"Statistical significance will be achieved if the 2-sided 95% CI is > 30%. The success criterion for the study will be statistical significance with an observed efficacy point estimate of greater than or equal to 50%."

Such a criterion would not be formally required and it was deleted based on health authority feedback. Still, fulfilment could provide reassurance of positive results.

Missing values and censoring

Participants who were unblinded to IMP assignment or who were vaccinated prior to experiencing a primary endpoint event, were censored at the earlier time of unblinding/vaccination. This is appropriate for a while-not-vaccinated estimand under plausible assumptions, but as stated above a treatment policy strategy without censoring might be preferred. Both analyses were provided.

It seems that missing values were not imputed, and in particular missing data on symptomatic infection was interpreted as absence of symptomatic infection. This is acceptable and may even be conservative in some scenarios. Despite some uncertainty on the potential impact on results there is currently no reason to assume that this might have artificially increased the effect estimate.

Interim analyses and timing of analyses

There were no interim analysis. During the conduct of the study an unblinded interim analysis was added and then removed again (before it was actually conducted). Again, this reflects some uncertainty in planning and conduct.

The planned timing of the primary analysis was adapted during the conduct of the study to be after *"24 primary endpoint events have been confirmed or 30% of study participants have become unblinded, whichever occurs first".* It is not fully understood why 30% of unblinded subjects should trigger the analysis, as this criterion does not reflect the information accrued. Eventually, unblinding triggered the analysis, but the two criteria coincided (there were 25 events), and no concern is raised on this issue.

Results

Participant flow

The participant disposition at the primary analysis DCO (05 May 2021) is summarised in table below.

Table 10: Participant Flow PROVENT

Category	Number (%) of Participants		
	AZD7442 300 mg IM	Placebo	Total
Participants screened, N	NA	NA	5973
Participants screen-failed, n (%)[a]	NA	NA	719 (12.0)
Reason for screen-failed[a]			
Entry criteria not met,	NA	NA	501 (8.4)
Withdrawal by participant	NA	NA	60 (1.0)
Adverse event	NA	NA	3 (0.1)
Lost to follow-up	NA	NA	33 (0.6)
Sponsor decision	NA	NA	10 (0.2)
Other	NA	NA	112 (1.9)
Participants randomized	3500 (100.0)	1754 (100.0)	5254 (100.0)
Participants randomized but not dosed[b]	40 (1.1)	17 (1.0)	57 (1.1)
Participants ongoing in study	3409 (97.4)	1700 (96.9)	5109 (97.2)
Participants who completed the study	0	0	0

Participants who discontinued early from study[c]	91 (2.6)	54 (3.1)	145 (2.8)
Age < 60 years	65 (71.4)	35 (64.8)	100 (69.0)
Age ≥ 60 years	26 (28.6)	19 (35.2)	45 (31.0)
Reason for discontinuing early from study[c]			
Adverse event	0	0	0
Death	4 (4.4)	4 (7.4)	8 (5.5)
Lost to follow-up	11 (12.1)	8 (14.8)	19 (13.1)
Non-compliance with study drug	0	0	0
Pregnancy	0	0	0
Protocol deviation	1 (1.1)	0	1 (0.7)
Physician decision	1 (1.1)	0	1 (0.7)
Study terminated by Sponsor	0	0	0
Withdrawal by participant	56 (61.5)	32 (59.3)	88 (60.7)
Other[d]	18 (19.8)	10 (18.5)	28 (19.3)

[a] Percentages are based on the number of screened participants.

[b] Most participants who were not dosed were randomized in error.

[c] Percentages are based on the number of randomized participants who discontinued the study by treatment group.

[d] In the 'Other' category, 4 participants received AZD7442 (reasons given were: withdrew consent, subject received vaccine and no longer wanted to continue, subject was moving, or incarcerated) and 2 received placebo (reason given was subject decision). All other participants in this category did not receive IMP due to screen failure.

Percentages are based on the number of randomized participants by treatment group unless otherwise noted.

AE, adverse event; COVID 19, coronavirus disease 2019; IMP, investigational medicinal product; N, total number of participants screened; n, number of participants in each group; NA, not applicable.

Source: Table 14.1.1.1 and Listing 16.2.1.1, Listing 16.2.2.2 (DCO: 05 May 2021).

At the June 2021 DCO, 5031 (95.8%) participants were ongoing in the study, 223 (4.2%) participants had discontinued the study, 1933 (36.8%) had been unblinded, and 1475 (28.1%) had received a COVID-19 vaccination. Other than COVID-19 vaccination, which was more frequent in the placebo group than the AZD7442 group (734 [41.8%] participants versus 741 [21.2%] participants, respectively), there were no notable differences between the treatment groups.
At the August 2021 DCO, 4991 (95.0%) participants were ongoing in the study, 263 (5.0%) participants had discontinued the study, 2162 (41.1%) had been unblinded, and 2014 (38.3%) had received a COVID-19 vaccination. Other than COVID-19 vaccination, which was more frequent in the placebo group than the AZD7442 group (853 [48.6%] participants versus 1161 [33.2%] participants, respectively), there were no notable differences between the treatment groups.

Baseline data

Demographic and other baseline characteristics are listed below.

Table 11: Demographic Characteristics, Full Analysis Set, Primary Analysis DCO, PROVENT

Characteristic	AZD7442 300 mg IM (N = 3460)	Placebo (N = 1737)	Total (N = 5197)
Age (years)			
n	3460	1737	5197
Mean (SD)	53.6 (14.99)	53.3 (14.93)	53.5 (14.97)
Median (Min, Max)	57.0 (18, 98)	57.0 (18, 99)	57.0 (18, 99)
Age group (n, %)			
≥ 18 to < 60 years	1960 (56.6)	980 (56.4)	2940 (56.6)
≥ 60 years	1500 (43.4)	757 (43.6)	2257 (43.4)
≥ 65 years	817 (23.6)	409 (23.5)	1226 (23.6)
≥ 75 years	148 (4.3)	70 (4.0)	218 (4.2)
Sex (n, %)			
Female	1595 (46.1)	802 (46.2)	2397 (46.1)
Male	1865 (53.9)	935 (53.8)	2800 (53.9)
Race (n, %)			
White	2545 (73.6)	1249 (71.9)	3794 (73.0)
Black or African American	597 (17.3)	302 (17.4)	899 (17.3)
Asian	110 (3.2)	60 (3.5)	170 (3.3)
American Indian or Alaska Native	19 (0.5)	10 (0.6)	29 (0.6)
Native Hawaiian or Other Pacific Islander	4 (0.1)	4 (0.2)	8 (0.2)
Not reported	89 (2.6)	56 (3.2)	145 (2.8)
Unknown	79 (2.3)	42 (2.4)	121 (2.3)
Other[a]	15 (0.4)	12 (0.7)	27 (0.5)
Missing	2 (0.1)	2 (0.1)	4 (0.1)
Ethnicity (n, %)			
Hispanic or Latino	539 (15.6)	215 (12.4)	754 (14.5)
Not Hispanic or Latino	2731 (78.9)	1412 (81.3)	4143 (79.7)
Not reported	116 (3.4)	72 (4.1)	188 (3.6)
Unknown	74 (2.1)	38 (2.2)	112 (2.2)
Baseline Body Mass Index (kg/m^2)			
n	3451	1728	5179
Mean (SD)	29.57 (6.877)	29.63 (6.993)	29.59 (6.915)
Median (Min, Max)	28.61 (13.6, 72.1)	28.37 (14.6, 67.3)	28.51 (13.6, 72.1)
Baseline BMI category (n, %)			
< 18.5 kg/m^2	43 (1.2)	18 (1.0)	61 (1.2)
≥ 18.5 to < 25 kg/m^2	885 (25.6)	460 (26.5)	1345 (25.9)
≥ 25 to < 30 kg/m^2	1067 (30.8)	538 (31.0)	1605 (30.9)
≥ 30 to < 40 kg/m^2	1187 (34.3)	571 (32.9)	1758 (33.8)
≥ 40 kg/m^2	269 (7.8)	141 (8.1)	410 (7.9)
Missing	9 (0.3)	9 (0.5)	18 (0.3)
SARS-CoV-2 RT-PCR status at baseline, n, %			
Positive	19 (0.5)	6 (0.3)	25 (0.5)
Negative	3334 (96.4)	1672 (96.3)	5006 (96.3)
Missing	107 (3.1)	59 (3.4)	166 (3.2)

[a] Includes all other participants, eg, who reported more than one race are reported under 'Multiple'.
Baseline is defined as the last non-missing measurement taken prior to the first dose of IMP (including unscheduled measurements, if any).
Age, in years, is relative to the date of signed informed consent.
Percentages are based on the number of participants with available data (n) in the analysis set by arm.
BMI, body mass index; DCO, data cut-off; IM, intramuscular; IMP, investigational medicinal product; Max, maximum; Min, minimum; N, number of participants in the full analysis set; n, number of participants in each category; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; RT-PCR, reverse transcriptase polymerase chain reaction.
Source: Table 14.1.4.1 (DCO: 05 May 2021).

Participants who were at high-risk for severe COVID-19 were identified using the US Centers for Disease Control and Prevention criteria (CDC 2020). A combination of data from medical history, concomitant medications, and a pre-defined list collected via the CRF were used.

Table 12: COVID-19 Comorbidities at Baseline, Full Analysis Set, Primary Analysis DCO, PROVENT

Characteristic	AZD7442 300 mg IM (N = 3460)	Placebo (N = 1737)	Total (N = 5197)
Any high-risk for severe COVID-19 at baseline (n, %)	2666 (77.1)	1362 (78.4)	4028 (77.5)
History of obesity (> 30 kg/m^2)	1474 (42.6)	729 (42.0)	2203 (42.4)
Obesity (≥ 30 kg/m^2)	1456 (42.1)	712 (41.0)	2168 (41.7)
Morbid obesity (≥ 40 kg/m^2)	269 (7.8)	141 (8.1)	410 (7.9)
Chronic kidney disease	184 (5.3)	86 (5.0)	270 (5.2)
Diabetes	492 (14.2)	242 (13.9)	734 (14.1)
Immunosuppressive disease	15 (0.4)	9 (0.5)	24 (0.5)
Immunosuppressive treatment	109 (3.2)	63 (3.6)	172 (3.3)
Cardiovascular disease	272 (7.9)	151 (8.7)	423 (8.1)
COPD	179 (5.2)	95 (5.5)	274 (5.3)
Chronic liver disease	149 (4.3)	91 (5.2)	240 (4.6)
Hypertension	1229 (35.5)	637 (36.7)	1866 (35.9)
Asthma	378 (10.9)	198 (11.4)	576 (11.1)
Cancer	250 (7.2)	133 (7.7)	383 (7.4)
Smoking	720 (20.8)	370 (21.3)	1090 (21.0)
Sickle cell disease	1 (0.0)	1 (0.1)	2 (0.0)

Baseline is defined as the last non-missing measurement taken prior to the first dose of IMP (including unscheduled measurements, if any).
Percentages are based on the number of participants with available data (n) in the analysis set by arm.
COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DCO, data cut-off; IM, intramuscular; IMP, investigational medicinal product; N, number of participants in the full analysis set.
Source: Table 14.1.4.1 (DCO: 05 May 2021).

Numbers analysed

The full analysis set (FAS) includes all 5172 participants who were randomised and had received at least one of the planned injections of IMP without having had prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 at the time of primary analysis.

Definition of all analysis sets are described in the PROVENT CSR.

Table 13: Analysis Sets, All Randomised Participants, Primary Analysis DCO

Analysis Set	Number (%) of participants		
	AZD7442 300 mg IM (N = 3500)	Placebo (N = 1754)	Total (N = 5254)
Participants included in the full analysis set[a]	3460 (98.9)	1737 (99.0)	5197 (98.9)
Reason for exclusion			
Not dosed	40 (1.1)	17 (1.0)	57 (1.1)
Participants included in the full pre-exposure analysis set[b]	3441 (98.3)	1731 (98.7)	5172 (98.4)
Reason for exclusion			
Not dosed	40 (1.1)	17 (1.0)	57 (1.1)
Prior SARS-CoV-2 positive confirmed COVID-19 infection	19 (0.5)	6 (0.3)	25 (0.5)
Participants included in the safety analysis set[c]	3461 (98.9)	1736 (99.0)	5197 (98.9)
Reason for exclusion			
Not dosed	40 (1.1)	17 (1.0)	57 (1.1)
Participants included in the nAb evaluable analysis set[d]	1071 (30.6)	5 (0.3)	1076 (20.5)
Reason for exclusion			
Not dosed	40 (1.1)	17 (1.0)	57 (1.1)
No quantifiable serum observation post-dose	2389 (68.3)	1731 (98.7)	4120 (78.4)
Blood samples affected by factors such as protocol violations	1 (0.0)	0	1 (0.0)
Participants included in the PK analysis set[e]	1853 (52.9)	0	1853 (35.3)
Reason for exclusion			
Not dosed with AZD7442	40 (1.1)	1753 (99.9)	1793 (34.1)
At data cut-off did not have serum concentration data available	1607 (45.9)	0	1607 (30.6)
Had an exclusionary protocol deviation	1 (0.0)	0	1 (0.0)

[a] The Full analysis set includes all participants who received at least one injection of IMP. Participants are classified according to randomized treatment.

[b] The Full pre-exposure analysis set includes all participants who were randomized and received at least one injection of IMP who did not have prior SARS- CoV-2 positive confirmed COVID-19 infection. Participants are classified according to randomized treatment.

[c] The Safety analysis set includes all participants who received at least one injection of IMP. Participants are classified according to actual treatment. A participant who received one injection of IMP is classified as active.

[d] The nAb evaluable analysis set included all participants who received at least one injection of IMP from whom blood samples are assumed not to be affected by factors such as protocol violations, and who had at least one quantifiable serum titer observation post-dose. Participants are classified according to actual treatment.

Outcomes and estimation

Primary Endpoint: First SARS-CoV-2 RT-PCR-Positive Symptomatic Illness

Primary Analysis: Relative Risk Reduction

At the primary analysis, there was a statistically significant reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness for participants who had received AZD7442 compared to placebo, RRR 76.73 (95% CI: 46.05, 89.96); $p < 0.001$. The median duration from dose of IMP to primary analysis was 83.0 days.

Table 14: First SARS-CoV-2 RT-PCR-Positive Symptomatic Illness – Primary Estimand, Full Pre-exposure Analysis Set, Primary Analysis DCO

Endpoint	AZD7442 300 mg IM (N = 3441)	Placebo (N = 1731)
Primary endpoint – first SARS-CoV-2 RT-PCR-positive symptomatic illness- censored at unblinding/receipt of COVID-19 preventative product		
n (%)	8 (0.2)	17 (1.0)
RRR	76.73	
(95% CI)	(46.05, 89.96)	
p-value	< 0.001	

Estimates are based on a Poisson regression with robust variance. The model includes covariate for treatment (AZD7442 versus placebo), and age at informed consent (≥ 60 years versus < 60 years), with the log of the follow-up time as an offset. Estimated RRR greater than 0% provides evidence in favor of AZD7442 with p-values less than 0.05 indicating statistical significance.

CI, confidence interval; COVID-19, coronavirus disease 2019; DCO, data cut-off; IM, intramuscular; n, number of participants with event; N, number of participants in the full pre-exposure analysis set; RRR, relative risk reduction; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Source: Table 14.2.1.1.1 (DCO: 05 May 2021).

Table 15: First SARS-CoV-2 RT-PCR-Positive Symptomatic Illness – Primary Estimand, Full Pre-exposure Analysis Set, August 2021 DCO

Endpoint	EVUSHELD 300 mg IM (N = 3441)	Placebo (N = 1731)
Primary endpoint - first SARS-CoV-2 RT-PCR-positive symptomatic illness - censored at unblinding/receipt of COVID-19 preventative product		
n (%)	11 (0.3)	31 (1.8)
RRR	82.80	
(95% CI)	65.79, 91.35	
p-value	<0.001	

Estimates are based on a Poisson regression with robust variance. The model includes covariate for treatment (EVUSHELD versus placebo), and age at informed consent (≥ 60 years versus < 60 years), with the log of the follow-up time as an offset. Estimated RRR greater than 0% provides evidence in favor of EVUSHELD with p-values less than 0.05 indicating statistical significance.

Percentages are based on the number of participants in the analysis by arm (N).

Data cut-off, 29 August 2021

CI, confidence interval; COVID-19, coronavirus disease 2019; DCO, data cut-off; IM, intramuscular; RRR, relative risk reduction; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Source: Table 14.2.1.1.1B, PROVENT CSR in Module 5.3.5.1

Qualifying symptoms for the primary endpoint are summarised below. In contrast to the primary analysis, the events presented here are not censored at time of unblinding and/or COVID-19 vaccination so more participants with SARS-CoV-2 positive symptomatic illness are included in this table.

Table 16: Summary of Qualifying Symptoms for Definition of Primary Efficacy Endpoint, Full pre-exposure analysis set, Primary Analysis DCO

Events occurring post-dose	Number (%) of participants	
	AZD7442 300 mg IM (N = 3441)	Placebo (N = 1731)
Headache	4 (40.0)	9 (45.0)
New loss of taste	1 (10.0)	6 (30.0)
New loss of smell	1 (10.0)	8 (40.0)
Sore throat	5 (50.0)	4 (20.0)
Congestion	7 (70.0)	7 (35.0)
Runny nose	3 (30.0)	11 (55.0)
Nausea	3 (30.0)	3 (15.0)
Vomiting	0	1 (5.0)
Diarrhea	0	3 (15.0)

[a] Events presented are not censored at time of unblinding and/or COVID-19 vaccination.

Percentages are based on the total number of participants with SARS-CoV-2 RT-PCR-positive symptomatic illness.

Presented event categories are mutually exclusive and participants are only counted once across the event categories.

COVID-19, coronavirus disease 2019; DCO, data cut-off; IM, intramuscular; N, number of participants in the full pre-exposure analysis set; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, reverse transcriptase polymerase chain reaction

Source: Table 14.2.1.6 (DCO: 05 May 2021).

Key Supportive Analyses

Two key supportive analyses were pre-specified in the study protocol within a formal hierarchical multiple testing framework to control the Type I error rate. If the primary analysis of the primary endpoint demonstrated statistical significance, then the key supportive analyses could sequentially be tested at a 2-sided significance level of 0.05. In the first key supportive estimand, participants who were unblinded to IMP assignment/took vaccine prior to experiencing a primary endpoint event were included and analyzed regardless of their unblinding or vaccine status, ie, all participants were included. For the second key supportive estimand, the analysis included first case of SARS-CoV-2 RT-PCR-positive symptomatic illness or death from any cause post dose of IMP. The 3 analyses of the primary endpoint (primary estimand and 2 key supportive estimands) all demonstrated statistical significance within the pre-defined testing strategy.

Table 17: Primary Endpoint - Key Supportive Estimands, Full pre-exposure analysis set, Primary Analysis DCO

Endpoint	AZD7442 300 mg IM (N = 3441)	Placebo (N = 1731)
Treatment Policy Estimand: First case of SARS-CoV-2 RT-PCR-positive symptomatic illness (regardless of unblinding/receipt of COVID-19 preventive product)		
n (%)	10 (0.3)	22 (1.3)
RRR	77.29	
(95% CI)	(52.01, 89.25)	
p-value	< 0.001	
While On Treatment With All Cause Deaths Estimand: First case of SARS-CoV-2 RT-PCR-positive symptomatic illness including all deaths		
n (%)	12 (0.3)	19 (1.1)
RRR	68.78	
(95% CI)	(35.64, 84.86)	
p-value	0.002	

Estimates are based on Poisson regression with robust variance. The model includes covariate for treatment (AZD7442 versus placebo), and age at informed consent (≥ 60 years versus < 60 years), with the log of the follow-up time as an offset. Estimated RRR greater than 0% provides evidence in favor of AZD7442 with p-values less than 0.05 indicating statistical significance.

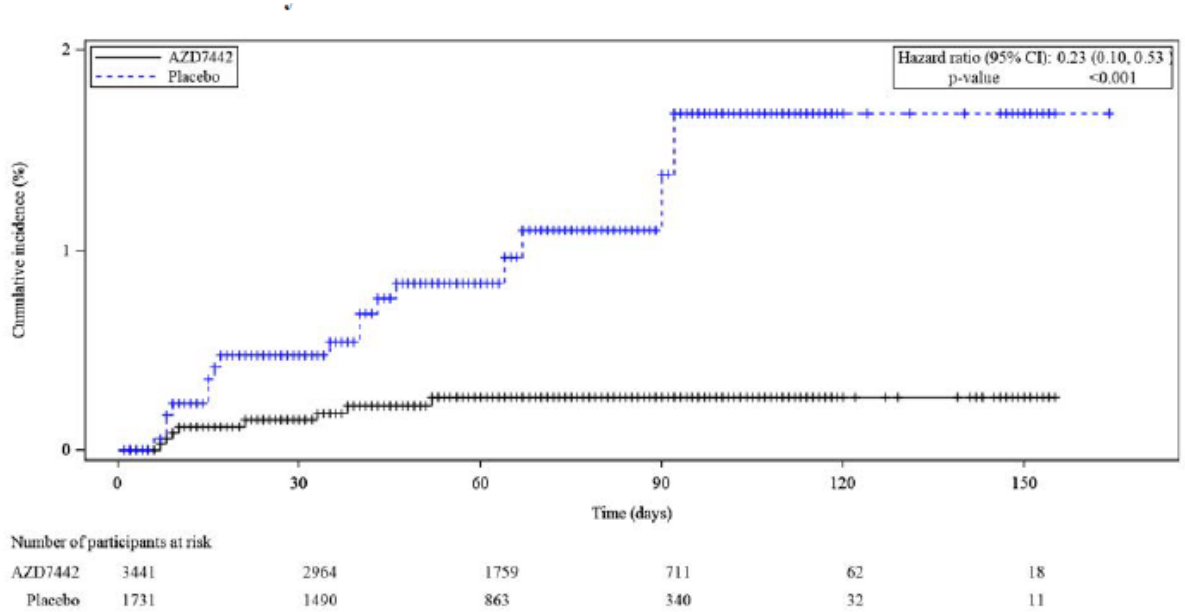
Percentages are based on the number of participants in the analysis by arm (N).

CI, confidence interval; COVID-19, coronavirus disease 2019; DCO, data cut-off; IM, intramuscular; N, number of participants in the full pre-exposure analysis set; n, number of participants with event; RRR, relative risk reduction; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Source: Tables 14.2.1.1.2 and 14.2.1.1.3 (DCO: 05 May 2021).

A Kaplan-Meier plot (DCo: 05 May 2021) and Cox Proportional Hazards analysis of the time to first SARS-CoV-2 RT-PCR-positive symptomatic illness is presented in below.

Figure 16: Time to First SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring Post-dose of IMP Kaplan-Meier Curves by Arm, Supplementary Analysis, Full Pre-exposure Analysis Set, Primary Analysis DCO



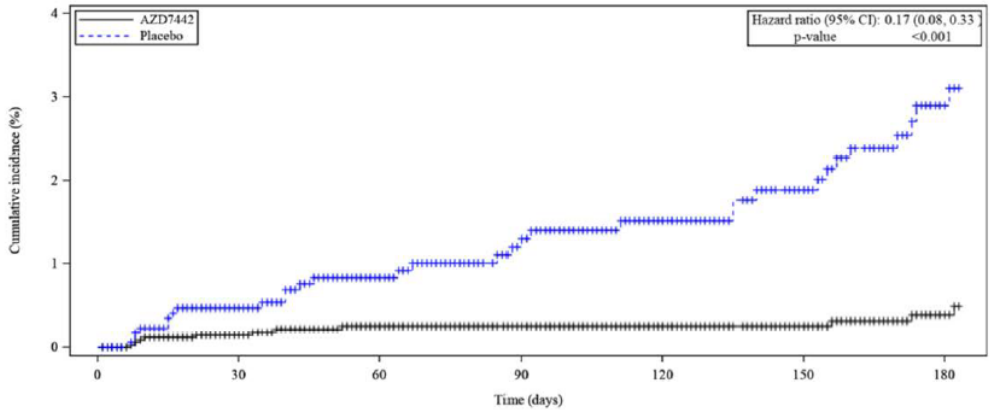
HR is from the PH model with Efron method. The 95% CI for the HR is obtained by taking 95% profile likelihood CI of the hazard ratio from the PH model with treatment group as a covariate, stratified by age at informed consent (≥ 60 years versus < 60 years).

P-value is obtained from log-rank test, stratified by age at informed consent (≥ 60 years versus < 60 years).

Data cut-off date: 05 May 2021

CI, confidence interval; DCO, data cut-off; HR, hazard ratio; IMP, investigational medicinal product; PH, proportional hazard; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; + indicates a censored observation.

Figure 17: Time to First SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring Post-dose of IMP Kaplan-Meier Curves by Arm, Supplementary Analysis, Full Pre-exposure Analysis Set, August 2021 DCO



Number of participants at risk

AZD7442	3441	2957	2393	2054	1815	1667	1044
Placebo	1731	1483	1177	991	856	774	472

HR is from the PH model with Efron method. The 95% CI for the HR is obtained by taking 95% profile likelihood CI of the hazard ratio from the PH model with group as a covariate, stratified by age at informed consent (≥ 60 years versus < 60 years).

P-value is obtained from log-rank test, stratified by age at informed consent (≥ 60 years versus < 60 years).

Data cut-off: 29 August 2021

CI, confidence interval, DCO, data cut-off; HR, hazard ratio, IMP, investigational medicinal product; PH, proportional hazard; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; + indicates a censored observation.

Source: Figure 14.2.1.3.3B, PROVENT CSR in Module 5.3.5.1

Key Secondary Endpoint: Incidence of Participants who had a Post-Treatment Response for SARS-CoV-2 Nucleocapsid Antibodies

The incidence of a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies was lower for participants who had received AZD7442 compared to placebo, with an RRR of 51.07 (95% CI: 10.57, 73.23); p-value 0.020.

Table 18: Incidence of Participants who had a Post-treatment response for SARS-Cov-2 Nucleocapsid Antibodies, Full Pre-exposure Analysis Set, Primary Analysis DCO

Endpoint	AZD7442 300 mg IM (N = 3123)	Placebo (N = 1564)
Secondary endpoint – SARS-CoV-2 Nucleocapsid Antibodies		
n (%)	21 (0.7)	21 (1.3)
RRR	51.07	
(95% CI)	(10.57, 73.23)	
p-value	0.020	

Post-treatment response is defined as negative at baseline and positive at any time post-baseline.

Estimates are based on a Poisson regression with robust variance. The model includes covariate for treatment (AZD7442 versus placebo), and age at informed consent (≥ 60 years versus < 60 years), with the log of the follow-up time as an offset. Estimated RRR greater than 0% provides evidence in favor of AZD7442 with p-values less than 0.05 indicating statistical significance.

Percentages are based on the number of participants in the analysis by arm (N).

CI, confidence interval; DCO, data cut-off; IM, intramuscular; N, number of participants in the full pre-exposure analysis set; n, number of participants with event; RRR, relative risk ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Source: Table 14.2.2.1.1 (DCO: 05 May 2021).

Table 19: Incidence of Participants who had a Post-treatment response for SARS-Cov-2 Nucleocapsid Antibodies, Full Pre-exposure Analysis Set, August 2021 DCO

Endpoint	EVUSHELD 300 mg IM (N = 3121)	Placebo (N = 1564)
Secondary endpoint – SARS-CoV-2 Nucleocapsid Antibodies Positive		
n (%)	38 (1.2)	42 (2.7)
RRR	57.73	
(95% CI)	34.65, 72.66	
p-value	<0.001	

Post-treatment response is defined as negative at baseline and positive at any time post-baseline.

Estimates are based on a Poisson regression with robust variance. The model includes covariate for treatment (EVUSHELD versus placebo), and age at informed consent (≥ 60 years versus < 60 years), with the log of the follow-up time as an offset. Estimated RRR greater than 0% provides evidence in favor of EVUSHELD with p-values less than 0.05 indicating statistical significance.

Percentages are based on the number of participants in the analysis by arm (N).

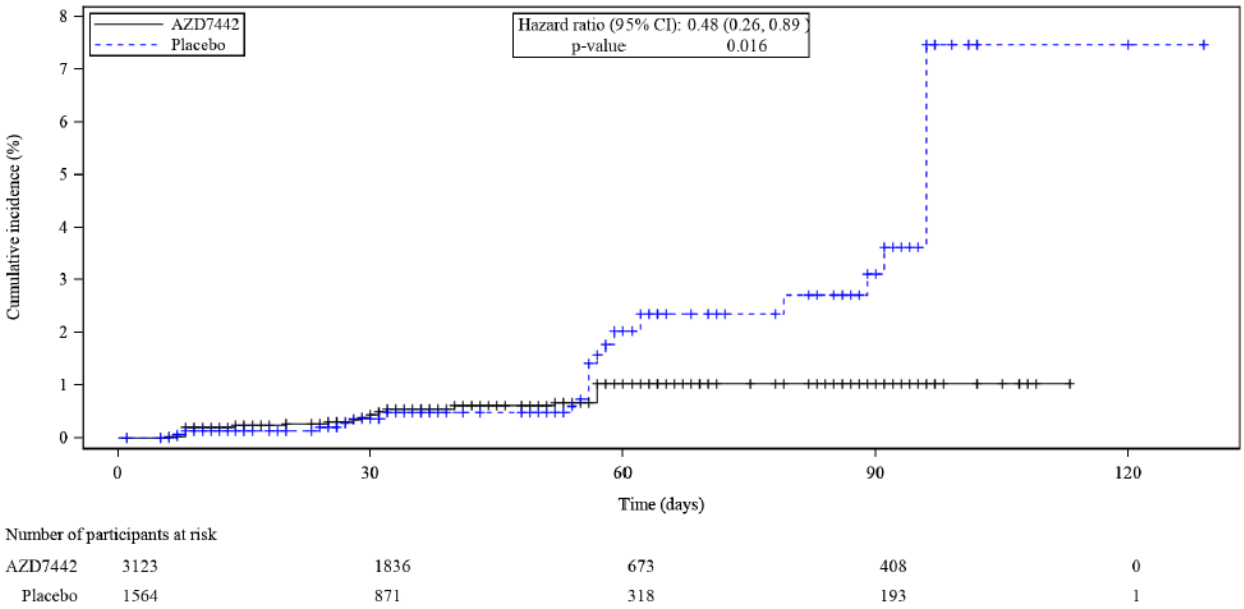
Data cut-off: 29 August 2021

CI, confidence interval; DCO, data cut-off; IM, intramuscular; N, number of participants in the full pre-exposure analysis set; n, Number of participants included in analysis; RRR, relative risk ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Source: Table 14.2.2.1.1B.

A Kaplan-Meier plot and Cox Proportional Hazards analysis of the time to first post-treatment response for a by treatment group is presented below. The time from baseline to first positive nucleocapsid antibody test was longer in the AZD7442 arm compared to placebo, with a hazard ratio of 0.48 (95% CI: 0.26, 0.89), p = 0.018.

Figure 18: Time to Post-Treatment Response for SARS-CoV-2 Nucleocapsid Antibodies – Kaplan-Meier Curves by Treatment Group (Full Pre-Exposure Analysis Set)



Subgroup Analyses: Key Secondary Endpoint

Subgroup analyses for the key secondary endpoint were conducted in pre-specified subgroups that included age, sex, race, ethnicity, COVID-19 co-morbidities at baseline, SARS-CoV-2 status at baseline, high risk for severe COVID-19 at baseline, and various individual risk factors for COVID-19. For the key secondary endpoint, the efficacy of AZD7442 versus placebo was consistent across pre-defined subgroups.

Ancillary analyses

Region as a covariate

The primary analysis of the primary efficacy endpoint was repeated including region as an additional covariate to assess the robustness of the efficacy results. The results were consistent with the primary analysis and indicated that there was no impact of region on the primary analysis: RRR 76.60 (95% CI: 45.81, 89.89); nominal p < 0.001.

Table 20: Efficacy for Incidence of First SARS-CoV-2 RT-PCR-Positive Symptomatic Illness Adjusted by Region; Supplemental Analysis, Full Pre-Exposure Analysis Set

Endpoint	Statistic	AZD7442	Placebo
Primary - first SARS-CoV-2 RT-PCR-positive symptomatic illness - censored at unblinding/receipt of COVID-19 preventive product	N	3441	1731
	n (%)	8 (0.2)	17 (1.0)
	RRR	76.60	
	RRR 95% CI	(45.81, 89.89)	
	P-value	<0.001	

Absolute Risk Reduction

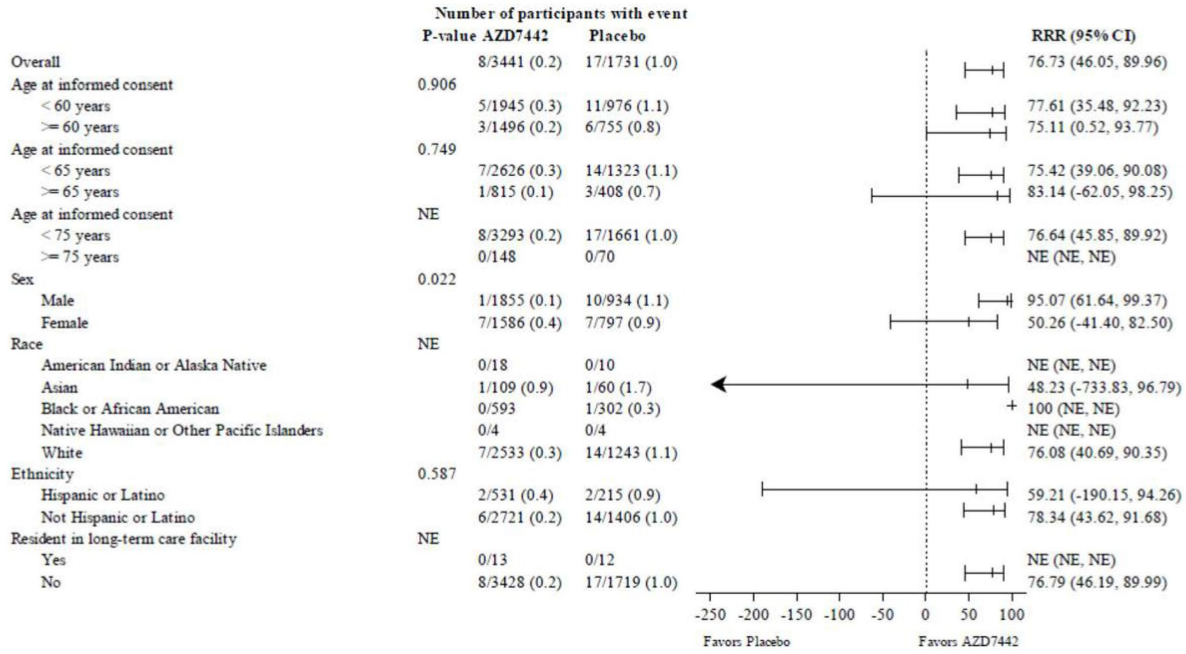
The findings from the supplementary analysis for the absolute risk reduction (0.75 [95% CI: 0.33, 1.35]; nominal p < 0.001) support the primary analysis showing superiority of AZD7442 compared with placebo in the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness.

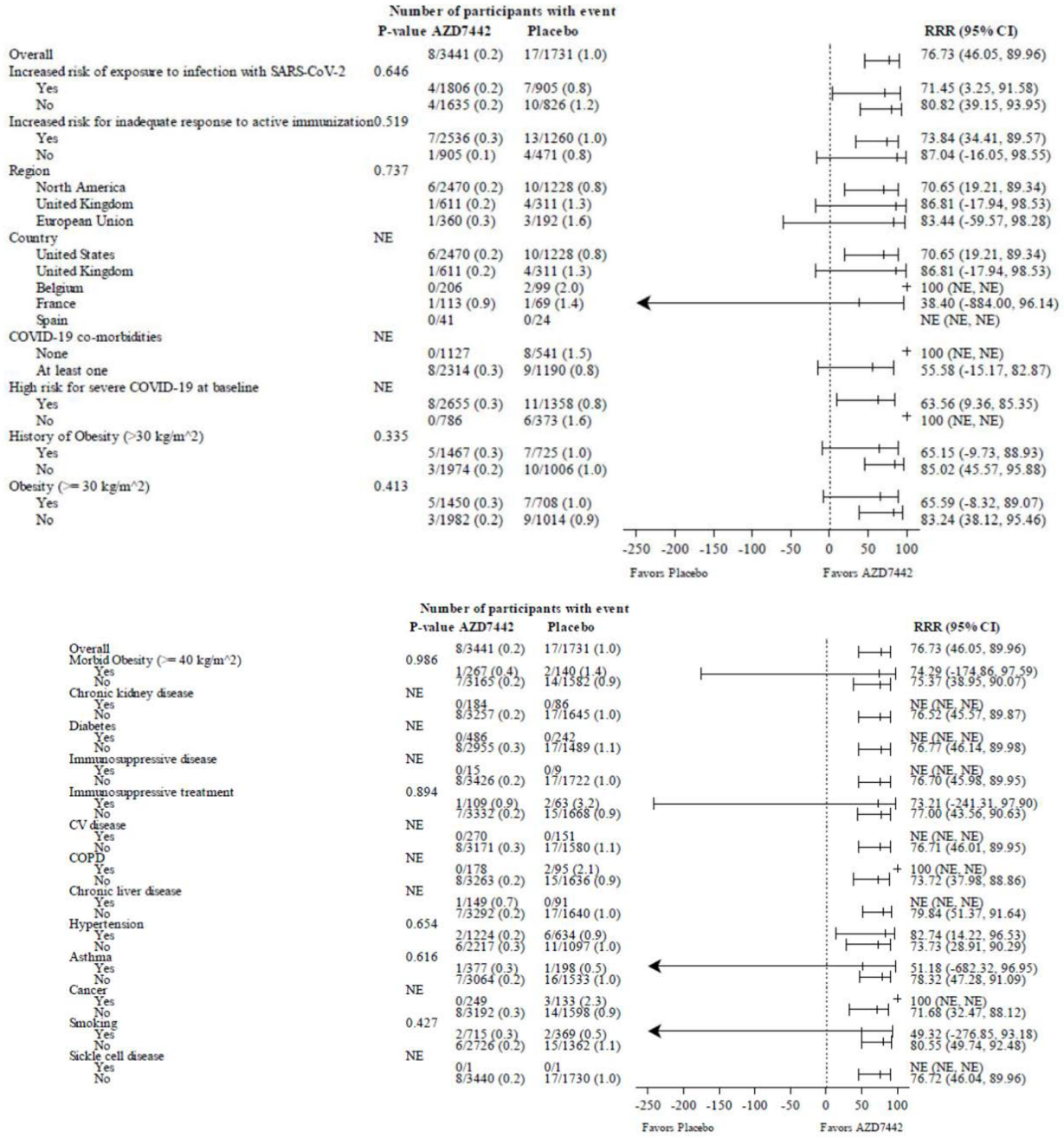
Table 21: Efficacy for Incidence of First SARS-CoV-2 RT-PCR-Positive Symptomatic Illness-Supplementary Analysis for Primary While on Treatment Estimand, Full Pre-Exposure Analysis Set

Endpoint	Statistic	AZD7442	Placebo
Participants with Observed Events	N	3441	1731
	n (%)	8 (0.2)	17 (1.0)
	ARR	0.75	
	ARR 95% CI	(0.33, 1.35)	
	P-value	<0.001	

Subgroup analysis

Figure 19: Forest Plot for Efficacy for Incidence of First SARS-CoV-2 RT-PCR-positive Symptomatic Illness by Subgroup, Full Pre-exposure Analysis Set, PROVENT, Primary Analysis





Estimates are based on Poisson regression with robust variance using full model or reduced model. The full model includes covariates for group, age at informed consent (≥ 60 years versus < 60 years), subgroup and treatment*subgroup interaction, and the log of the follow-up time as an offset. If it is not converged, a reduced model by excluding age at informed consent will be applied. P-values are for the treatment*subgroup interaction. Within each level of a subgroup, same approach is utilized. Estimated RRR greater than 0 provides evidence in favor of EVUSHELD.

Percentages are based on the number of participants in the subgroup (if applicable) in the analysis set by arm.

Data cut-off: 05 May 2021

CI, confidence interval; COPD, chronic obstructive pulmonary disorder; COVID-19, coronavirus disease 2019; CV, cardiovascular; NE, not estimable; RT-PCR, reverse transcriptase polymerase chain reaction; RRR, relative risk reduction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; + indicates a censored observation.

Source: Figure 14.2.1.5.2, PROVENT CSR in Module 5.3.1.5

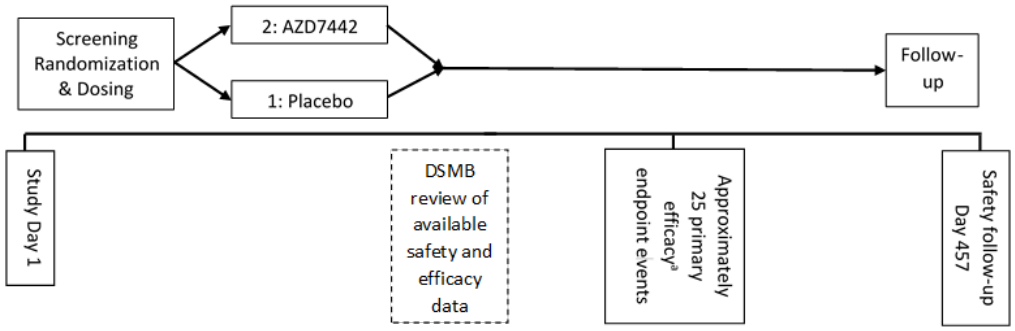
STORM CHASER (study code D8850C00003)

Methods

STORM CHASER is an ongoing Phase III, randomised, double-blind, placebo-controlled, multicenter study assessing the safety and efficacy of a single dose of AZD7442 (2 sequential IM injections) compared to placebo for the prevention of COVID-19.

Participants were adults ≥ 18 years of age with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed symptomatic or asymptomatic SARS-CoV-2 infection, and who were therefore at appreciable risk of imminently developing COVID-19.

Figure 20: STORM CHASER flow chart of study design



[a] Primary analysis was conducted 30 days after the 25th primary endpoint event was observed.
An independent DSMB reviewed available safety and efficacy data after the first 100 participants had been dosed, or after 4 weeks from first participant dosed, whichever comes first. Enrollment was not paused pending the DSMB's review. DSMB was to meet monthly throughout the study.

DSMB, Data Safety Monitoring Board.

Data Cut-off Dates (DCO) for STORM CHASER efficacy analysis:

Primary DCO (07 April 2021) – is the cut of data that aligns with the primary efficacy analysis. For STORM CHASER this was 30 days after the 25th primary efficacy event had been reported across the active and placebo groups. At the time of conducting the primary analysis, enrollment was complete (last participant in 19 March 2021), and 53 sites in the US and 6 sites in the UK had randomised 1131 participants of which 1121 received IMP.

August 2021 DCO (19 August 2021) – is a cut of data to provide longer-term safety and efficacy data, providing a median duration of follow-up of approximately 6 months where all ongoing participants have a minimum of 5 months' safety and efficacy data; this was not pre-specified. Only key safety and efficacy data are available and included in the primary Phase III CSR.

Study Participants

Inclusion criteria:

Age

1. Participants were ≥ 18 years of age at the time of signing the informed consent.

Type of Participant and Exposure Characteristics

2. Participants were adults with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection, symptomatic or asymptomatic, who are therefore at appreciable risk of imminently developing COVID-19, based on available risk assessment at time of enrolment, within any of the following settings:
    - Long-term care facilities, including skilled nursing homes, assisted living homes, facilities, and other staff of such facilities are eligible under this criterion. For participants entering the study from these settings, "potential exposure to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection" is defined to mean the occurrence of SARS-CoV-2 infection, symptomatic or asymptomatic, in another resident of the facility or in a staff member of the facility.
    - Industrial settings shown to have been at high risk for SARS-CoV-2 transmission, including but not limited to meatpacking plants. Workers in such facilities were eligible under this criterion.
    - Military settings including but not limited to barracks, ships, or other close-quarters working environments. Military and civilian personnel exposed in such settings were eligible.
    - Health care facilities. Health care workers and other staff exposed in such setting were eligible under this criterion.
    - University or college dormitories. Students exposed in such setting were eligible.
    - Household contacts. Any adult living in the same household as an index case was eligible under this criterion.
    - Other settings of similar close or high-density inter-personal proximity. The potential for exposure in such settings may be assessed on a case-by-case basis by Investigators. Individuals exposed in such settings are eligible under this criterion.
3. Prior to enrolment, participants must not have had COVID-19 symptoms, within 10 days of dosing.
4. Negative result from point of care SARS-CoV-2 serology testing at screening.

Exclusion criteria:

Medical Conditions

1. History of laboratory-confirmed SARS-CoV-2 infection or SARS-CoV-2 seropositivity at screening.
2. History of infection with severe acute respiratory syndrome or Middle East respiratory syndrome.
3. Known history of allergy or reaction to any component of the study drug formulation.
4. Previous hypersensitivity, infusion-related reaction, or severe adverse reaction following administration of a mAb.
5. Any prior receipt of investigational or licensed vaccine or other mAb/biologic indicated for the prevention of SARS-CoV-2 or COVID-19 or expected receipt during the period of study follow-up.
6. Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture.
7. Any other significant disease, disorder, or finding that, in the judgment of the Investigator, may significantly increase the risk to the participant because of participation in the study, affect the ability of the participant to participate in the study, or impair interpretation of the study data.

Prior/Concurrent Clinical Study Experience

8. Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

<u>Participants were enrolled into one of 2 cohorts:</u>

- Cohort 1: Adults, ≥ 60 years of age, living in LTCFs. In this context, LTCFs included skilled nursing facilities, assisted living facilities, and independent living facilities for senior adults. In this cohort, "potential exposure to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection" was defined to mean the occurrence of SARS-CoV-2 infection, symptomatic or asymptomatic, in another resident of the facility or in a staff member of the facility.
- Cohort 2: Other adults, ≥ 18 years of age with potential exposure to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection. Such individuals could include but were not limited to those living in institutional residences (military lodging, dormitories, etc), household contacts, health care workers, long-term care facility workers, and workers in occupational or industrial settings in which close contact was common.

Additional information on exposure to SARS-CoV-2:

Exposure within 8 days should be confirmed, and investigator attestation that they were able to confirm the details of the potential exposure is required. Confirmation should be made either directly through the participant's medical record or via official documentation from another source attesting to exposure (eg, letter from employer, notification from local health department, etc). A verbal/written statement from the participant, without independent substantiation, is not acceptable.

Treatments

A single dose (2 sequential IM injections) of either **300 mg of AZD7442** (n = 756) or saline placebo (n = 375), given as two sequential IM injections of AZD8895 and AZD1061, (one in each gluteal region), or corresponding placebo. Study staff administered the single dose.

Objectives

Primary objectives

- To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19
- To assess the safety and tolerability of a single IM dose of AZD7442 compared to placebo

Outcomes/endpoints

Table 22: Efficacy Objectives and Endpoints – STORM CHASER

Objective	Estimand Description/Endpoint
Primary	
To estimate the efficacy of a single IM dose of Evusheld compared to placebo for the prevention of COVID-19	**Population:** Full analysis set
	Endpoint: A binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs post dose of IMP and prior to Day 183.
	Intercurrent events: For participants who become unblinded to properly consider vaccination for COVID-19, take COVID-19 vaccine or other COVID-19 preventive product prior to having met the criteria for the primary efficacy endpoint, the data will be collected and analyzed regardless (ie, intercurrent events will be handled using treatment policy strategy).

Table 22: Efficacy Objectives and Endpoints – STORM CHASER

Objective	Estimand Description/Endpoint
	Summary measure: Prophylactic efficacy, calculated as 1-relative risk. (Relative risk is the incidence of infection in the Evusheld group relative to the incidence of infection in the control group).
Key Secondary	
To estimate the efficacy of a single IM dose of Evusheld compared to placebo for the prevention of severe or critical symptomatic COVID-19	**Population:** Full analysis set
	Endpoint: The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring after dosing with IMP.
	Intercurrent events: For participants who become unblinded to properly consider vaccination for COVID-19, take COVID-19 vaccine or other COVID-19 preventive product prior to having met the criteria for this endpoint, data will be collected and analyzed regardless (ie, intercurrent events will be handled using treatment policy strategy).
Other Secondary	
To estimate the efficacy of a single IM dose of Evusheld compared to placebo for the prevention of SARS-CoV-2 infection	The incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies.
To estimate the efficacy of a single IM dose of Evusheld compared to placebo for the prevention of COVID-19-related death	The incidence of COVID-19-related death occurring after dosing with IMP.
To estiate the efficacy of a single IM dose of Evusheld compared to placebo for the prevention of all-cause mortality	The incidence of all-cause mortality occurring after dosing with IMP.

COVID-19, coronavirus disease 2019; IM, intramuscular; IMP, investigational medicinal product; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

Randomisation and blinding (masking)

All participants were planned to be centrally assigned to a randomised IMP using an IRT. Before the study was initiated, user guides, the log-in information, and directions for the IRT were planned to be provided to each study site. Randomization was planned to be maintained in a 2:1 ratio within each of the 2 cohorts:

- Cohort 1: Adults ≥ 60 years of age, living in long-term care facilities. In this context, long-term care facilities included skilled nursing facilities, assisted living facilities, and independent living facilities for senior adults. In this cohort, "potential exposure to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection" was defined to mean the occurrence of SARS-CoV-2 infection, symptomatic or asymptomatic, in another resident of the facility or in a staff member of the facility.
- Cohort 2: Other adults ≥ 18 years of age with potential exposure to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection. Such individuals could include, but were not limited to, those living in institutional residences (military lodging, dormitories, etc.),

household contacts, health care workers, long-term care facility workers, and workers in occupational or industrial settings in which close contact is common.

Where a participant did not meet all the eligibility criteria but incorrectly received IMP, the investigator should inform the Study Physician immediately, and a discussion should occur between the Study Physician and the investigator regarding whether to continue or discontinue the participant.

Neither the participant nor any of the investigators or Sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants were planned to be aware of the IMP received. Since AZD7442 and placebo are visually distinct prior to dose preparation (due to differences in container closure), IMP was planned to be handled by an unblinded pharmacist (or designee, in accordance with local and institutional regulations) at the study site. Syringe masking was planned to be required in order to maintain the blind.

The IRT was planned to provide the investigator(s) or pharmacists with a dose tracking number to be allocated to the participant at the dispensing visit. Routines for this were planned to be described in the IRT user manual that will be provided to each study site.

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization. The investigator was planned to document and report the action to the Sponsor, without revealing the treatment given to the participant to the Sponsor staff.

The Sponsor retained the right to break the code for SAEs that are unexpected and are suspected to be causally related to the IMP and that potentially require expedited reporting to regulatory authorities. Randomization codes were not planned to be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

COVID-19 Vaccine

For prospective participants for STORM CHASER who have not yet been dosed:

- In LTCFs in which an outbreak has been identified, and in which the residents have not been vaccinated, STORM CHASER could still be executed because a vaccine will not evoke immunity fast enough to protect participants in the post-exposure setting.

For STORM CHASER participants who have been dosed with investigational product, when an individual becomes eligible for the nationally deployed COVID-19 vaccine and the vaccine is locally available:

Participants will be able to be unblinded if they request this, after a fully informed, objective discussion based on all available up-to-date information, and remain in the study.

- Unblinded participants who received placebo should be advised that no study-associated contraindication to receiving a vaccine exists.
- Unblinded participants who received AZD7442 should be advised that the 300 mg dose may provide 6 to 9 months of protection, but that this has not been demonstrated. In these participants, there would be little or no urgency for receiving a vaccine. In addition, in the presence of adequate neutralising antibody titres, an appropriate and effective response to the vaccine might be impaired. Such participants should be advised to consider waiting an appropriate length of time (6 to 9 months) before receiving an anti-SARS-CoV-2 vaccine. For AZD7442, 6 to 9 months will represent 2 or 3 elimination half-lives of the mAbs, after which the potential for the mAbs to protect against COVID-19 should be reduced, and after which their potential interference with a vaccine may be reduced.

For participants who have received investigational product (blinded) and develop COVID-19, and are sick with it at some point in the study:

- There is no reason to believe that administration of a vaccine during acute COVID-19 will ameliorate the illness.
- In almost all placebo recipients, and in most mAb recipients, an infection-induced immune response will occur, and this response should be protective. At this time, there is no reason to believe that the protection afforded by natural infection is less frequent or less robust than the protection provided by any vaccine, so the benefit of vaccination may be limited.
- The risk of receiving a vaccine after resolution of the illness should be low.

Statistical methods

Efficacy analysis

The primary endpoint was planned to be the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose of IMP and prior to Day 183. The primary endpoint (variable) was a binary response, whereby a participant was defined as a COVID-19 case if their first case of SARSCoV-2 RT-PCR-positive symptomatic illness occurred post dose of IMP prior to Day 183. If a participant's first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurred on or after Day 183, the participant was not planned to meet the primary endpoint

The primary estimand was planned to be based on participants in the full analysis set, defined as all randomised participants who received at least one dose of IMP, analyzed according to their randomised treatment. For participants with multiple events, only the first occurrence was planned to be used for the primary efficacy endpoint analysis. The set of intercurrent events for this estimand was planned to consist of participants who become unblinded to properly consider vaccination for COVID-19, take a COVID-19 vaccine or other COVID-19 preventive product prior to having met the primary efficacy endpoint. The intercurrent events were planned to be handled using the treatment policy strategy.

The primary efficacy was planned to be calculated as relative risk reduction (RRR) which was planned to be 100% x (1- relative risk). Efficacy summaries were planned to be presented with a 2-sided 95% CI. Statistical significance was planned to be achieved if the lower bound of the 2-sided 95% CI was > 0.

Absence of data following participants' withdrawal prior to having met the primary efficacy endpoint was planned to be treated as missing. Participants were planned to be considered as not having the event through the time of last observation. Deaths that are caused by COVID-19 and hospitalizations that are characterised to be severe COVID-19 were also planned to be considered as primary efficacy endpoints.

A hierarchical approach was planned to control for multiplicity of the primary, key supportive, and key secondary analyses. The primary efficacy endpoint was planned to be assessed at the primary analysis, using the primary estimand. If the statistical significance of the primary efficacy endpoint was demonstrated at 2-sided alpha of 0.05, a formal assessment of the primary endpoint using the key supportive estimand (treatment policy strategy) was to be conducted also at the primary analysis. If the statistical significance of the key supportive analysis of the primary endpoint was demonstrated at 2-sided alpha of 0.05, a formal assessment of the key secondary efficacy endpoint (incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring after dosing through Day 457) was planned to be conducted at the final analysis when all participants have completed the study.

An interim analysis included in the original protocol was removed in accordance with protocol amendment 5 (12 March 2021).

Results

Participant Flow

Study Participant flow as of the time of primary analysis (07 April 2021):

Table 23: Participant Disposition, All Participants Analysis Set; STORM CHASER

Category	Number (%) of Participants		
Sub category	AZD7442 300 mg IM	Placebo	Total
Participants screened	NA	NA	1305
Participants screen-failed [a]	NA	NA	174 (13.3)
Entry criteria not met	NA	NA	153 (11.7)
Withdrawal by participant	NA	NA	6 (0.5)
Adverse event	NA	NA	1 (0.1)
Lost to follow-up	NA	NA	0
Sponsor decision	NA	NA	1 (0.1)
Other	NA	NA	13 (1.0)
Participants randomized	756 (100)	375 (100)	1131 (100)
Participants randomized but not dosed	7 (0.9)	3 (0.8)	10 (0.9) [b]
Participants ongoing in study	741 (98.0)	369 (98.4)	1110 (98.1)
Participants who completed the study	0	0	0
Participants who discontinued early from study [c]	15 (2.0)	6 (1.6)	21 (1.9)
Adverse event	0	0	0
Death	0	0	0
Lost to follow-up	2 (13.3)	0	2 (9.5)
Non-compliance with study drug	0	0	0
Pregnancy	0	0	0
Protocol deviation	0	1 (16.7)	1 (4.8)
Physician decision	1 (6.7)	0	1 (4.8)
Study terminated by Sponsor	0	0	0
Withdrawal by participant	7 (46.7)	3 (50.0)	10 (47.6)
Other	5 (33.3)	2 (33.3)	7 (33.3) [d]
Participant unblinded [e]	62 (8.2)	53 (14.1)	115 (10.2)
Participant received COVID-19 vaccination subsequently	26 (3.4)	47 (12.5)	73 (6.5)

a Percentages are based on the number of screened participants.
b Of these 10 participants, 7 were screen failures who were randomised in error, 1 was withdrawn by Investigator decision, 2 were withdrawn by participant.
c Percentages are based on the number of randomised participants who discontinued the study by treatment group.
d Of these 7 participants, all were randomised but not dosed: 6/7 were screen failures and 1/7 left the site before being
dosed.
e Number of randomised participants who were unblinded during the study by treatment group.

Percentages are based on the number of randomised participants by treatment group unless otherwise noted. COVID-19, coronavirus disease 2019; IM, intramuscular; NA, not applicable. Source: Table 14.1.1 (Data cut-off, 07 April 2021).

Participant flow as of the August 2021 DCO (19 August 2021):

Table 24: Participant disposition (all participants analysis set) at 6-month DCO, STORM CHASER

Category	AZD7442 300 mg IM	Placebo	Total
Participants randomized	756 (100)	375 (100)	1131(100)
Participants randomized but not dosed	7 (0.9)	3 (0.8)	10 (0.9)
Participants ongoing in study	720 (95.2)	348 (92.8)	1068 (94.4)
Participants who discontinued early from study[a]	36 (4.8)	27 (7.2)	63 (5.6)
Reason for discontinuation			
AE	1 (2.8)	0	1 (1.6)
Death	1 (2.8)	1 (3.7)	2 (3.2)
Lost to follow-up	14 (38.9)	10 (37.0)	24 (38.1)
Protocol deviation	0	1 (3.7)	1 (1.6)
Physician decision	1 (2.8)	0	1 (1.6)
Withdrawal by subject	13 (36.1)	11 (40.7)	24 (38.1)
Other	6 (16.7)	4 (14.8)	10 (15.9)
Participant unblinded[b]	134 (17.7)	95 (25.3)	229 (20.2)
Participant received COVID-19 vaccination	112 (14.8)	102 (27.2)	214 (18.9)

[a] Percentages are based on the number of randomized participants who discontinued the study by treatment group.
[b] Number of randomized participants who were unblinded during the study by treatment group.
Percentages are based on the number of randomized participants by treatment arm unless otherwise noted.
AE, adverse event; COVID-19, coronavirus disease 2019; DCO, data-cut off; IM, intramuscular
6-month DCO: 19 August 2021
Source: STORM CHASER TABLE 14.1.1B, Appendix 3

Baseline data

A total of 548 (48.9%) participants had potential COVID-19 comorbidities identified from their medical history at baseline. In addition to COVID-19 comorbidities, the study population was further categorised using CDC criteria (CDC 2020). The CDC criteria provide an indicator of individuals thought to be at high-risk for severe COVID-19. A combination of data from medical history, concomitant medications, and a predefined list collected via the CRF were used.

Table 25: Key Demographic Characteristics, FAS, Primary Analysis, STORM CHASER

Characteristic	Statistic or subcategory	AZD7442 300 mg IM (N = 749)	Placebo (N = 372)	Total (N = 1121)
Cohort, n (%)	1: Adults ≥ 60 years residing in a LTCF	5 (0.7)	2 (0.5)	7 (0.6)
	2: Other adults ≥ 18 years	744 (99.3)	370 (99.5)	1114 (99.4)
Age (years)	n	749	372	1121
	Mean (SD)	46.6 (15.73)	46.0 (16.20)	46.4 (15.89)
	Median	48.0	47.0	48.0
	Min, max	18, 92	18, 89	18, 92
Age group, n (%)	≥ 18 - < 60 years	600 (80.1)	297 (79.8)	897 (80.0)
	≥ 60 - < 70 years	96 (12.8)	45 (12.1)	141 (12.6)
	≥ 70 - < 80 years	41 (5.5)	25 (6.7)	66 (5.9)
	≥ 80 years	12 (1.6)	5 (1.3)	17 (1.5)
	≥ 60 years	149 (19.9)	75 (20.2)	224 (20.0)
	≥ 65 years	91 (12.1)	43 (11.6)	134 (12.0)
	≥ 75 years	23 (3.1)	16 (4.3)	39 (3.5)
Sex, n (%)	Male	376 (50.2)	191 (51.3)	567 (50.6)
	Female	373 (49.8)	181 (48.7)	554 (49.4)
Ethnicity, n (%)	Hispanic or Latino	435 (58.1)	210 (56.5)	645 (57.5)
	Not Hispanic or Latino	299 (39.9)	159 (42.7)	458 (40.9)
	Not reported	11 (1.5)	1 (0.3)	12 (1.1)
	Unknown	4 (0.5)	2 (0.5)	6 (0.5)
Race, n (%)	White	628 (83.8)	315 (84.7)	943 (84.1)
	Black or African American	76 (10.1)	36 (9.7)	112 (10.0)
	Asian	15 (2.0)	13 (3.5)	28 (2.5)
	American Indian or Alaska Native	6 (0.8)	1 (0.3)	7 (0.6)
	Native Hawaiian or other Pacific Islander	2 (0.3)	1 (0.3)	3 (0.3)
	Not reported	15 (2.0)	3 (0.8)	18 (1.6)
	Unknown	3 (0.4)	0	3 (0.3)
	Other [a]	4 (0.5)	3 (0.8)	7 (0.6)
Baseline BMI (kg/m^2)	n	746	372	1118
	Mean (SD)	29.7 (6.7)	29.9 (6.7)	29.7 (6.7)
	Median	28.62	29.08	28.73
	Min, max	15.6, 72.7	16.9, 61.7	15.6, 72.7
Resident in LTCF, n (%)	Yes	7 (0.9)	3 (0.8)	10 (0.9)
	No	742 (99.1)	369 (99.2)	1111 (99.1)
SARS-CoV-2 RT-PCR status at baseline, n (%)	Positive	34 (4.5)	14 (3.8)	48 (4.3)
	Negative	646 (86.2)	328 (88.2)	974 (86.9)
	Missing	69 (9.2)	30 (8.1)	99 (8.8)
Any COVID-19 comorbidities at baseline, n (%)		375 (50.1)	173 (46.5)	548 (48.9)

[a] Includes all other participants, eg, those who reported more than one race are reported under multiple.

Baseline is defined as the last non-missing measurement taken prior to the first dose of IMP (including unscheduled measurements, if any).

Cohort is derived from the data recorded in the eCRF.

Age in years is relative to the date of the signed informed consent.

BMI, body mass index; COVID-19, coronavirus disease 2019; eCRF, electronic case report form; LTCF, long-term care facility; IM, intramuscular; IMP, investigational medicinal product; Max, maximum; Min, minimum; N, number in treatment group; n, number in category/class; RT-PCR, reverse-transcriptase polymerase chain reaction; SARS-CoV-2, Severe acute respiratory syndrome-coronavirus-2; SD, standard deviation.

Source: Table 14.1.4.1 (Data cut-off, 07 April 2021).

Table 26: High Risk for Severe COVID-19 at Baseline, FAS, STORM CHASER

Characteristic	AZD7442 300 mg IM (N = 749)	Placebo (N = 372)	Total (N = 1121)
	n (%)		
Any high risk for severe COVID-19 at baseline	492 (65.7)	244 (65.6)	736 (65.7)
History of obesity (> 30 kg/m^2)	225 (30.0)	108 (29.0)	333 (29.7)
Obesity (≥ 30 kg/m^2)	295 (39.4)	162 (43.5)	457 (40.8)
Morbid obesity (≥ 40 kg/m^2)	49 (6.5)	26 (7.0)	75 (6.7)
Chronic kidney disease	14 (1.9)	7 (1.9)	21 (1.9)
Diabetes	90 (12.0)	38 (10.2)	128 (11.4)
Immunosuppressive disease	0	0	0
Immunosuppressive treatment	7 (0.9)	2 (0.5)	9 (0.8)
CV disease	19 (2.5)	14 (3.8)	33 (2.9)
COPD	7 (0.9)	11 (3.0)	18 (1.6)
Chronic liver disease	8 (1.1)	2 (0.5)	10 (0.9)
Hypertension	184 (24.6)	84 (22.6)	268 (23.9)
Asthma	49 (6.5)	27 (7.3)	76 (6.8)
Cancer	24 (3.2)	10 (2.7)	34 (3.0)
Smoking	144 (19.2)	71 (19.1)	215 (19.2)
Sickle cell disease	1 (0.1)	0	1 (0.1)

Baseline is defined as the last non-missing measurement taken prior to the first dose of IMP (including unscheduled measurements, if any).

COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CV, cardiovascular; IM, intramuscular; IMP, investigational medicinal product; N, number in treatment group; n, number in category/class.

Source: Table 14.1.4.1 (Data cut-off, 07 April 2021).

Numbers analysed

As of the primary efficacy analysis based on the April 2021 DCO, 1131 participants had been randomised, 1121 had received IMP, and 1110 were ongoing in the study. Twenty-one participants had discontinued from the study (see participant flow and recruitment above). A total of 1121 participants were included in the full analysis set (primary efficacy analysis: April 2021 DCO) and the safety analysis set (June 2021 DCO).

Table 27: Analysis Sets, All Randomised Participants, STORM CHASER

Analysis set Reason for exclusion	Number (%) of participants		
	AZD7442 300 mg IM (N=756)	Placebo (N=375)	Total (N=1131)
Participants included in the full analysis set [a]	749 (99.1)	372 (99.2)	1121 (99.1)
Not dosed	7 (0.9)	3 (0.8)	10 (0.9)
Participants included in the safety analysis set [b]	749 (99.1)	372 (99.2)	1121 (99.1)
Not dosed	7 (0.9)	3 (0.8)	10 (0.9)
Participants included in the nAb evaluable analysis set [c]	170 (22.5)	4 (1.1)	174 (15.4)
Not dosed	7 (0.9)	3 (0.8)	10 (0.9)
No quantifiable serum observation post dose	579 (76.6)	368 (98.1)	947 (83.7)
Blood sample affected by factors such as protocol violations	0	0	0
Participants included in the PK analysis set [d]	198 (26.2)	0	198 (17.5)
Not dosed with AZD7442	7 (0.9)	375 (100)	382 (33.8)
Did not have plasma concentration data	551 (72.9)	0	551 (48.7)
Had an exclusionary protocol deviation	0	0	0

[a] The full analysis set included all participants who were randomized and received at least one injection of IMP. Participants are classified according to randomized treatment.

[b] The safety analysis set included all participants who received at least one injection of IMP. Participants are classified according to actual treatment. A participant who received one injection of active IMP was classified as active.

[c] The nAb evaluable analysis set included all participants who received at least one injection of IMP from whom blood samples were assumed not to be affected by factors such as protocol violations, and who had at least one quantifiable serum observation post dose. Participants were classified according to actual treatment.

[d] The PK analysis set included all participants who received at least one injection of AZD7442 components and from whom PK blood samples were assumed not to be affected by factors such as protocol violations, and who had at least one quantifiable serum PK observation post dose. Participants were classified according to actual treatment.

Percentages are based on the number of all randomized participants by randomized treatment group.

IM, intramuscular; IMP, investigational medicinal product; N, number in treatment group; nAb, neutralizing antibody; PK, pharmacokinetic.

Source: Table 14.1.3 (Data cut-off, 07 April 2021).

Outcomes and estimation

- **Outcomes and estimation**

Primary endpoint

The primary endpoint was not met. At the primary analysis, the RRR in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness was 33.31 [95% CI: -25.92, 64.68] with AZD7442 compared to placebo, which was not statistically significant (p = 0.212). There were 23/79 (3.1%) participants with SARS-CoV-2 RT-PCR-positive symptomatic illness in the AZD7442 arm compared to 17/372 (4.6%) participants in the placebo arm.

The median (min, max) duration from dose of IMP to primary analysis was 49.0 (5, 115) days for the AZD7442 group and 48.0 (20, 113) days for the placebo group

Table 28: First SARS-CoV-2 RT-PCR-Positive Symptomatic Illness, Full Analysis Set, STORM CHASER, Primary Analysis

Statistic	Evusheld 300 mg IM (N = 749)	Placebo (N = 372)
n (%)	23 (3.1)	17 (4.6)
RRR	33.31	
(95% CI)	(-25.92, 64.68)	
P-value	0.212	

Estimates are based on Poisson regression with robust variance. The model includes the log of the follow-up time as an offset and a covariate for treatment (Evusheld vs Placebo). Estimated RRR greater than 0% provides evidence in favor of Evusheld with p-values less than 0.05 indicating statistical significance.
Percentages are based on the number of participants in the analysis by treatment group (N).
Data cut-off, 07 April 2021
CI, confidence interval; IM, intramuscular; N, number of participants; n, number of participants included in analysis; RRR, relative risk ratio; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
Source: Table 14.2.1.1.1, STORM CHASER CSR in Module 5.3.1.5

Secondary endpoints

Incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring after dosing with IMP and prior to Day 183 (Key secondary endpoint)

During the study the incidence of SARS-CoV-2 RT-PCR-positive severe or critical illness, was low, with one event occurring in the placebo arm.

With updated results for the August 2021 DCO, no additional case had occurred.

The incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies.

The incidence of a post-treatment response (negative at baseline and positive at any time postbaseline) for SARS-CoV-2 nucleocapsid antibodies (produced in response to a natural infection and therefore a measure of symptomatic or asymptomatic SARS-CoV-2 infection) was similar in both treatment arms, consistent with the primary result.

Table 29: Incidence of Participants who have a Post-Treatment Response for SARS-CoV-2 Nucleocapsid Antibodies, FAS, Primary Analysis, STORM CHASER

Category	AZD7442 300 mg IM (N = 444)	Placebo (N = 231)
Number (%) of participants with event	23 (5.2)	11 (4.8)
Percent RRR, (95% CI) P-value	-12.28, (-128.69, 44.87) P = 0.750	

Post-treatment response is defined as negative at baseline and positive at any time post-baseline.
Estimates are based on Poisson regression with robust variance. The model includes covariate for treatment (AZD7442 vs Placebo) and the log of follow-up time as an offset. Estimated RRR greater than 0% provides evidence in favor of AZD7442 with p-values less than 0.05 indicating statistical significance.
Percentages are based on the number of participants in the analysis by treatment group (N) for those who were negative for nucleocapsid antibodies at baseline.
ARR, absolute risk reduction; CI, confidence interval; IM, intramuscular; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.
Source: Table 14.2.3.1 (Data cut-off, 07 April 2021).

The incidence of COVID-19-related death occurring after dosing with IMP.

There were no COVID-19-related deaths occurring after dosing in the AZD7442 arm or placebo arm.

The incidence of all-cause mortality occurring after dosing with IMP.

There were no all-cause mortality events in the AZD7442 or placebo arms.

As apparent from participant flow of the August 2021 DCO, 1 additional all-cause mortality event occurred in each treatment group with this data cut-off.

Ancillary analyses

The findings from the supplementary analyses for ARR and hazard ratio confirmed the primary analysis and also found no statistical difference between AZD7442 and placebo in the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness.

Table 30: First SARS-CoV-2 RT-PCR-Positive Symptomatic Illness: Supplementary Analysis on Absolute Risk Reduction, FAS, Primary Analysis

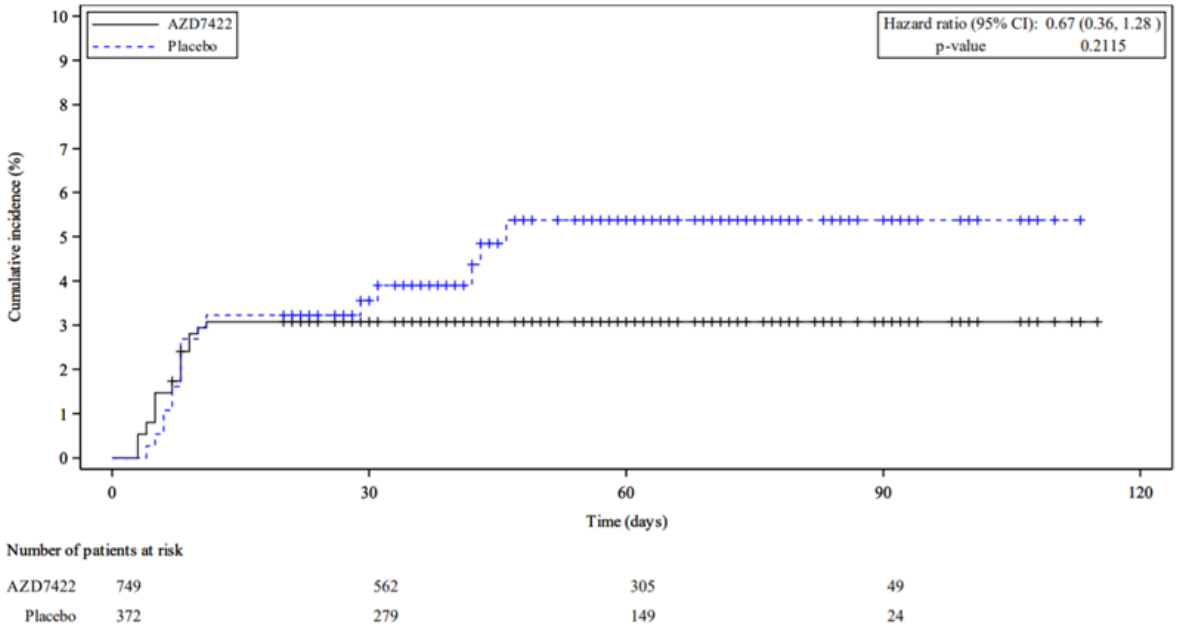
Category	AZD7442 300 mg IM (N = 749)	Placebo (N = 372)
Number (%) of participants with event	23 (3.1)	17 (4.6)
ARR, (95% CI) P-value	1.50, (-0.76, 4.32) P = 0.2314	

Estimated ARR greater than 0 provides evidence in favor of AZD7442 with p-values (Fisher's exact test) less than 0.05 indicating statistical significance. 2-sided 95% CI using the Miettinen and Nurminen's score method is provided (Miettinen and Nurminen 1985).
Percentages are based on the number of participants in the analysis by treatment group (N).
ARR, absolute risk reduction; CI, confidence interval; IM, intramuscular; N, number in treatment group; RT-PCR, reverse-transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.
Source: Table 14.2.1.3.2 (Data cut-off, 07 April 2021).

The hazard ratio for the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness in the AZD7442 group was 0.67 (95% CI 0.36, 1.28); p-value = 0.215. The Kaplan-Meier plot shows that there were no cases of SARS-CoV-2 RT-PCR-positive symptomatic illnesses in the AZD7442 group after Day 11 compared with the placebo group where there were 5 cases. The median incubation period of COVID-19, from exposure to occurrence of symptoms, is estimated to be 5.1 days (95% CI: 4.5 to 5.8 days),

and 97.5% of those who develop symptoms do so within 11.5 days (95% CI: 8.2 to 15.6 days) of infection (Lauer et al 2020). Therefore, the cases occurring in the first 11 days are likely to reflect those participants who were probably infected prior to IMP but were SARS-CoV-2 RTPCR- negative at baseline as they were still in the incubation period following exposure to the index cases. Cases occurring after 11 days are likely to reflect a new exposure to COVID-19 that occurred after IMP administration.

Figure 21: Time to First SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring Post dose of IMP, Kaplan-Meier Curves by Arm, Supplementary Analysis, Full Analysis Set, STORM CHASER, Primary Analysis



Hazard ratio is from the PH model with Efron method. The 95% CI for the hazard ratio is obtained by taking 95% profile likelihood CI of the hazard ratio from the PH model.
P-value is obtained from log-rank test.
Data cut-off, 07 April 2021
CI, confidence interval; IMP, investigational medicinal product; PH, proportional hazard; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2;
+, indicates a censored observation.
Source: Figure 14.2.1.3.3, STORM CHASER CSR in Module 5.3.5.1

The analyses for the primary endpoint as of August 2021 DCO (19 August 2021):

At the additionally provided 6-months data cut the median follow-up was 182 days (range 5 to 249 days) in the AZD7442 arm and 178 days (range 11 to 247 days) in the placebo arm.

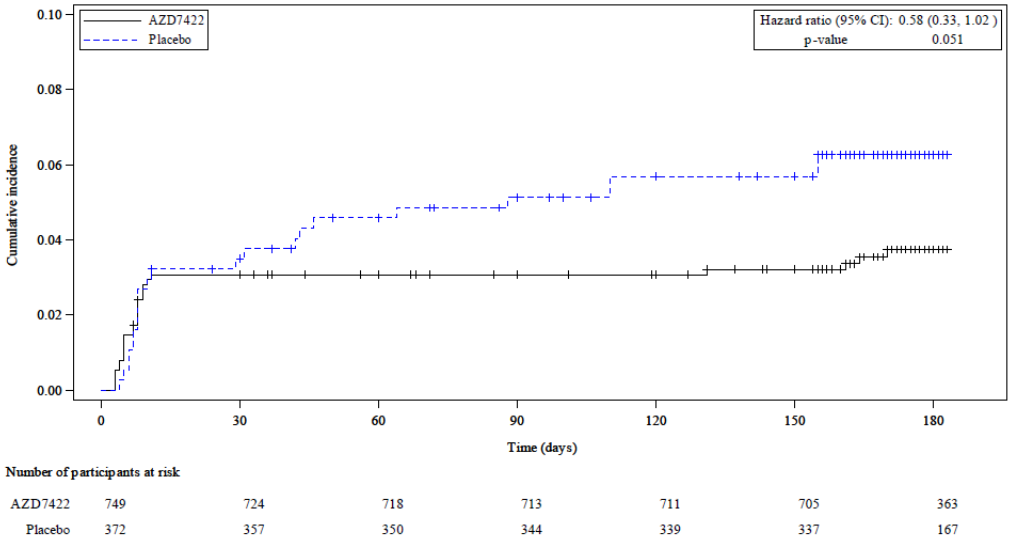
Table 31: Primary and Key Secondary Efficacy Results, August 2021 DCO, STORM CHASER

Endpoint	Statistic	AZD7442	Placebo
Primary - first SARS-CoV-2 RT-PCR-positive symptomatic illness	N	749	372
	n (%)	27 (3.6)	23 (6.2)
	RRR	43.21	
	RRR 95% CI	(0.14, 67.70)	
	P-value	0.049	
Secondary - SARS-CoV-2 RT-PCR-positive with severe or critical symptom	N	749	372
	n (%)	0	1 (0.3)
	RRR	100	
	RRR 97.5% One-sided CI	(-1836.98, NE)	
	P-value	0.664	

Abbreviations: CI = Confidence Interval; RRR = Relative Risk Reduction (i.e., 1-Relative risk of AZD7442 versus Placebo, in Percentage).
Note: Estimates are based on Poisson regression with robust variance for the primary endpoint and the Exact Conditional Method for Poisson for the secondary endpoint. The model includes covariate for treatment (AZD7442 vs Placebo) and the log of follow-up time as an offset. Estimated RRR greater than 0% provides evidence in favor of AZD7442 with p-values less than 0.05 indicating statistical significance.
Note: Percentages are based on the number of participants in the analysis by treatment group (N).

Kaplan-Meier plot as of the August 2021 DCO (19 August 2021)

Figure 22: Time to First SARS CoV 2 RT PCR positive Symptomatic Illness Occurring Post-dose of IMP, Kaplan Meier Curves by Arm, Supplementary Analysis, Full Analysis Set, STORM CHASER, August 2021 DCO



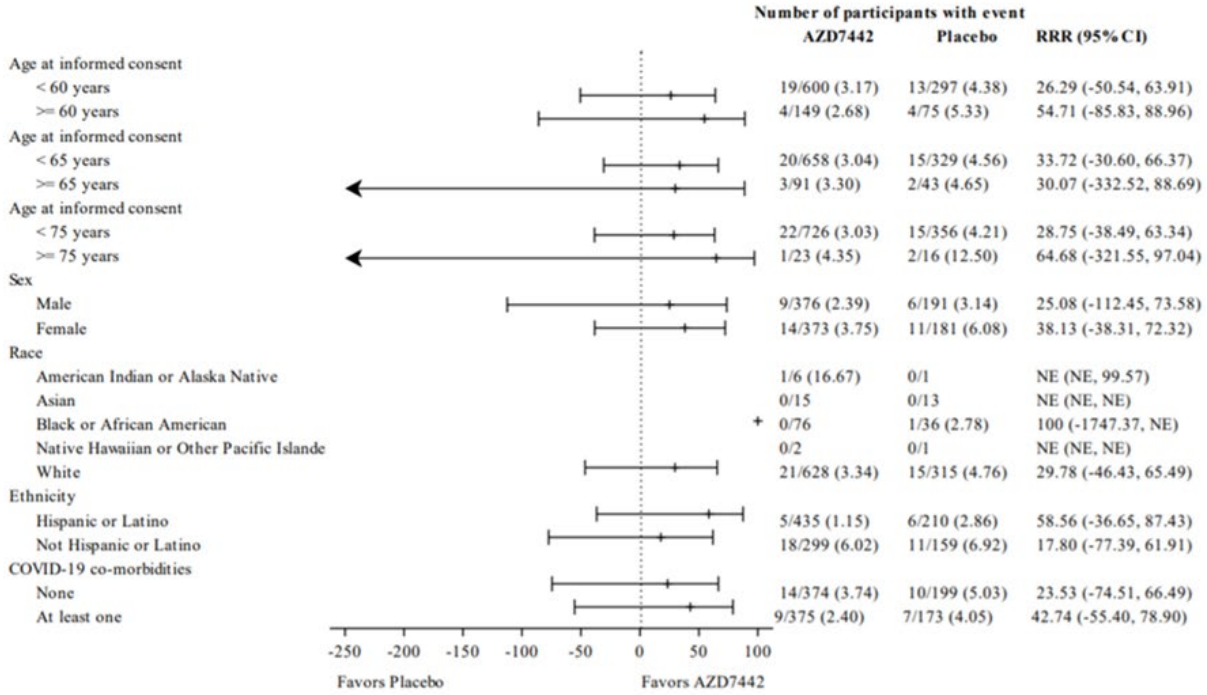
Abbreviation: CI = Confidence interval; HR = Hazard ratio; + Indicates a censored observation.
Note: Hazard ratio is from the PH model with Efron method. The 95% confidence interval (CI) for the Hazard Ratio is obtained by taking 95% profile likelihood CI of the hazard ratio from the PH model.
Note: p-value is obtained from log-rank test.

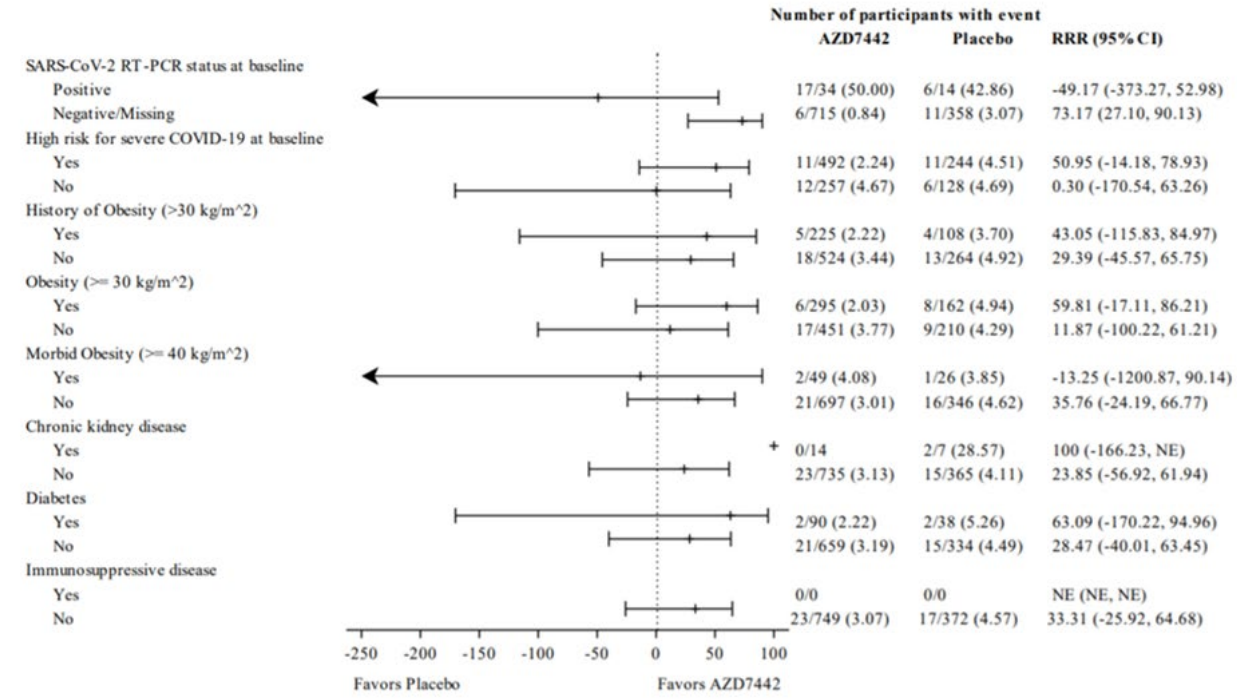
Predefined subgroup analysis at the time of primary DCO (07 April 2021)

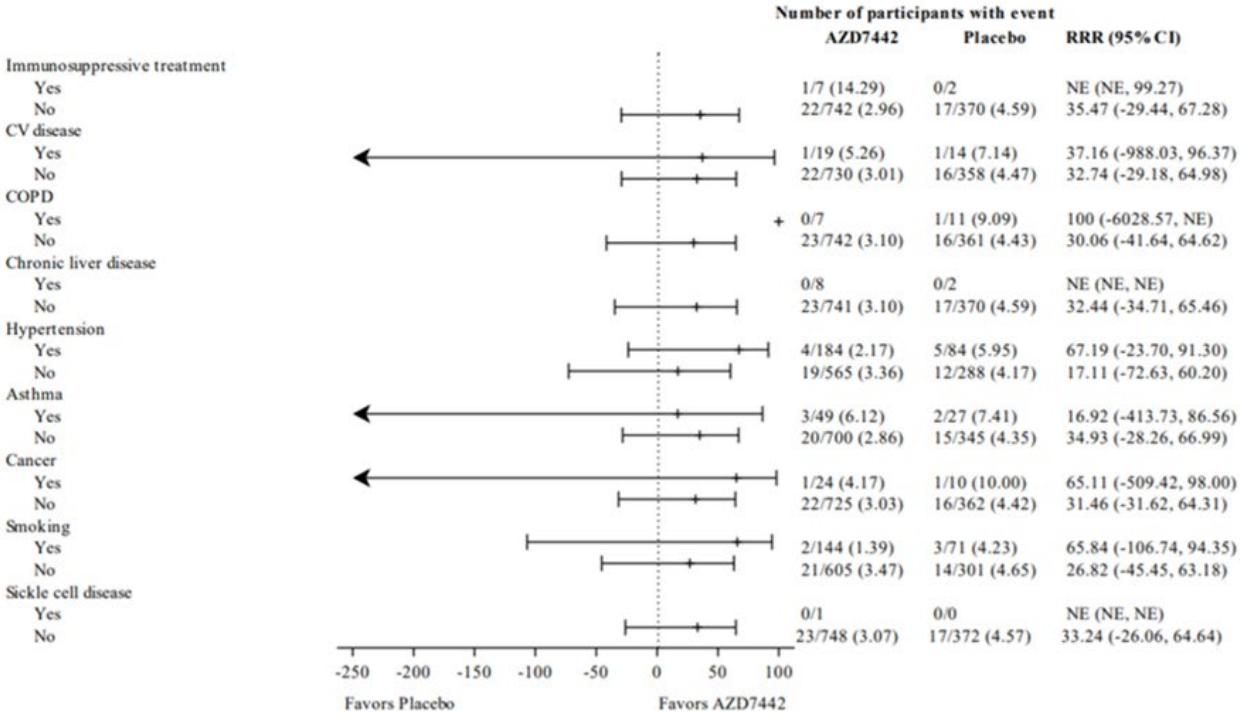
Although the study was not designed to detect treatment differences with high statistical power within subgroups, analyses were conducted in pre-specified subgroups for the incidence of first SARS-CoV-2 RT-PCR-positive symptomatic illness.

No statistically significant difference in relative risk was observed for AZD7442 compared with placebo for most subgroups, which was consistent with the primary endpoint result. However, a nominally significant RRR was observed for the subgroup of SARS-CoV-2 RTPCR status negative or missing at baseline. For this subgroup, RRR was 73.17 (95% CI: 27.10, 90.13); there were 6/715 (0.84%) participants with SARS-CoV-2 RT-PCR-positive symptomatic illness in the AZD7442 group compared to 11/358 (3.07%) participants in the placebo group. By comparison, the RRR in participants who were SARS-CoV-2 RT-PCR positive at baseline was -49.17 (95% CI: -373.27, 52.98).

Figure 23: Forest Plot for Efficacy for Incidence of First SARS-CoV-2 RT-PCR-positive Symptomatic Illness by Subgroup, Full Analysis Set, STORM CHASER, Primary Analysis







Estimates are based on Poisson regression with robust variance or Exact Poisson regression or Exact Conditional Method for Poisson. The model includes the log of the follow-up time as an offset and a covariate for treatment (Evusheld vs Placebo). Estimated RRR greater than 0 provides evidence in favor of Evusheld.

Data cut-off, 07 April 2021

CI, confidence interval; COPD, chronic obstructive pulmonary disorder; COVID-19, coronavirus disease 19; CV disease, cardiovascular disease; NE, not evaluable; RRR, relative risk reduction (ie, 1-relative risk of Evusheld

versus placebo in percentage); RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; vs, versus.
Source: Figure 14.2.1.5.2, STORM CHASER CSR in Module 5.3.1.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 32: Summary of Efficacy for Trial D8850C00002 (PROVENT)

Title: A Phase III Randomized, Double-blind, Placebo-controlled, Multi-center Study in Adults to Determine the Safety and Efficacy of AZD7442, a Combination Product of Two Monoclonal Antibodies (AZD8895 and AZD1061), for Pre-exposure Prophylaxis of COVID-19			
Study identifier	D8850C00002; PROVENT		
Design	Randomised, double-blind, placebo-controlled, multi-center		
	Duration of main phase:		457 days
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Superiority		
Treatments groups	Evusheld		Evusheld, single dose, 300 mg intramuscular (IM), 3500 participants randomised
	Placebo		Placebo, single dose, IM, 1754 participants randomised
Endpoints and definitions	Primary endpoint	Symptomatic illness	First case of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) reverse transcriptase polymerase chain reaction (RT-PCR)-positive symptomatic illness occurring post dose of investigational medicinal product (IMP) and prior to Day 183. Participants who were unblinded for vaccination and/or took vaccine or other Coronavirus Disease 2019 (COVID-19) preventive product prior to experiencing a primary endpoint event were censored at the earlier time of unblinding or vaccine
	Supportive analysis of the primary endpoint	Symptomatic illness	First case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose of IMP and prior to Day 183, regardless of their unblinding or vaccine status
	Supportive analysis of the primary endpoint	Symptomatic illness (including all cause deaths)	First case of SARS-CoV-2 RT-PCR-positive symptomatic illness or death from any cause post dose of IMP and prior to Day 183
	Key secondary endpoint	Nucleocapsid antibodies	Incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies
	Secondary endpoint	Severe or critical symptomatic illness	Incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring after dosing with IMP

Table 32: Summary of Efficacy for Trial D8850C00002 (PROVENT)

	Secondary endpoint	Emergency Department visits	Incidence of COVID-19-related Emergency Department visits occurring after dosing with IMP
Database lock	05 May 2021 (primary analysis data cut-off [DCO]) 29 August 2021 (August 2021 DCO)		
Results and Analysis			
Analysis description	**Primary endpoint: Incidence of SARS-CoV-2 RT-PCR positive symptomatic illness occurring post dose of IMP and prior to Day 183 (unblinded or vaccinated participants censored)**		
Analysis population and time point description	Full pre-exposure analysis set (FPAS) (all participants who were randomised and received at least one of the planned injections of IMP, irrespective of their protocol adherence and continued participation in the study, and who did not have a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection. The primary analysis was conducted after 30% of the study participants had been unblinded across the active and placebo groups. The August 2021 DCO was 5 months after last participant dosed, with a median follow-up of approximately 6 months. This DCO was not pre-specified; it was requested by health authorities after unblinding and all p-values are nominal.		
Descriptive statistics and estimate variability	Treatment group	Evusheld	Placebo
	Number of participants	3441	1731
	Symptomatic illness (primary analysis) n (%)	8 (0.2)	17 (1.0)
	Symptomatic illness (August 2021 DCO) n (%)	11 (0.3)	31 (1.8)
Effect estimate per comparison	Symptomatic illness (primary analysis)	Comparison groups	Evusheld versus placebo
		Relative risk reduction (RRR)	76.73
		95% confidence interval (CI)	46.05, 89.96
		P-value	< 0.001
	Symptomatic illness (August 2021 DCO)	Comparison groups	Evusheld versus placebo
		RRR	82.80
		95% CI	65.79, 91.35
		P-value	< 0.001
Notes	There was a statistically significant reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness for participants who had received Evusheld compared to placebo. The median duration from dose of IMP to primary analysis was 83.0 days. Results from the August 2021 DCO were consistent with the primary estimand.		
Analysis description	**Supportive analysis of the primary endpoint: Incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness, regardless of participants' unblinding or vaccine status (pre-specified)**		
Analysis population	FPAS		

Table 32: Summary of Efficacy for Trial D8850C00002 (PROVENT)

Descriptive statistics and estimate variability	Treatment group	Evusheld	Placebo
	Number of participants	3441	1731
	Symptomatic illness (all participants) (Primary analysis) n (%)	10 (0.3)	22 (1.3)
	Symptomatic illness (all participants) (August 2021 DCO) n (%)	20 (0.6)	44 (2.5)
Effect estimate per comparison	Symptomatic illness (Primary analysis)	Comparison groups	Evusheld versus placebo
		RRR	77.29
		95% CI	52.01, 89.25
		P-value	< 0.001
	Symptomatic illness (August 2021 DCO)	Comparison groups	Evusheld versus placebo
		RRR	77.43
		95% CI	61.72, 86.69
		P-value	< 0.001
Notes	There was a statistically significant reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness for participants who had received Evusheld compared with placebo. Results from the August 2021 DCO were consistent with the primary analysis.		
Analysis description	**Supportive analysis of the primary endpoint: Incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness (including all cause deaths) (pre-specified)**		
Analysis population	FPAS		
Descriptive statistics and estimate variability	Treatment group	Evusheld	Placebo
	Number of participants	3441	1731
	Symptomatic illness (including all cause deaths) (primary analysis) n (%)	12 (0.3)	19 (1.1)
	Symptomatic illness (including all cause deaths) (August 2021 DCO) n (%)	18 (0.5)	36 (2.1)
Effect estimate per comparison	Symptomatic illness (including all cause deaths) (primary analysis)	Comparison groups	Evusheld versus placebo
		RRR	68.78
		95% CI	35.64, 84.86
		P-value	0.002

Table 32: Summary of Efficacy for Trial D8850C00002 (PROVENT)

	Symptomatic illness (including all cause deaths) (August 2021 DCO)	Comparison groups	Evusheld versus placebo
		RRR	75.77
		95% CI	57.33, 86.23
		P-value	< 0.001
Notes	There was a statistically significant reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness or death from any cause for participants who had received Evusheld compared with placebo. Results from the August 2021 DCO were consistent with the primary estimand.		
Analysis description	**Key secondary endpoint: Incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS CoV-2 nucleocapsid antibodies**		
Analysis population and time point description	FPAS (primary analysis)		
Descriptive statistics and estimate variability	Treatment group	Evusheld	Placebo
	Number of participants	3123	1564
	Nucleocapsid antibodies n (%) (primary analysis)	21 (0.7)	21 (1.3)
Effect estimate per comparison	Nucleocapsid antibodies (primary analysis)	Comparison groups	Evusheld versus placebo
		RRR	51.07
		95% CI	10.57, 73.23
		P-value	0.020
Notes	The incidence of a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies, was statistically significantly lower for participants who had received Evusheld compared to placebo.		
Analysis description	**Secondary endpoint: Incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring after dosing with IMP**		
Analysis population and time point description	FPAS (primary analysis)		
Descriptive statistics and estimate variability	Treatment group	Evusheld	Placebo
	Number of participants	3441	1731
	Severe or critical symptomatic illness n (%) (primary analysis)	0	1 (0.1%)
Notes	Number of participants who had severe or critical symptomatic illness was numerically low in both groups, and thus a comparison cannot be made.		
Analysis description	**Secondary endpoint: Incidence of COVID-19-related Emergency Department visits occurring after dosing with IMP**		

Table 32: Summary of Efficacy for Trial D8850C00002 (PROVENT)

Analysis population and time point description	FPAS (primary analysis)		
Descriptive statistics and estimate variability	Treatment group	Evusheld	Placebo
	Number of participants	3441	1731
	Emergency department visits n (%) (primary analysis)	6 (0.2%)	0
Notes	The relative risk reduction of Evusheld compared to placebo for COVID-19-related Emergency Department visits could not be estimated due to low numbers.		

Table 33: Summary of Efficacy for Trial D8850C00003 (STORM CHASER)

Title: A Phase III Randomized, Double-blind, Placebo-controlled, Multi-center Study in Adults to Determine the Safety and Efficacy of AZD7442, a Combination Product of Two Monoclonal Antibodies (AZD8895 and AZD1061), for Post-exposure Prophylaxis of COVID-19			
Study identifier	D8850C00003; STORM CHASER		
Design	Randomised, double-blind, placebo-controlled, multi-center		
	Duration of main phase:		457 days
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		not applicable
Hypothesis	Superiority		
Treatments groups	Evusheld		Evusheld, single dose, 300 mg IM, 756 participants randomised
	Placebo		Placebo, single dose, IM, 375 participants randomised
Endpoints and definitions	Primary endpoint	Symptomatic illness	First case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose of IMP and prior to Day 183
	Key secondary endpoint	Severe or critical symptomatic illness	Incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring after dosing with IMP
	Secondary endpoint	Nucleocapsid antibodies	Incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies
	Secondary endpoint	COVID-19-related death	Incidence of COVID-19-related death occurring after dosing with IMP
	Secondary endpoint	All-cause mortality	Incidence of all-cause mortality occurring after dosing with IMP
Database lock	07 April 2021 (primary analysis DCO) 19 August 2021 (August 2021 DCO)		
Results and Analysis			
Analysis description	**Primary endpoint: Incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose of IMP and prior to Day 183**		
Analysis population and time point description	Full analysis set (FAS; all participants who were randomised and received at least one of the planned injections of IMP, irrespective of their protocol adherence and continued participation in the study). The primary analysis was conducted 30 days after the 25th primary efficacy event had been reported across the active and placebo groups. The August 2021 DCO was 5 months after last participant dosed, with a median follow-up of 6 months. This DCO was not pre-specified; it was requested by health authorities after unblinding and all p-values are nominal.		
Descriptive statistics and estimate variability	Treatment group	Evusheld	Placebo
	Number of participants	749	372
	Symptomatic illness (primary analysis) n (%)	23 (3.1)	17 (4.6)

Table 33: Summary of Efficacy for Trial D8850C00003 (STORM CHASER)

	Symptomatic illness (August 2021 DCO) n (%)	27 (3.6)	23 (6.2)
Effect estimate per comparison	Symptomatic illness (primary analysis)	Comparison groups	Evusheld versus placebo
		RRR	33.31
		95% CI	-25.92, 64.68
		P-value	0.212
	Symptomatic illness (August 2021 DCO)	Comparison groups	Evusheld versus placebo
		RRR	43.21
		95% CI	0.14, 67.70
		P-value	0.049
Notes	The primary endpoint was not met.		
Analysis description	**Key secondary endpoint: Incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring after dosing with IMP**		
Analysis population	FAS		
Descriptive statistics and estimate variability	Treatment group	Evusheld	Placebo
	Number of participants	749	372
	Severe or critical symptomatic illness n (%) (primary analysis)	0	1 (0.3)
Notes	The incidence of SARS-CoV-2 RT-PCR-positive severe or critical illness, was low, and therefore, no conclusion can be made on the effect of Evusheld on severe or critical symptomatic illness in this setting.		
Analysis description	**Secondary endpoint: Incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies**		
Analysis population	FAS		
Descriptive statistics and estimate variability	Treatment group	Evusheld	Placebo
	Number of participants	444	231
	Nucleocapsid antibodies n (%) (primary analysis)	23 (5.2)	11 (4.8)
Effect estimate per comparison	Nucleocapsid antibodies (primary analysis)	Comparison groups	Evusheld versus placebo
		RRR	-12.28
		95% CI	-128.69, 44.87
		P-value	0.750
Notes	The incidence of a post-treatment response (negative at baseline and positive at any time postbaseline) for SARS-CoV-2 nucleocapsid antibodies (a measure of symptomatic and asymptomatic COVID-19 infection) was similar in both treatment arms, consistent with the primary result.		

Table 33: Summary of Efficacy for Trial D8850C00003 (STORM CHASER)

Analysis description	**Secondary endpoint: Incidence of COVID-19-related death occurring after dosing with IMP**
Analysis population	FAS
Notes	At the time of the primary analysis, there were no COVID-19-related deaths in this study.
Analysis description	**Secondary endpoint: Incidence of all-cause mortality occurring after dosing with IMP**
Analysis population	FAS
Notes	At the time of the primary analysis, there were no deaths in this study.

2.5.5.3. Clinical studies in special populations

No specific studies in special populations have been conducted.

Age

In phase 3 portion of PROVENT, 43.4% of the subjects were ≥60 years old. Overall, 5.2% had chronic kidney disease, 4.6% had chronic liver disease. No paediatric patients were included.

A tabular summary of participants stratified based on age by study is presented below:

Table 34: Study participants by Age Group

	Age ≥ 65 to < 74 (Older Subjects Number/Total Number)	Age ≥ 75 to < 84 (Older Subjects Number/Total Number)	Age ≥ 85+ (Older Subjects Number/Total Number)
Study D8850C00001	0/50	0/50	0/50
PROVENT	413/1870	71/1870	2/1870
STORM CHASER	27/198	8/198	1/198
Total in PK studies	440/2118	79/2118	3/2118
Total in Controlled Studies	440/2068	79/2068	3/2068
Total in Uncontrolled Studies	0	0	0

PK, pharmacokinetics

2.5.5.4. In vitro biomarker test for patient selection for efficacy

N/A

2.5.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

N/A

2.5.5.6. Supportive study(ies)

See clinical pharmacology section for study results of study D8850C00001 (Phase I FTIH).

2.5.6. Discussion on clinical efficacy

The phase 3 studies PROVENT (pre-exposure setting) and STORM CHASER (post-exposure setting) are considered as basis for the evaluation of efficacy of the monoclonal antibody combination tixagevimab and cilgavimab (Evusheld) for a broad prophylaxis indication. Both studies investigate a single dose of 300 mg Evusheld IM, i.e. 2 sequential 150 mg IM doses of tixagevimab and cilgavimab, respectively.

The submitted date on efficacy are based on 2 data cut-offs: The first cut-off (primary DCO) is the time point of the primary efficacy analyses at which 30% of all study participants had become unblinded (PROVENT) or 25 subjects had a primary endpoint event (STORM CHASER). The following cut-off (August 2021 DCO) provides a minimum of 5 months efficacy follow-up data; It was not pre-specified and adapted based on Evulsheld's level of development in the context of other emerging therapies. Longer follow up of subjects is still ongoing at the time of the present assessment.

Design and conduct of clinical studies

PROVENT is an ongoing Phase III, randomised, double blind, placebo-controlled, multicenter, multinational study assessing the efficacy of a single dose of Evusheld compared to placebo for the prevention of COVID-19 in a pre-exposure prophylaxis setting. The use of placebo as comparator is endorsed in the studied population, as the study started the recruitment in November 2020 where no approved prophylaxis treatment was available. Overall, the study design is considered adequate regarding the evaluation of Evusheld in the pre-exposure prophylaxis setting.

The inclusion criteria were chosen to represent a population on higher risk for inadequate response to active immunization (included ≥ 60 years old, BMI ≥ 30, congestive heart failure, COPD, GFR < 30 mL/min/1.73 m2, chronic liver disease, immunocompromised state, intolerant of vaccine) or appreciable risk of exposure to SARS-CoV-2 and COVID-19. Subjects were to be unvaccinated and seronegative for SARS-CoV-2, adult and non-pregnant/not breast-feeding. The eligibility criteria are considered adequate to define a representative study population that could benefit from a passive immunization with Evusheld in a time where active immunization was not yet available.

The objectives and endpoints are clearly defined and appropriate to investigate the efficacy of a single dose of Evusheld relative to placebo. The primary endpoint was a binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs post dose of IMP prior to Day 183. The presented definition of qualifying symptoms for the primary endpoint is acceptable; symptoms are rather unspecific but will be counted as primary endpoint event only in combination with a positive SARS-CoV-2 RT-PCR result. The key secondary endpoint aimed at detection of a host immune response to SARS-CoV-2 after administration of the study drug and was introduced in the multiple testing hierarchy with protocol amendment 7 in June 2021. With the same amendment, longer observation of COVID-19 prevention (until day 366) was removed from the multiple testing hierarchy and became an exploratory endpoint only. By that, the time point for participants' unblinding became more flexible which is comprehensible in light of the fact that alternative treatment options, e.g. vaccines became available. Further secondary endpoints presented with the present data cut-offs are considered adequate to support the efficacy analyses by investigation of progress to severe disease (e.g. incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness/COVID-19-related Emergency Department visits).

Overall, 5150 participants were planned to be randomised (Evusheld: n = approximately 3433; placebo: n = approximately 1717). The planned sample size appears reasonable. The sample size and power considerations, as well as considerations around the timing of analysis were amended several times during the conduct of the study. This indicates that the study was planned and conducted with relevant uncertainty. It was planned to conduct a blinded sample size re-estimation, in order to mitigate uncertainty around the assumptions. The protocol contained considerations on potential risks

to the study integrity, and these are generally endorsed and agreed. It is acknowledged that considerations were made on expected unblinding and vaccination and it was clarified upon request that only blinded information on outcomes (overall rates) and extent of unblinding were used in the revisions of the planned analysis time. While the extent of participant unblinding and the substantial reduction in information are not optimal, it is considered unlikely that any opportunistic choices could have been made and only small uncertainty remains. The overall sample size was only little affected by the changes (initial estimation: n=5000; re-estimation and final choice: n=5150).

A 2:1 (verum:placebo) randomization ratio may not be optimal in terms of power and precision, but does not *per se* raise any concerns. Randomization was stratified within 2 cohorts that were based on patient's age at baseline (<60/≥60 years). The number of strata seems feasible with the overall sample size and stratified recruitment (i.e. a sample size cap at 80%) for the 2 cohorts is reasonable. However, randomization was not stratified for region or study site. The applicant acknowledged that rapid emergence and spread of variants was not anticipated at the planning stage, but that it was expected that the pandemic would be similar in the study regions as these are all on the northern hemisphere. Study results (baseline characteristics, subgroup analysis on primary endpoint) do not indicate any major impact of geographic region. Nonetheless, some uncertainty remains, as incidences and governmental measures could have been different across regions throughout the course of the study and it is not fully clear how that might have affected the estimation. Irrespective, it is agreed that this does not change the overall interpretation.

Blinding procedures were appropriately defined. However, participants were unblinded during the ongoing study, to allow for an individual decision for the best timing of COVID-19 vaccination. For the primary analysis, participants who were unblinded to IMP assignment or who were vaccinated prior to experiencing a primary endpoint event, were censored at the earlier time of unblinding or vaccination. Thus, the primary estimand is not a treatment policy estimand, but a "while-not-vaccinated-or-unblinded" estimand, excluding events that occur after vaccination. A supportive treatment policy estimand (regardless of vaccination) is provided and consistency of the two estimands provides some reassurance on the extent that unblinding and vaccination may have affected results.

The statistical analyses are in principle supported. Initially it was planned to conduct the primary analysis on the full analysis set (FAS), but this was changed in an amendment to the "Full Pre-Exposure Analysis Set", comprising all subjects randomised and treated who were not infected with SARS-CoV-2 prior to baseline. Initially, the applicant aimed at a broad prevention indication statement including all asymptomatic subjects (irrespective of SARS-CoV-2 PCR status. Thus, results of SARS-CoV-2 PCR positive subjects were of interest and were provided upon request. The analysis model using a poisson regression is in principle acceptable. Uncertainty due to stratification factors not being accounted for in the analysis could be largely resolved by additional analyses. A two-sided significance level of $\alpha = 0.05$ is acceptable. However, whether the level of statistical significance is considered persuasive for a regulatory decision may also depend on the results of supportive studies or analyses, as PROVENT was the only study in a pre-exposure setting. A stricter success criterion (point estimate >50% and lower bound of 95% confidence interval >30%) was initially planned, but discarded in an early amendment based on Health Authority Feedback. Such a stricter criterion would not be formally required; the final choice (null hypothesis testing no difference between Evusheld and placebo) is deemed acceptable. Still, this may reflect uncertainty at planning and conduct of the study. It seems that missing values were not imputed, and in particular, missing data on symptomatic infection was interpreted as absence of symptomatic infection. This is acceptable and may even be conservative in some scenarios. Despite some uncertainty on the potential impact on results, there is currently no reason to assume that this might have artificially increased the effect estimate. The planned timing of the primary analysis was adapted during the conduct of the study to be after "24 primary endpoint events have been confirmed or 30% of study participants have become unblinded, whichever occurs

first". It is not fully understood why 30% of unblinded subjects should trigger the analysis, as this criterion does not reflect the information accrued. Eventually, unblinding triggered the analysis, but the two criteria coincided (there were 25 events), and no concern is raised on this issue.

STORM CHASER is an ongoing Phase III, randomised, double-blind, placebo-controlled, multicenter study assessing the efficacy of a single dose of Evusheld (2 sequential IM injections) compared to placebo for the prevention of COVID-19 in post-exposure prophylaxis setting.

The chosen population seems overall adequate for investigation of a post- exposure prophylaxis setting in adults. Participants were to be at risk of imminently developing COVID-19, as they were in contact with a subject with confirmed SARS-CoV-2 infection within 8 days. Risk may vary between subjects as contact persons could have been both, symptomatic or asymptomatic and included household contacts, as well as other residents of a long-term care facility, staff members of a long-term care facility, other workers in industrial setting, and university or college dormitories. As index cases were not part of the study, it cannot further be retraced how differences in risk of exposure might be reflected by study results. No criterion was chosen to exclude subjects with a positive SARS-CoV-2 RT-PCR test at screening. Thus, the chosen population was allowed to include subjects that were already infected, but asymptomatic. Otherwise, eligibility criteria were similar to the ones in study PROVENT.

The same primary endpoint as in study PROVENT was applied and is considered adequate. It should be notated that due to the relatively long investigation period (183 days) also potentially unknown cases of exposure resulting in symptomatic COVID-19 at a later time points (i.e. in a pre-exposure setting) will be counted for the primary endpoint. The key secondary endpoint investigates whether Evusheld may inhibit severe or critical COVID-19 until day 183 p.a.. The chosen definition for severe/critical illness is acceptable: patients need to be hospitalised, with pneumonia or hypoxia and under respiratory support (at least oxygen by mask or nasal prongs) to be counted as event. The investigation of deaths (all-cause or COVID-19 related) as well as occurrence of asymptomatic disease (by nucleocapsid antibodies) as secondary endpoints is deemed appropriate in the chosen population.

Up to 1125 participants were planned to be randomised in a 2:1 ratio to receive a single IM dose of Evusheld (n = approximately 750) or placebo (n = approximately 375). The sample size calculations were based on the primary efficacy endpoint and were derived following a modified Poisson regression approach. The sample size considerations appear reasonable and are overall acceptable. The need to plan a sample size re-estimation reflects uncertainty at the planning stage.

Also here, a 2:1 (verum:placebo) randomization ratio was planned. A randomization in 2 cohorts ("adults ≥ 60 years of age, living in long-term care facilities" and "all other adults") was planned. With initial planning, the percentage of subjects ≥ 60 years of age living in long term care facilities had to be between 50 and 80% of overall population. This requirement was removed in 2 steps (with protocol amendments 3 and 5) due to availability of an efficacious vaccine for this vulnerable population and finally, the large majority (1114 [99.4%]) of participants included in the study were enrolled under Cohort 2 ("all other adults"). Again, randomisation was not stratified for region or study site; discussions provided for PROVENT study above also apply here.

Blinding procedures are acceptable. In order to receive a COVID-19 vaccine, participants were able to be unblinded if they request this. In contrast to study PROVENT, unblinded subjects were not censored in the primary analysis. However, at the primary DCO, there were no participants with primary events occurring post unblinding and 2 participants, both on placebo arm, who discontinued trial early after unblinding Thus, based on these results the impact of unblinding on primary endpoint analysis is expected to be marginal.

The statistical methods seem overall reasonable. The analysis population, comprising all participants who were randomised and treated is supported. This is considered close to a treatment policy

estimand. The primary analysis model is in principle acceptable. However, it is not adjusted for any baseline covariates. This is not optimal, provided that regional or study site heterogeneity could be expected. The significance level of α=0.05 is acceptable, but was not met. Thus, any findings should be interpreted in a descriptive manner and with care. Of note, initially a stricter criterion (lower bound of 2-sided 95% CI > 30%, plus point estimate >50%) was defined, but this was removed in a protocol amendment. While this criterion would not be required for approval, the changes may reflect some uncertainty in the planning and conduct of the study. The analysis was initially planned after 90 events. This was reduced 2 times with ongoing study and in the end, an analysis 30 days after observing 25 events was planned in protocol version 6.0. Considerations around the timing of the analysis may also reflect uncertainty and may indicate that the trial faced difficulties in accruing the necessary cases.

Efficacy data and additional analyses

The **PROVENT** study is still running. 5973 participants were screened, 5254 thereof were randomised. Most screen-failures had not met the eligibility criteria. A minority of 1.1% were randomised, but not treated and 2.8% discontinued their participation, mainly due to participant's withdrawal or lost to follow-up. At the August 2021 DCO, 2162 (41.1%) had been unblinded but the majority was still ongoing in the study (95.0%). With the presented data cut-off, 5109 (97.2%) study subjects are ongoing in the study, and no patient completed.

The full analysis set (FAS) includes 3460 participants randomised to the Evusheld group and 1737 randomised to the PBO group; numbers were only slightly different for the "Full Pre-Exposure Analysis Set" (including non-infected subjects only) used for the primary analysis (3441 and 1731 subjects).

Almost 30% of the participants in each treatment group had one major protocol violation. An additional estimand was provided upon request, in which participants who had any important protocol deviation at any time were excluded from the analysis. As results are consistent with the results of the primary analysis the impact of protocol deviations on data integrity is considered insignificant.

The patient population was balanced as to age (<60 years 56.6%, >60 years 43.4%), gender (female 46.1%, male 53.9%) and the remainder of baseline characteristics. The majority was White (73%) and obese (72.9%) with a mean BMI of 30 kg/m^2. Overall, the majority of subjects (77.5%) was considered to be at increased risk for progression to severe COVID-19 due to underlying medical conditions. The definition of this high-risk population based on CDC criteria is endorsed. Patients with immunosuppressive disease or treatment, as a population that is presumed to benefit from a passive immunization, were underrepresented (0.5% and 3.3%).

At the primary analysis, there was a statistically significant reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness for participants who had received Evusheld compared to placebo, RRR 76.73 (95% CI: 46.05, 89.96; p < 0.001). Overall numbers were low: 8/3441 (0.2%) participants assigned to the Evusheld group and 17/1731 (1.0%) subjects in the placebo group experienced an event. Of note, the 95% confidence interval excludes 30% and the point estimate is greater than 50%. These criteria were initially defined as success criteria and dropped in an amendment. Although fulfilment of the criteria is not required, this supports the conclusion of a prophylactic treatment effect. The results of the primary analysis results are in some ways substantiated by those obtained at the second data cut-off (August 2021 DCO) and the key supportive analyses, respectively. Data collected and analysed at the August 2021 DCO (median duration of follow-up of 196 days in both treatment arms) provide evidence that the treatment effect of Evusheld was sustainable, i.e. RRR was 82.80 (CI 46.79, 91.35). As the primary analysis population excluded subjects tested PCR-positive at baseline, but PCR testing is not foreseen in clinical practice, the applicant provided upon request results all

treated subjects, irrespective of PCR-status, at the August 2021 DCO. Results did not raise concern, but suggest a somewhat smaller benefit, i.e. RRR= 78.16 (58.96, 88.38). These results are considered more relevant and have been included in the SmPC. As shown by Kaplan-Meier-plots, the time to first SARS-CoV-2 RT-PCR positive symptomatic illness is delayed in the Evusheld group compared to placebo with consistent results over time (until August 2021 DCO) (HR 0.23 (95% CI: 0.10, 0.53); p-value < 0.001). Furthermore, results of the primary analysis are substantiated by the primary analysis adjusted by region as well as the findings from the supplementary analysis for the absolute risk reduction. It is not fully clear how the large extent of unblinding might have affected results. In the primary analysis, participants were censored at the time of (voluntary) unblinding or vaccination (whichever occurred earlier). Additional analyses without censoring lead to similar results, only minor uncertainty remains. Subgroup analyses do not raise concerns on potential heterogeneity of the treatment effect across subgroups. However, this should be interpreted with caution, as the overall number of events is small. As subjects with immunosuppressive disease or treatment were underrepresented, results do not allow data-based conclusion for these subjects.

The incidence of SARS-CoV-2 nucleocapsid antibodies (as a measure of symptomatic and asymptomatic infections) was lower for participants who had received AZD7442 compared to placebo, with an RRR of 51.07% (95% CI: 10.57, 73.23; p-value 0.020). This key secondary endpoint was included in hierarchy in a late amendment (protocol version 8) and can be considered confirmatory. As evident from Kaplan-Meier-plots, the incidence was comparable between both treatment groups until day 60. Afterwards, the Evusheld group reached a plateau whereas in the placebo group more positive tests were reported.

The effect of Evusheld on disease progression is currently unknown, as results of other secondary and exploratory endpoints "Incidence of SARS-CoV-2 RT-PCR-Positive Severe or Critical Symptomatic Illness After Dosing With IMP" and "Incidence of COVID-19-related Emergency Department Visits Occurring After Dosing With IMP" are not interpretable due to very few events in both treatment groups. At least no negative signals were detected with the presented DCO that would raise any concern.

Data on SARS-CoV-2 viral loads in infected subjects are currently sparse. At all timepoints, viral load (determined as viral genome copies in NP swabs) was numerically lower in patients treated with Evusheld compared to placebo. However, sample size is extremely low and chance findings are likely. Currently it is not established how viral load correlates with clinical outcomes and thus, relevance of this endpoint is deemed low.

In study **STORM CHASER**, less than 1% of the subjects were randomised but not dosed. As number of early discontinuations was overall moderate and slightly lower in the Evusheld group compared to the placebo group, these results do not raise concerns. At the timing of the primary analysis, the number of unblinded subjects (in order to receive COVID-19 vaccination or for other unknown reasons) was higher in the placebo group (14.1%) compared to the Evusheld group (8.2%). As discussed above, as a result of unblinding, an effect on patient behavior (and thus potential exposure) cannot be excluded. The full analysis set (for primary efficacy analysis) and safety analysis set are identical. The large majority of randomised subjects (>99%) was dosed and became part of the 2 analysis sets (SAS, FAS). Treatment arms together included 1121 subjects (Evusheld N=749, placebo N=372).

According to the data provided, demographics were balanced across Evusheld treatment group and placebo group. Approximately half of the subjects were female and approximately 20% were ≥ 60 years old. Overall, only 10 subjects living in a long-term care facility were included, which is far away from initial study planning (i.e. 50-80% of subjects living in a long-term care facility). The majority of subjects had a negative SARS-CoV-2 PCR test at baseline (86.9%), with a comparable percentage in both treatment groups (86.2% for Evusheld group vs 88.2% for PBO group). Thus, no impact on

investigated treatment effect is expected. Approximately 65% of the subjects were considered to be at an increased risk due to underlying medical condition, with a comparable percentage in both treatment groups. Obesity, hypertension, smoking and diabetes were the most prominent risk factors in the enrolled population. Overall, only 9 subjects under immunosuppressive treatment and no subjects with immunosuppressive disease were included. When compared to the study PROVENT, the STORM CHASER population was younger (median 48 vs 57 years), less at risk for disease progression due to underlying medical conditions (65.7 vs 77.5%), had a lower proportion of SARS-CoV-2 RT-PCR negatives (86.9 vs 96.3%) and a higher proportion of Hispanic/Latino subjects (57.5 vs 14.5%).

The primary endpoint was not met: At the primary analysis, the RRR in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness was 33.31 [95% CI: -25.92, 64.68] with Evusheld compared to placebo, which was not statistically significant (p = 0.212). There were 23/79 (3.1%) participants with SARS-CoV-2 RT-PCR-positive symptomatic illness in the Evusheld arm compared to 17/372 (4.6%) participants in the placebo arm. The median (min, max) duration from dose of IMP to primary event was comparable: 49.0 (5, 115) days for the Evusheld arm and 48.0 (20, 113) days for the placebo arm. Thus, efficacy of Evusheld in the post-exposure prophylaxis setting could not be demonstrated in the chosen population and the broad indication statement cannot be agreed.

Furthermore, Evusheld was not able to prevent symptomatic or asymptomatic infection detected as post-baseline nucleocapsid antibodies until day 183 in the post-exposure prophylaxis setting. Approximately 5% of subjects were positive for nucleocapsid antibodies in both, the Evusheld and the placebo group.

No statement on Evusheld's effect on incidence of severe or critical symptomatic illness (key secondary endpoint) or deaths (COVID-19-related and all cases, other secondary endpoints) is possible, as almost no such cases occurred. With an overall number of 25 events of symptomatic illness (primary DCO), the sample size was too small for investigation of disease progression/death.

A similar impression as by the primary analysis was given by the supplementary analysis on absolute risk reduction and the updated August 2021 DCO data. Kaplan-Meier plot of the time to first SARS-CoV-2 RT-PCR positive symptomatic illness illustrates that Evusheld was not able to prevent symptomatic infections when administered post-exposure: There is no obvious difference in the Evusheld curve compared to the PBO curve considering the 4 weeks after treatment. The applicant highlights that with the primary DCO there were no cases of SARS-CoV-2 RT-PCR-positive symptomatic illnesses in the AZD7442 group after Day 11 compared with the placebo group where there were 5 cases and these should reflect cases with exposure after IMP administration (pre-exposure setting). Although this is agreed for this data snapshot, it does not hold true for the longer observation period presented with August 2021 DCO, where 4 additional cases occurred in the Evusheld group. However, as slightly less new cases occurred in the Evusheld group (4/749) compared to the placebo group (6/372) since timing of the primary analysis, these results might tend to show a beneficial treatment effect of Evusheld in a pre-exposure prophylaxis setting. Nevertheless, due to the overall very low number of cases and the post-hoc nature of these analyses, findings are highly uncertain, and results should be perceived with great care. Furthermore, Kaplan-Meier plot of the August 2021 DCO indicates that all new cases in the Evusheld group occurred later than d120 p.a., questioning somewhat the claimed long-term protective effect of Evusheld.

A predefined subgroup analysis at the timing of the primary analysis excluded subjects with SARS-CoV-2 RT-PCR status positive at baseline and showed a nominally statistically significant difference for Evusheld compared to placebo. In the subgroup SARS-CoV-2 RT-PCR status negative or missing at baseline there were 6/715 (0.84%) participants with SARS-CoV-2 RT-PCR-positive symptomatic illness in the Evusheld arm compared to 11/358 (3.07%) participants in the placebo arm. As these subjects share SARS-CoV-2 RT-PCR status with the PROVENT population (96.3% SARS-CoV-2 RT-PCR

negatives), these subgroup results do not raise concern for the Evusheld prevention indication and might be considered as supportive. However, results should be interpreted with great caution. As this was a subgroup analysis only, the explorative character of such an analysis needs to be emphasised. In contrast, half of the subjects with positive SARS-CoV-2 RT-PCR test prior to treatment had a primary event in the Evusheld group (17/34; 50.00%) while 42.86% (6/14) had an event in the placebo group. Furthermore, no positive tendency was seen for subjects not at risk for progression to severe COVID-19 and there was a tendency of less treatment effect in the younger population.

Thus, based on these data and in absence of relevant data from study PROVENT (SARS-CoV-2 RT-PCR positive subjects excluded from primary analysis), subjects with SARS-CoV-2 RT-PCR status positive were requested to be excluded from an indication statement for the planned prevention indication. In response, the applicant restricted the indication to pre-exposure prophylaxis. However, he also proposed to waive the request for a mandatory SARS-CoV-2 RT-PCR test with regard to results of the TACKLE study and circumstances in a real-world setting, i.e. timely availability of this test, and thus, a potential delay of an administration. This rationale can be followed.

2.5.7. Conclusions on the clinical efficacy

Evidence for efficacy of Evusheld in the prophylaxis setting has been generated in 2 pivotal studies investigating treatment effect on prevention of COVID-19 (any severity). Even though various design changes were performed in the running study, they did not have the potential to impact study results to an extent that would make the entire conclusion on efficacy questionable.

In study PROVENT, investigating pre-exposure prophylaxis setting, Evusheld demonstrated a statistically significant effect for the primary endpoint (RRR% (95%CI): 76.73 (52.01, 89.25)) as well as signs of efficacy across all secondary/exploratory endpoints studied and supportive/ancillary analysis performed. In contrast, study STORM CHASER, investigating the post-exposure prophylaxis setting, failed to meet its primary endpoint ((RRR% (95%CI): 33.31 (-25.92, 64.68)). This is mainly attributed to the small subgroup of already infected but asymptomatic subjects (positive SARS-CoV-2 RT-PCR test prior to treatment), from whom half (17/34; 50%) developed COVID-19 despite Evusheld treatment. Hence, the lack of efficacy seen in post-exposure setting and the negative signals seen in PCR positive subjects had raised concern against the proposed broad indication including individuals irrespective of exposure or PCR test result. However, the major objection was solved as the applicant accepted the indication proposed by the Committee (see discussion above).

The CHMP considers the following measures necessary to address issues related to efficacy:

Please see the list of recommendations in the appendix at the end of this document

2.5.8. Clinical safety

2.5.8.1. Patient exposure

Due to the nature of the drug product, exposure for all participants included in the safety analysis set in each study was 100%.

Two data cut-offs (DCO) are used regarding the analysis of safety data:

- PROVENT: 1st DCO: 29 June 2021, 2nd DCO: 29 August 2021
- STORM CHASER: 1st DCO: 19 June 2021, 2nd DCO: 19 August 2021.

Participants in both studies received a single dose of either 300 mg of Evusheld or saline placebo.

During PROVENT up to 1st DCO, 5172 participants had been dosed with IMP. At the time of 1st DCO used for the primary STORM CHASER CSR (19 June 2021), 1121 participants had been dosed with IMP. In total, pooled safety data is available from 6318 patients. Further safety data is available at 2nd DCO providing a minimum of 5 months safety follow-up for all ongoing participants (see Table below).

Table 35: Extent of Exposure and Follow-Up (DCO June 2021)

Study, Data cut-off	Treatments and Doses	Number of participants		Safety follow-up duration in days [a]
		EVUSHELD	Placebo	
PROVENT, 29 June 2021	300 mg EVUSHELD/placebo administered as 2 sequential IM injections on Day 1	3441	1731	137 [b] (3, 221)
STORM CHASER, 19 June 2021	300 mg EVUSHELD/placebo administered as 2 sequential IM injections on Day 1	749	372	121 [b] (5, 188)
Study D8850C00001, 06 June 2021	**Cohort 1a:** 300 mg EVUSHELD/placebo administered as 2 sequential IM injections **Cohort 1b:** 300 mg EVUSHELD/placebo administered as 2 sequential IV infusions **Cohort 2**: 1000 mg EVUSHELD/placebo administered as 2 sequential IV infusions **Cohort 3:** 3000 mg EVUSHELD/placebo administered as 2 sequential IV infusions **Cohort 4:** 3000 mg EVUSHELD/placebo administered as IV infusion (co-administration of the 2 mAbs)	50 (10 each cohort)	10 (2 each cohort)	**Cohort 1a and 1b**: 271 days **Cohort 2,3, and 4:** 211 days

[a] Duration of safety follow-up in days, from Day 1 to data cut-off.

[b] Median (min, max).

DCO, data cut-off; IM, intramuscular; IV, intravenous; mAbs, monoclonal antibodies; max, maximum; min, minimum.

Demographics: Phase III Studies

Demographic and other baseline characteristics of the participants are summarised in Table above for PROVENT and STORM CHASER, respectively (please see *Clinical efficacy*).

Across both studies, 4742 (75.1%) participants were recruited from the US (PROVENT 3719 [71.6%], STORM CHASER 1023 [91.3%]), and 1576 (24.9%) were recruited from Europe (including United Kingdom) (PROVENT 1478 [28.4%], STORM CHASER 98 [8.7%]). Overall, the median (min, max) age of participants was 55 (18, 99) years. Most participants were male (53.3%) and white (75.0%).

The study population in PROVENT, when compared to STORM CHASER, comprised participants with a higher median age (57 vs 48 years), a higher proportion who were Black or African American (17.3% vs 10.0%), a lower proportion who were Hispanic or Latino (14.5% vs 57.5%), a higher proportion who had COVID-19 co-morbidities at baseline (67.7% vs 55.8%), a higher proportion who were high risk for developing severe COVID-19 (77.5% vs 64.8%), and a higher proportion who were SARS-CoV-2 RT-PCR negative at baseline (96.3% vs 87.1%).

Demographics: Study D8850C00001

The mean age of Evusheld-treated participants was 39.4 years. Most Evusheld-treated participants were male (32 [64.0%]) and White (34 [68.0%]). The demographic characteristics of the participants were generally balanced between treatment groups and placebo.

Co-morbidities: Phase III Studies

The COVID-19 co-morbidities of study participants in PROVENT and STORM CHASER are presented in the Table 36. For each study, the COVID-19 co-morbidities of the study populations were balanced between treatment groups. Overall, the most frequently reported co-morbidities were history of obesity (42.0%) and history of high blood pressure (33.8%).

Table 36: COVID-19 Co-morbidities Medical History – PROVENT, STORM CHASER, and POOLED

	PROVENT[a]		STORM CHASER[a]		POOLED[b]		
Characteristic	EVUSHELD 300 mg IM (N = 3460) n (%)	Placebo (N = 1737) n (%)	EVUSHELD 300 mg IM (N = 749) n (%)	Placebo (N = 372) n (%)	EVUSHELD 300 mg IM (N = 4210) n (%)	Placebo (N = 2108) n (%)	Total (N = 6318) n (%)
Any COVID-19 Co-morbidities at Baseline	2325 (67.2)	1194 (68.7)	418 (55.8)	207 (55.6)	2744 (65.2)	1400 (66.4)	4144 (65.6)
History of Chronic kidney disease	184 (5.3)	86 (5.0)	16 (2.1)	7 (1.9)	200 (4.8)	93 (4.4)	293 (4.6)
History of Chronic obstructive pulmonary disease (COPD)	179 (5.2)	95 (5.5)	7 (0.9)	12 (3.2)	186 (4.4)	107 (5.1)	293 (4.6)
History of Asthma	378 (10.9)	198 (11.4)	50 (6.7)	27 (7.3)	428 (10.2)	225 (10.7)	653 (10.3)
History of Cystic fibrosis	1 (0.0)	1 (0.1)	0	0	1 (0.0)	1 (0.0)	2 (0.0)
History of scarring in the lungs (pulmonary fibrosis)	6 (0.2)	3 (0.2)	0	0	6 (0.1)	3 (0.1)	9 (0.1)
History of Type 1 diabetes	25 (0.7)	16 (0.9)	1 (0.1)	2 (0.5)	26 (0.6)	18 (0.9)	44 (0.7)
History of Type 2 diabetes	467 (13.5)	227 (13.1)	90 (12.0)	36 (9.7)	557 (13.2)	263 (12.5)	820 (13.0)
History of Sickle cell disease	1 (0.0)	1 (0.1)	1 (0.1)	0	2 (0.0)	1 (0.0)	3 (0.0)
History of Serious heart conditions	272 (7.9)	151 (8.7)	19 (2.5)	14 (3.8)	291 (6.9)	165 (7.8)	456 (7.2)
History of Thalassemia (a blood disorder)	5 (0.1)	1 (0.1)	0	0	5 (0.1)	1 (0.0)	6 (0.1)
History of High blood pressure	1231 (35.6)	637 (36.7)	184 (24.6)	84 (22.6)	1416 (33.6)	720 (34.2)	2136 (33.8)
History of Cerebrovascular diseases	86 (2.5)	45 (2.6)	6 (0.8)	3 (0.8)	92 (2.2)	48 (2.3)	140 (2.2)
History of Obesity-- those with a BMI greater than 30	1474 (42.6)	729 (42.0)	289 (38.6)	160 (43.0)	1763 (41.9)	889 (42.2)	2652 (42.0)
History of Lower immune health because of a solid organ transplant	17 (0.5)	10 (0.6)	0	0	17 (0.4)	10 (0.5)	27 (0.4)
History of Dementia	10 (0.3)	15 (0.9)	0	0	10 (0.2)	15 (0.7)	25 (0.4)
History of Liver disease	149 (4.3)	91 (5.2)	8 (1.1)	2 (0.5)	157 (3.7)	93 (4.4)	250 (4.0)

[a] Full Analysis Set
[b] Safety Analysis Set

BMI, body mass index; COVID-19, coronavirus disease 2019; IM, intramuscular.

2.5.8.2. Adverse events

Overview Adverse Events

Phase 3 studies PROVENT and STORM CHASER

The number (%) of participants with any AE in any category is summarised below:

Table 37: Overall summary of Adverse Events in Any Category (DCO June 2021)

Number of participants with at Least One	Number (%) of Participants					
	PROVENT		STORM CHASER		POOLED	
	EVUSHELD 300 mg IM (N = 3461)	Placebo (N = 1736)	EVUSHELD 300 mg IM (N = 749)	Placebo (N = 372)	EVUSHELD 300 mg IM (N = 4210)	Placebo (N = 2108)
AE	1417 (40.9)	698 (40.2)	229 (30.6)	150 (40.3)	1646 (39.1)	848 (40.2)
SAE	92 (2.7)	42 (2.4)	9 (1.2)	7 (1.9)	101 (2.4)	49 (2.3)
Related[a] SAEs	1 (0.0)	0	0	0	1 (0.0)	0
AE leading to permanent discontinuation of IMP	0	0	0	0	0	0
Related[a] AE leading to permanent discontinuation of IMP	0	0	0	0	0	0
AE leading to study discontinuation	4 (0.1)	1 (0.1)	0	0	4 (0.1)	1 (0.0)
Related[a] AE leading to study discontinuation	0	0	0	0	0	0
MAAE	503 (14.5)	227 (13.1)	64 (8.5)	30 (8.1)	567 (13.5)	257 (12.2)
Related[a] MAAE leading to permanent discontinuation of IMP	0	0	0	0	0	0
AEs with outcome of death	7 (0.2)	5 (0.3)	0	0	7 (0.2)	5 (0.2)
AESI	92 (2.7)	37 (2.1)	5 (0.7)	5 (1.3)	97 (2.3)	42 (2.0)
Related[a] AESI	87 (2.5)	36 (2.1)	3 (0.4)	5 (1.3)	90 (2.1)	41 (1.9)

[a] AEs are determined to be 'related' to IMP and/or study procedures by the Investigators based on their judgement.

AEs are defined as any adverse event that started or worsened in severity on or after the first dose of IMP.

Percentages are based on the number of participants in the analysis set by treatment group (N).

AE, adverse event; AESI, adverse event of special interest; DCO, data cut-off; IM, intramuscular; IMP, investigational medicinal product; MAAE, medically attended adverse event; SAE, serious adverse event,

Source: Table 14.3.1.1.1A, PROVENT CSR in Module 5.3.5.1; Table 14.3.1.1, STORM CHASER CSR in Module 5.3.5.1; and Table 14.3.1.1.1, Pooled Safety in Module 5.3.5.3.

Common Adverse Events

Phase 3 Studies PROVENT and STORM CHASER

Common Adverse Events (AE) of both Phase 3 studies PROVENT and STORM CHASER are presented below in the Table below.

A total of 1646 (39.1%) subjects assigned to Evusheld group and 848 (40.2%) participants in the placebo group reported treatment-emergent AEs. 468 participants, i.e. 327 (7.8%) and 141 (6.7%) in the Evusheld and placebo group, had AEs assessed as possibly related to IMP by the Investigator.

The majority of participants had AEs that were mild to moderate in intensity, with no major differences between PROVENT and STORM CHASER.

Table 38: Number of Participants with Adverse Events, Most Common (frequency of ⩾= 1%), by Preferred Term – Safety Analysis Set, PROVENT, STORM CHASER, and POOLED (June 2021 DCO)

	Number (%) of Participants					
	PROVENT		STORM CHASER		POOLED	
Preferred Term	EVUSHELD 300 mg IM (N = 3461)	Placebo (N = 1736)	EVUSHELD 300 mg IM (N = 749)	Placebo (N = 372)	EVUSHELD 300 mg IM (N = 4210)	Placebo (N = 2108)
Number of participants with at least one AE	1417 (40.9)	698 (40.2)	229 (30.6)	150 (40.3)	1646 (39.1)	848 (40.2)
Headache	227 (6.6)	112 (6.5)	50 (6.7)	36 (9.7)	277 (6.6)	148 (7.0)
Fatigue	163 (4.7)	76 (4.4)	29 (3.9)	22 (5.9)	192 (4.6)	98 (4.6)
Cough	120 (3.5)	63 (3.6)	31 (4.1)	19 (5.1)	151 (3.6)	82 (3.9)
Oropharyngeal pain	109 (3.1)	42 (2.4)	29 (3.9)	16 (4.3)	138 (3.3)	58 (2.8)
Rhinorrhoea	106 (3.1)	41 (2.4)	32 (4.3)	12 (3.2)	138 (3.3)	53 (2.5)
Diarrhoea	105 (3.0)	42 (2.4)	11 (1.5)	14 (3.8)	116 (2.8)	56 (2.7)
Nasal congestion	86 (2.5)	28 (1.6)	25 (3.3)	18 (4.8)	111 (2.6)	46 (2.2)
Nausea	87 (2.5)	37 (2.1)	14 (1.9)	12 (3.2)	101 (2.4)	49 (2.3)
Myalgia	83 (2.4)	35 (2.0)	11 (1.5)	14 (3.8)	94 (2.2)	49 (2.3)
Urinary tract infection	70 (2.0)	33 (1.9)	12 (1.6)	11 (3.0)	82 (1.9)	44 (2.1)
Pain	64 (1.8)	23 (1.3)	16 (2.1)	18 (4.8)	80 (1.9)	41 (1.9)
Arthralgia	66 (1.9)	26 (1.5)	5 (0.7)	1 (0.3)	71 (1.7)	27 (1.3)
Chills	54 (1.6)	30 (1.7)	14 (1.9)	15 (4.0)	68 (1.6)	45 (2.1)
Dyspnoea	54 (1.6)	24 (1.4)	10 (1.3)	7 (1.9)	64 (1.5)	31 (1.5)
Pyrexia	37 (1.1)	31 (1.8)	22 (2.9)	16 (4.3)	59 (1.4)	47 (2.2)
Hypertension	53 (1.5)	26 (1.5)	6 (0.8)	1 (0.3)	59 (1.4)	27 (1.3)
Back pain	50 (1.4)	34 (2.0)	3 (0.4)	4 (1.1)	53 (1.3)	38 (1.8)
Vaccination complication	43 (1.2)	32 (1.8)	0	0	43 (1.0)	32 (1.5)
Vomiting	35 (1.0)	20 (1.2)	8 (1.1)	4 (1.1)	43 (1.0)	24 (1.1)
COVID-19	15 (0.4)	27 (1.6)	18 (2.4)	20 (5.4)	33 (0.8)	47 (2.2)
Pain in extremity	20 (0.6)	19 (1.1)	2 (0.3)	4 (1.1)	22 (0.5)	23 (1.1)

AEs are defined as any AE that started or worsened in severity on or after the first dose of IMP through to the data cut-off.

Most common AEs are defined as AEs that occur with incidence of at least 1% in either treatment group

Percentages are based on the number of participants in the analysis set by treatment group.

PTs are sorted by decreasing order of frequency in EVUSHELD group

Participants with more than one events within a PT are counted only once for that PT.

AEs are coded using MedDRA dictionary version 24.0

AE, adverse event; COVID-19, coronavirus disease 2019; DCO, data cut-off; IM, intramuscular; IMP, investigational medicinal product; MedDRA, Medical Dictionary for Regulatory Activities; N, number of participants in safety analysis set; PT, preferred term,

Individual AE preferred terms are presented below:

Table 39: Number of Participants with Adverse Events and Adjusted by Duration of Follow-up (in 100 participant-years), by Preferred Term – Safety Analysis Set, POOLED (June 2021 DCO)

	Number (%) of Participants, Exposure Adjusted Rate	
	POOLED	
Preferred Term	EVUSHELD 300 mg IM (N = 4210) Exp.[a] = 1563.1	Placebo (N = 2108) Exp.[a] = 779.2
Participants with at least one AE	1646 (39.1), 105.3	848 (40.2), 108.8
Headache	277 (6.6), 17.7	148 (7.0), 19.0
Fatigue	192 (4.6), 12.3	98 (4.6), 12.6
Cough	151 (3.6), 9.7	82 (3.9), 10.5
Rhinorrhoea	138 (3.3), 8.8	53 (2.5), 6.8
Oropharyngeal pain	138 (3.3), 8.8	58 (2.8), 7.4
Diarrhoea	116 (2.8), 7.4	56 (2.7), 7.2
Nasal congestion	111 (2.6), 7.1	46 (2.2), 5.9
Nausea	101 (2.4), 6.5	49 (2.3), 6.3
Myalgia	94 (2.2), 6.0	49 (2.3), 6.3
Urinary tract infection	82 (1.9), 5.2	44 (2.1), 5.6
Pain	80 (1.9), 5.1	41 (1.9), 5.3
Arthralgia	71 (1.7), 4.5	27 (1.3), 3.5
Chills	68 (1.6), 4.4	45 (2.1), 5.8
Dyspnoea	64 (1.5), 4.1	31 (1.5), 4.0
Pyrexia	59 (1.4), 3.8	47 (2.2), 6.0
Hypertension	59 (1.4), 3.8	27 (1.3), 3.5
Back pain	53 (1.3), 3.4	38 (1.8), 4.9
Vomiting	43 (1.0), 2.8	24 (1.1), 3.1
Vaccination complication	43 (1.0), 2.8	32 (1.5), 4.1
COVD-19	33 (0.8), 2.1	47 (2.2), 6.0

[a]: Total duration of exposure for the treatment group. Exposure time is calculated from the first dose date to the end of study date or data cut-off if the participant is ongoing at the time of the data cut-off. Exposure time is converted to patient years by dividing the number of days with 365.25

AEs are defined as any adverse event that started or worsened in severity on or after the first dose of IMP.

AEs are coded using the MedDRA dictionary, version 24.0.

Participants with multiple events in the same preferred term are counted only once in that preferred term. Participants with events in more than one preferred term are counted once in each of those preferred terms.

Percentages are based on the number of participants in the analysis set by treatment group.

Rate adjusted by duration of exposure is calculated with number of participants with the events divided by the duration of exposure (in years) x 100.

AE, adverse event; COVID-19, coronavirus disease 2019; DCO, data cut-off; IM, intramuscular; IMP, investigational medicinal product; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term

Study D8850C00001

At the time of DCO, there were no deaths, SAEs, or AEs resulting in discontinuation of IMP in any participant. One participant in the Evusheld 3000 mg IV group had one AE leading to dose interruption

due to arthralgia and headache. The AEs resolved after stopping the infusion which could be continued after the pause.

TEAE by relationship to IMP

The most frequently reported PTs considered possibly related to IMP by the Investigator were headache (1.6% AZD7442, 1.5% PBO), fatigue (1.1% AZD7442, 1.0% PBO), and injection site pain (0.7% AZD7442, 0.8% for placebo).

TEAE by severity

Small percentages of the overall AEs (2.7%) and SAEs (1.4%) were considered severe without significant differences between the treatment groups.

2.5.8.3. Serious adverse event/deaths/other significant events

Serious Adverse Events

Phase 3 Studies PROVENT and STORM CHASER

Overall, the incidence of SAEs was similar between treatment groups (2.4% AZD7442, 2.3% PBO). One participant reported a SAE of mesenteric artery thrombosis during PROVENT that was assessed possibly related to AZD7442.

In PROVENT, there was a numerical imbalance in SAEs in the Cardiac disorders SOC between the treatment groups. 0.4% in the AZD7442 group and 0.2% in the placebo group experienced events including 11 different PTs. All reported SAEs were considered unrelated to IMP by the Investigator, each 0.1% were considered severe and potentially life threatening, and 0.1% were fatal. Based on medical history at baseline, all participants who experienced cardiac disorder SAEs had cardiac risk factors and/or a prior history of cardiovascular disease at baseline. There was no clear temporal pattern, and a causal relationship between AZD7442 and these events has not been established.

Study D8850C00001.

No SAEs or deaths were reported during Study D8850C00001.

Deaths

Phase 3 studies PROVENT and STORM CHASER (June 2021 DCO)

In PROVENT, a total of 12/6318 (0.2% in each treatment group) participants had an AE leading to death (see table below). In STORM CHASER, there were no AEs with outcome death. In the placebo arm, 2 (0.1%) participants died due to COVID-19 (PTs COVID-19 pneumonia and Acute respiratory distress syndrome), and the causes of death were adjudicated to be related to COVID-19 by an independent committee. None of the AEs leading to death were assessed as possibly related to IMP by the investigator.

Table 40: Deaths and Adverse Events with an Outcome of Death, by Preferred Term – Safety Analysis Set, PROVENT, STORM CHASER, and POOLED (June 2021 DCO) Study D8850C00001

System Organ Class / Preferred Term	Number (%) of Participants					
	PROVENT		STORM CHASER		POOLED	
	EVUSHELD 300 mg IM (N = 3461)	Placebo (N = 1736)	EVUSHELD 300 mg IM (N = 749)	Placebo (N = 372)	EVUSHELD 300 mg IM (N = 4210)	Placebo (N = 2108)
Total number of deaths	7 (0.2)	5 (0.3)	0	0	7 (0.2)	5 (0.2)
Deaths related to COVID-19	0	2 (0.1)[b]	0	0	0	2 (0.1)
Participants with at least one AE with an outcome of death	7 (0.2)	5 (0.3)	0	0	7 (0.2)	5 (0.2)
Cardiac disorders	2 (0.1)	0	0	0	2 (0.0)	0
Arrhythmia	1 (0.0)	0	0	0	1 (0.0)	0
Myocardial infarction	1 (0.0)	0	0	0	1 (0.0)	0
Infections and infestations	1 (0.0)	1 (0.1)	0	0	1 (0.0)	1 (0.0)
COVID-19	0	1 (0.1)	0	0	0	1 (0.0)
Septic shock	1 (0.0)	0	0	0	1 (0.0)	0
Injury, poisoning and procedural complications	2 (0.1)	2 (0.1)	0	0	2 (0.0)	2 (0.1)
Overdose[a]	2 (0.1)	1 (0.1)	0	0	2 (0.0)	1 (0.0)
Toxicity to various agents	0	1 (0.1)	0	0	0	1 (0.0)

[a] Refers to illicit drugs overdose.

[b] Based on the adjudicated cause of death

AEs are defined as any adverse event that started or worsened in severity on or after the first dose of IMP.

AEs are coded using the MedDRA dictionary, version 24.0.

AEs are sorted alphabetically by SOC, and within each SOC, PTs are sorted by decreasing order of total frequency.

Deaths are summarised in the tables above and below. An adjudication committee assessed the relatedness of deaths to COVID-19; the outcomes of these adjudications are included in the tables below.

Between the June 2021 and August 2021 DCOs, 4 participants had an AE with an outcome of death (2 in the Evusheld group and 2 in the placebo group).

Table 41: Deaths and Adverse Events with an Outcome of Death, by SOC and PT – Safety Analysis Set, PROVENT (DCO August 2021)

System Organ Class / Preferred Term	Number (%) of Participants		
	EVUSHELD 300 mg IM (N = 3461)	Placebo (N = 1736)	Total (N = 5197)
Total number of deaths	9 (0.3)	7 (0.4)	16 (0.3)
Deaths related to COVID-19[a]	0	2 (0.1)	2 (0.0)
Participants with at least one AE with an outcome of death	9 (0.3)	7 (0.4)	16 (0.3)
Cardiac disorders	4 (0.1)	0	4 (0.1)
Arrythmia	1 (0.0)	0	1 (0.0)
Cardiac failure congestive	1 (0.0)	0	1 (0.0)
Cardio-respiratory arrest	1 (0.0)	0	1 (0.0)
Myocardial infarction	1 (0.0)	0	1 (0.0)
Hepatobiliary disorders	0	1 (0.1)	1 (0.0)
Hepatic cirrhosis	0	1 (0.1)	1 (0.0)
Infections and infestations	1 (0.0)	1 (0.1)	2 (0.0)
COVID-19	0	1 (0.1)	1 (0.0)
Septic shock	1 (0.0)	0	1 (0.0)
Injury, poisoning and procedural complications	2 (0.1)	2 (0.1)	4 (0.1)
Overdose[b]	2 (0.1)	1 (0.1)	3 (0.1)
Toxicity to various agents	0	1 (0.1)	1 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.1)	1 (0.0)
Malignant neoplasm of unknown primary site	0	1 (0.1)	1 (0.0)
Nervous system disorders	0	1 (0.1)	1 (0.0)
Dementia Alzheimer's type	0	1 (0.1)	1 (0.0)
Renal and urinary disorders	2 (0.1)	0	2 (0.0)
End stage renal disease	1 (0.0)	0	1 (0.0)
Renal failure	1 (0.0)	0	1 (0.0)
Respiratory, thoracic and mediastinal disorders	0	1 (0.1)	1 (0.0)
Acute respiratory distress syndrome	0	1 (0.1)	1 (0.0)

Table 42: Details of Death between DCOs June/August 2021 – PROVENT – Safety Analysis Set

Age/Sex/Race	IMP	Study day	Investigator considered death related to COVID-19	Adjudicated death related to COVID-19	Primary cause of death	Secondary cause of death
98/M/White	AZD7442	202	No	No	Congestive heart failure	Acute cardiac arrest secondary to fatal arrythmia
65/M/White	AZD7442	149	No	No	Cardiopulmonary arrest	Missing
61/M/Black or African American	Placebo	154	No	No	Cancer	No secondary cause available
37/M/White	Placebo	133	No	No	Alcoholism	Missing

[a] While additional details might offer further support, this death is not consistent with COVID-19. There were no symptoms of COVID-19 within 4 days of the participant's death at home and several chronic medical problems which likely contributed included hypertension, chronic kidney disease, fluid overload, and anemia.

Age, in years, is relative to the date of informed consent.

Study day is relative to the first dose of IMP.

DCO: 29 August 2021

COVID-19, coronavirus disease 19; DCO, data cut-off; IMP, investigational medicinal product; M, male.

Source: Listings 16.2.6.2.1B and 16.2.6.2.2B, PROVENT CSR in Module 5.3.5.1

By August 2021 DCO, 2 participants (1 from each group) were reported by the investigator to have discontinued from the study due to an AE. In both cases the AE resulted in death and each are summarised below. In total, 3 deaths were reported between the June 2021 and August 2021 DCOs in STORM CHASER, 2 (0.3%) in the Evusheld group and 1 (0.3%) in the placebo group.

Table 43: Details of Deaths STORM CHASER – Safety Analysis Set, August 2021 DCO

Age/Sex/Race	IMP	Study day	Investigator considered death related to COVID-19	Primary cause of death [a]	Secondary cause of death
92/F/W	AZD7442	137	No	Cerebral ischaemia	Waiting for death certificate [b]
48/M/W	AZD7442	131	No	Metastatic lung cancer	Septic shock secondary to Metastatic squamous cell cancer of lung with metastatic lesions to bone, liver, spleen, and brain
39/F/B	Placebo	187	Unknown	Death	Unknown [b]

[a] PT recorded in Table 14.3.2.6.1B

[b] At database lock, no further information was available.

Age, in years, is relative to the date of signed informed consent.

Study day is relative to the first dose of study drug.

DCO: 19 August 2021

B, black; COVID-19, coronavirus disease 19; DCO, data cut-off; F, female; IMP, investigational medicinal product; M, male; PT, preferred term; W, white.

Source: Module 5.3.5.1 STORM CHASER CSR Table 14.3.2.6.1B and Listing 16.2.6.2B.

2.5.8.4. Laboratory findings

Phase 3 studies PROVENT and STORM CHASER

Haematology

None of the studies showed apparent differences between treatment groups in mean hematology or coagulation parameters over time, or in shifts from normal to high/low in individual parameters. In addition, there were no individual clinically important abnormalities.

Clinical Chemistry

Clinical chemistry parameters (sodium, potassium, urea, creatinine, albumin, calcium, phosphate, glucose, and C-reactive Protein) were measured. None of the studies showed apparent differences between treatment groups in mean clinical chemistry parameters over time, or in shifts from normal to high/low in individual parameters.

Urinalysis

Urinalysis (glucose, protein, and blood) was conducted. None of the studies showed apparent differences between treatment groups in mean urinal analysis parameters over time, or in shifts from normal to high/low in individual parameters.

Other safety findings

Vital signs (BP, pulse rate, oral temperature, and respiratory rate) were measured at different time points. There were no treatment-related effects on vital signs or ECGs observed following administration of Evusheld.

2.5.8.5. In vitro biomarker test for patient selection for safety

N/A

2.5.8.6. Safety in special populations

Intrinsic Factors

The difference between simulated PK profiles (10 trials of 2029 participants) and AUC (0 to 91 days or 3 months and 0 to 270 days or 9 months) for 2 groups, "All weight (36 to 177 kg)" and "Adolescents 40 to 95 kg" have been studied. Overall, derived AUCs are comparable between these 2 groups at 3 and 9 months; hence, a 300 mg IM fixed dose can be considered for a body weight > 40 kg and age ≥ 12 years. Any marginal increase in exposure in these adolescents compared to adults is considered as safe since the exposure safety margin was ~ 33-fold and ~ 62-fold for AUC(0-60) and Cmax, respectively, based on PK data from the Phase I study.

Extrinsic Factors

Based on the mechanism of action, PK/PD results, and AEs presented in the tables, there is no reason to believe that the safety profile of Evusheld will be affected by diet, concomitant medication use or other extrinsic factors.

There are limited data from the use of Evusheld in pregnant women. In line with ICH S6 (addendum), nonclinical reproductive toxicity studies have not been performed with tixagevimab and cilgavimab. In a tissue cross-reactivity study with tixagevimab and cilgavimab using human fetal tissues, no binding was detected. There are no available data on the presence of Evusheld in human milk or animal milk, the effects on the breastfed infant.

A Summary of pregnancies and their outcomes is provided below:

Table 44: Summary on Pregnancy Outcomes

PROVENT

Outcome[a]
Live
Live
Abortion
SAE: Spontaneous abortion (miscarriage)
Not reported
Not reported
Abortion (elective, no medical reason)
Not reported
Not reported

[a] Outcome reported at the time of the Clinical Study Report preparation.

[b] This notification occurred after the August 2021 data cut-off.

Data reported from study start to 06 December 2021.

STORM CHASER

Outcome [a]
Normal (live) birth with no birth defects or anomalies
No outcome yet
Abortion on 17 Feb 21 due to unknown pregnancy risk factor
No outcome yet
No outcome yet

a Outcome reported at the time of the Clinical Study Report preparation.

2.5.8.7. Immunological events

Immunogenicity data relevant for clinical safety was provided with the responses (See Q 132).

The applicant presents immunogenicity data until the latest DCO (August 2021) from 28 participants with cardiac SAEs (23 received AZD7442, 5 PBO) and from 2 subjects with elevated troponin; all were enrolled in PROVENT study. 6/30 subjects were ADA-positive, however, all but one were considered non-treatment-emergent. One patient had an isolated positive low ADA titre at Day 183 after the onset of the cardiac event.

Additionally, non-cardiac thrombotic SAEs were analysed as to increased ADA titres, however, no patient that had been treated with AZD7442 was positive.

Considering the dosing schedule of Evusheld, ADA formation is unlikely and thus, the immunogenic potential is considered low which is in some ways confirmed by the provided, though limited data. There are currently no additional safety issues that would require further analyses related to immunogenicity.

2.5.8.8. Safety related to drug-drug interactions and other interactions

No interaction studies have been conducted. There is a theoretical risk that Evusheld may interfere with COVID-19 vaccines by neutralising antibodies to SARSCoV-2 that are produced in response to vaccination.

Evusheld Interaction with COVID-19 Vaccination

It is expected that a COVID-19 vaccination may be given either before or after administration of Evusheld. Data from animal studies reported that prior Evusheld administration did not alter the cellular or the humoral immune responses elicited by subsequent COVID-19 vaccinations. The available clinical safety data did not reveal any additional safety concerns for the participants who were exposed to Evusheld in PROVENT and STORM CHASER and then subsequently received COVID-19 vaccines. Based on these results, Evusheld is not anticipated to interfere with vaccine safety or efficacy. Although there is no clinical data available on the use of Evusheld following COVID-19 vaccination,

there is no evidence that prior vaccination for other diseases (eg, rabies, hepatitis) impacts the safety or efficacy of subsequent immunoglobulin treatment (Veronese et al 2021).

2.5.8.9. Discontinuation due to adverse events

Phase 3 studies PROVENT and STORM CHASER

During PROVENT, 5 (0.1%) participants were recorded as having discontinued the study, 3 of these participants died and were incorrectly reported as discontinued. A total of 2 participants discontinued the study due to the AEs of Cerebrovascular accident (AZD7442 group) and Alcoholism (placebo group). None of the AEs leading to study discontinuation were assessed as possibly related to IMP by the Investigator.

There were no AEs leading to study discontinuation in STORM CHASER.

Table 45: Number of Participants with Adverse Events Leading to Discontinuation of Study, by System Organ Class and Preferred Term – Safety Analysis Set, PROVENT, STORM CHASER, and POOLED (June 2021 DCO)

	Number (%) of Participants					
	PROVENT		STORM CHASER		POOLED	
System Organ Class / Preferred Term	EVUSHELD 300 mg IM (N = 3461)	Placebo (N = 1736)	EVUSHELD 300 mg IM (N = 749)	Placebo (N = 372)	EVUSHELD 300 mg IM (N = 4210)	Placebo (N = 2108)
Participants with at least one AE	4 (0.1)	1 (0.1)	0	0	4 (0.1)	1 (0.0)
Cardiac disorders	2 (0.1)	0	0	0	2 (0.0)	0
Arrhythmia	1 (0.0)	0	0	0	1 (0.0)	0
Cardiac failure congestive	1 (0.0)	0	0	0	1 (0.0)	0
Nervous system disorders	1 (0.0)	0	0	0	1 (0.0)	0
Cerebrovascular accident	1 (0.0)	0	0	0	1 (0.0)	0
Psychiatric disorders	0	1 (0.1)	0	0	0	1 (0.0)
Alcoholism	0	1 (0.1)	0	0	0	1 (0.0)
Renal and urinary disorders	1 (0.0)	0	0	0	1 (0.0)	0
Renal failure	1 (0.0)	0	0	0	1 (0.0)	0

AEs are defined as any adverse event that started or worsened in severity on or after the first dose of IMP.

AEs are coded using the MedDRA dictionary, version 24.0.

AEs are sorted alphabetically by SOC, and within each SOC, PTs are sorted by decreasing order of total frequency.

Participants with multiple events in the same preferred term are counted only once in that preferred term. Participants with events in more than one preferred term are counted once in each of those preferred terms. Participants with events in more than one preferred term within the same SOC will be counted only once in that SOC.

Percentages are based on the number of participants in the analysis set by treatment group.

AE, adverse event; DCO, data cut-off; IM, intramuscular; IMP, investigational medicinal product; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, System Organ Class

Source: Table 14.3.2.4.1.1A, PROVENT CSR in Module 5.3.5.1; Table 14.3.2.4.1A, STORM CHASER CSR in Module 5.3.5.1; and Table14.3.2.4.1.1, Pooled Safety in Module 5.3.5.3.

2.5.8.10. Post marketing experience

Evusheld was authorised for emergency use in the United States on 08 December 2021, and has since received multiple early access authorizations globally. The first 2 monthly safety reports on Evusheld are available which contain an evaluation of the cumulative safety data from post-authorization/marketing use available up to 31 January 2022.No new safety concerns have been identified and no significant actions relating to safety were taken. Additional data-cuts for the PROVENT and STORM CHASER studies have not been conducted beyond the August data-cut provided in the MAA. Most commonly reported events were headache, fatigue, and COVID-19. Three of the 92 reported events were hypersensitivity, rash, and injection site pain. 21 serious events and 1 fatal

outcome (subarachnoid haemorrhage and brain death in a 25-35-year-old subject 2 days after administration of Evusheld) were reported, moreover 6 serious events of hypersensitivity. Detailed information on the death case are lacking. So far, little post-marketing data is available. Regarding both safety reports, no unexpected safety findings are present apart from the fatal case, however, exact circumstances of the fatal case are too vague to establish a causal relationship. Currently, monitoring within the framework of routine surveillance for Adverse Events is proposed, which is acceptable.

2.5.9. Discussion on clinical safety

The applicant provides pooled safety data from both phase 3 studies PROVENT and STORM CHASER up to August 2021 (second data cut-off). Enrolment was completed at the time of the data cut-offs, however, safety follow-up is currently ongoing. During PROVENT, 5172 patients received IMP (3441 Evusheld and 1731 placebo); the median safety follow-up is 137 days. During STORM CHASER, 1121 patients were dosed (749 Evusheld, 372 placebo) with a median safety follow-up of 121 days. Thus, overall 4210 adult participants received Evusheld 300 mg i.m. in both Phase 3 studies. The pooling strategy is adequate.

Additional safety data from 50 patients dosed during study D8850C00001 are available; the median safety follow-up depending on the cohort is 211-271 days. In total, 4240 study subjects have been exposed to Evusheld.

Evusheld (AZD7442, components: AZD8895/tixagevimab and AZD1061/cilgavimab) is a monoclonal antibody with a non-host target. Considering the half-life of Evusheld, drug exposure is presumed to be sufficiently in all treated subjects after a single administration up to the time of the second data cut-off (see above). As to the size of safety database, there is currently no formal requirement existing with respect to the pandemic situation. The treated patient numbers are however, considered sufficient and further safety data are expected.

Overall, 39.1% participants assigned to the AZD7442 group and 40.2% of those assigned to the placebo (PBO) group experienced at least one treatment-emergent Adverse Event (TEAE) after a single intramuscular administration of both Evusheld components tixagevimab and cilgavimab. A small percentage of study participants, i.e. 2.4% (AZD7442) vs. 2.3% (PBO) reported Serious Adverse Events (SAEs). Few patients discontinued the PROVENT study due to TEAEs. 2.3% (AZD7442) and 2.0% (PBO) of the patients reported Adverse Events of Special Interest (AESI). Approximately every tenth study subject of each group had a medically attended TEAE.

Most frequently reported TEAEs were headache, fatigue and cough with similar percentages regarding the different treatment groups. In both Phase 3 studies, the majority of participants had TEAEs that were mild to moderate in intensity. As to the exposure adjusted TEAE rate, frequencies were comparable between verum and placebo group. As participants were allowed to take concomitant medications for the management of chronic medical conditions and/or for health maintenance, and investigators could prescribe drugs for the management of underlying medical conditions during study participation, it is difficult to disentangle adverse effects.

Subgroup analysis on the intrinsic factors gender, age, race, ethnicity, and specific risk factors as body mass index, renal function or hepatic function were provided with the responses to the LOQ, and do not give rise to specific safety concerns so far; however, overall numbers the analysed categories are limited and should be interpreted with caution. No subgroup analysis based on concomitant

medications was performed. As a variety of concomitant medication for the treatment of prior diseases were used, this may be acceptable.

Serious adverse events (SAE) occurred with a slightly higher frequency during PROVENT (2.7% AZD7442 vs. 2.4% PBO) compared with STORM CHASER (1.2% AZD7442 vs. 1.9% PBO), however, were similar between the treatment groups and no major differences were observed in most SOCs. Within the SOC 'Cardiac disorders', a slight imbalance was observed. Up to the latest DCO (August 2021) in PROVENT, 0.5% of the participants assigned to the AZD7442 group versus 0.2% in the placebo group experienced embolic or thrombotic events; the exposure-adjusted adverse event rate of cardiac disorder SAEs was 1.2 % in the AZD7442 group vs. 0.5% in the placebo group. Most common events in the AZD7442 group were myocardial infarction (n = 5) and acute myocardial infarction (n = 4); one of the myocardial infarction SAEs was fatal and assessed unrelated to the IMP. Additionally, cases with mesenteric artery thrombosis (n=1) and pulmonary embolism (n=1) were reported; in the placebo group, acute myocardial infarction were reported in 2 subjects. In SOC Nervous system disorders, no PTs associated with embolic and thrombotic dominated in either treatment group. During STORM CHASER, 3 participants had embolic and thrombotic events, 2 thereof in the Evusheld group (cerebral ischaemia and deep vein thrombosis), 1 in the placebo group (renal infarct). The study populations of both Phase 3 studies were relatively similar regarding baseline disease characteristics, i.e. 77.5% and 64.8% had any high risk for severe COVID-19 at baseline in PROVENT and STORM CHASER, respectively. The frequencies as to history of obesity (>30 kg/m2), current obesity (>30 kg/m2), diabetes, and smoking were similar. Differences were present regarding pre-existing cardiovascular diseases (8.1% vs. 2.9%), Hypertension (35.9% vs. 23.9%), Asthma (11.1% vs. 6.9%), COPD (5.3% vs. 1.7%), chronic liver disease (4.6% vs. 0.9%), and immunosuppressive treatment (3.2% vs. 0.7%), suggesting that the PROVENT study population might have been more susceptible to adverse events. As requested, the applicant provided a time-to-onset analysis of all cardiac serious adverse events. Here, periods between Evusheld administration and the diverse events varied between 6 and 215 days, 21/23 cases occurred beyond day 45, 16/23 cases had resolved, 4/23 were ongoing, and 3/23 were fatal at data DCO. None of the reported cardiac events were considered related to the study drug. Due to the pre-existing conditions and multiple risk factors, patients had a variety of concomitant medications that render the assessment of treatment effects more difficult. Currently, no further safety data available at this time beyond the second DCO in August 2021. The presented narratives suggest that the reported serious adverse events were most likely associated with the pre-existent medical conditions and multiple risk factors, respectively. Based on the provided clinical data, the mechanism of action, the preclinical findings without observed tissue cross-reactivity, and missing true imbalances between treatment groups, no specific safety concern as to cardiac events are present that would require further regulatory action. Currently, it seems reasonable that cardiac events are monitored as potential risk via routine pharmacovigilance activities. This is reflected in the RMP. However, to address the observations made during PROVENT, a corresponding warning was included in the SmPC.

Potential concerns associated with protein-based infusion therapies include anaphylaxis, hypersensitivity reactions, and infusion-related reactions. Antibody-dependent enhancement of disease is a theoretical risk. Most frequently reported Adverse Events of Special Interest (AESI) were Injection

site reactions (ISR) (2.0% AZD7442 vs. 1.9% PBO). During PROVENT, ISR were more frequent compared with STORM CHASER, however, their occurrence was balanced between verum and placebo within each of the Phase 3 studies. Medically attended adverse events were rarely judged to be IMP-related (0.4% in both AZD7442 and PBO group) and overall balanced across SOCs and PTs, respectively.

Adverse events that were classified as Adverse Drug Reactions (ADR) were Hypersensitivity (1.0% AZD7442 vs. 0.9% PBO) and injection site reactions (1.3% AZD7442 vs. 1.2% PBO) in line with available safety data and the mode of action; their inclusion in the product information is endorsed. Incidences were overall low suggesting a good tolerability.

In PROVENT at 1st DCO, overall 13/5172 (0.3%) patients died; 7/3461 (0.2%) subjects in the AZD7442 and 5/1736 (0.3%) participants in the placebo group died following TEAEs. In the verum group, reasons for death were myocardial infarction, arrhythmia, septic shock, overdose due to illicit drug use, overdose of an unknown substance, end renal stage disease, and unknown but most likely cause kidney failure. In the placebo group, patients died due to COVID-19 (2), dementia, hepatic cirrhosis, cancer of unknown primary site. At 2nd DCO, 4 more cases with fatal outcome were recorded, thereof 2 in the AZD7442 group (congestive heart failure and cardiopulmonary arrest) and 2 in the placebo group (cancer and alcoholism). Additionally, 3 more patients deceased during STORM CHASER, 2 (0.3%) in the AZD7442 group (cerebral ischaemia, lung cancer) and 1 (0.3%) in the placebo group (unknown, report pending). No deaths occurred during Study D8850C00001. None of the deaths were considered related to the study drug. Based on the provided narratives, it seems that the deaths were most likely associated with the underlying health conditions as severe primary diseases and co-morbidities were present in these patients at baseline or the temporal relationship appears implausible.

Immunogenicity data that are relevant for clinical safety were provided with the responses to the LOQ. The applicant presents immunogenicity data until the latest DCO (August 2021) from 28 participants with cardiac SAEs (23 received AZD7442, 5 PBO) and from 2 subjects with elevated troponin; all were enrolled in PROVENT study. 6/30 subjects were ADA-positive, however, all but one were considered non-treatment-emergent. One patient had an isolated positive low ADA titre at Day 183 after the onset of the cardiac event. Additionally, non-cardiac thrombotic SAEs were analysed as to increased ADA titres, however, no patient that had been treated with AZD7442 was positive. Considering the dosing schedule of Evusheld, ADA formation is unlikely and thus, the immunogenic potential is considered low which is in some ways confirmed by the provided, though limited data. There are currently no additional safety issues that would require further analyses related to immunogenicity.

So far, the safety data suggest a tolerable safety profile. The majority of recorded TEAEs may be regarded as symptoms without causal relationship to ATZ7442. However, further long-term data are needed to fully characterize the safety profile.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.5.10. Conclusions on the clinical safety

Overall, the presented safety data suggest that Evusheld is well tolerated in the target population. The safety profile appears favourable and is in accordance with what is expected from a monoclonal antibody directed against an external target.

2.6. Risk Management Plan

2.6.1. Safety concerns

Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	Use in pregnant women

2.6.2. Pharmacovigilance plan

Summary of on-going and planned additional pharmacovigilance activities

Study [Status]	Summary of objectives	Safety concerns addressed	Milestones	Due dates for EMA
Category 1 –– Not applicable				
Category 2 –– Not applicable				
Category 3 - Required additional pharmacovigilance activities				
A post-authorization Observational Study of Women exposed to Evusheld During Pregnancy Study Code:- D8850R00006: **Status:** Planned	To evaluate obstetric, neonatal and infant outcomes among women exposed to AZD7442 during pregnancy	Use in pregnant women	Protocol submission Final report	30/09/2022 31/12/2027

EMA, European Medicines Agency

2.6.3. Risk minimisation measures

Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
None	NA	NA
Important potential risks		
None	NA	NA
Missing information		

Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Use in pregnant women	Routine Risk Minimization Measures: SmPC Section 4.6 and Package Leaflet Section 2	Additional Pharmacovigilance Activities: A post-authorization Observational Study of Women exposed to Evusheld During Pregnancy Final report: 31/12/2027

NA, not applicable; SmPC, Summary of Product Characteristics.

2.6.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 14 November 2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

An updated "Package leaflet User testing" summary report, dated 17 March 2022 was provided by the applicant.

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meet the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Evusheld (tixagevimab / cilgavimab) is included in the additional monitoring list as:

It contains a new active substance which, on 1 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.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The applicant is seeking approval for the use of Evusheld for the **prophylaxis of COVID-19** in adult and adolescent patients ≥12 years and weighing ≥40 kg.

SARS-CoV-2 is the coronavirus responsible for the current COVID-19 global pandemic. Coronavirus entry into host cells is mediated by the transmembrane S glycoprotein that binds to the cellular receptor hACE2 allowing the viral genome to enter and replicate in the cell (Tortorici and Veesler 2019). As the S protein is surface-exposed and mediates the entry into host cells, it is the main target of neutralising antibodies and is the primary target for mAbs and vaccines.

Unlike the majority of coronaviruses that mainly cause mild disease in humans and animals, SARS-CoV-2 can replicate in the lower respiratory tract to cause acute respiratory distress syndrome and fatal pneumonia. The uncontrolled pulmonary inflammation and increased secretion of pro-inflammatory cytokines associated with severe disease is suggestive of a cytokine storm, especially in patients who are critically ill (Huang et al 2020, CDC 2020, Guan et al 2020).

As of 18 March 2022, there have been 464,809,377 confirmed cases of SARS-CoV-2 infection globally with approximately 6,062,536 deaths resulting from infection and subsequent coronavirus disease (COVID-19) as registered by WHO (https://covid19.who.int/ last accessed on 20/3/2022).By region, 191.842.819 cases have been confirmed in Europe.

With a basic reproduction number *R*0 value at the start of the pandemic estimated between 2.43 to 3.10 without medical intervention, SARS-CoV-2 is highly transmissible from person to person, which has contributed to its exponential dissemination worldwide (D'Arienzo and Coniglio 2020). The emergence of more virulent variants (eg, Delta with an *R*0 of 3.2 to 8 [Liu and Rocklöv 2021] and Omicron [*R0* unknown at the time of writing]) is further increasing the rate of spread globally. The Omicron variant is currently the most prevalent variant globally, comprising 71% of all cases sequenced (as of 19 January 2022; GISAID 2022).

The estimated incubation period for COVID-19 is up to 14 days, with a median of 4 to 5 days from exposure to initial onset of symptoms (reviewed in Zhou et al 2020b). The symptoms of COVID-19, if present, differ with severity of disease. The symptoms most frequently associated with symptomatic mild to moderate illness include fever, cough, fatigue, muscle or body aches, headache, sore throat, nasal congestion, shortness of breath or difficulty breathing, nausea, vomiting, diarrhea, and a loss in sense of taste or smell. COVID-19 is a systemic disease affecting not just the respiratory tract but also in myocardial, renal, neurologic, gastrointestinal, and pharyngeal tissues and where hACE2 receptors have been identified (Gupta et al 2020). Patients may progress to severe pneumonia or develop acute respiratory distress syndrome, which is the primary cause for respiratory failure, and direct organ damage by the virus likely contributes to multiorgan failure. Some people who recover from COVID-19

go on to suffer from symptoms long-term. Signs and symptoms of COVID-19 in children are similar to adults but are typically milder. Some paediatric patients who are infected with SARS-CoV-2 never develop symptoms (asymptomatic), with 2 studies (Toba et al 2021) reporting that as many as 19% of PCR-confirmed cases of SARS-CoV-2 infection in children are asymptomatic (Lu et al 2020). Mortality risk factors associated with COVID-19 include age > 60 years (significantly greater for those 80 years and older), male sex, and chronic medical conditions including hypertension, diabetes, obesity, and cardiovascular disease (Zhou et al 2020a).

3.1.2. Available therapies and unmet medical need

Globally, a number of vaccines are authorised for active immunization to prevent COVID-19 caused by SARS-CoV-2. Despite the rollout of these effective vaccines, there remains a clear unmet medical need to provide effective prophylaxis to neutralize SARS-CoV-2 and ensure protection against emerging variants, particularly in those individuals not expected to mount an adequate response to active immunization (CDC 2021a), and those for whom vaccination is not suitable.

As recorded in section 2, several therapeutic options have been approved since the beginning of the pandemic including other monoclonals (please see *Management, section* 2).

While vaccines remain the primary prophylactic approach to COVID-19 the immunogenicity, or the type and magnitude of immune response a vaccine generates over time, is expected to be limited in those who have a weakened immune system compared to the general population. Breakthrough infections of fully vaccinated individuals continue to emerge both in the general population (Hacisuleyman et al 2021) and in high-risk populations such as those patients on immunosuppressants (Geisen et al 2021), patients with hematological malignancy (Agha et al 2021, ACIP 2021), patients who have received a solid organ transplant (Boyarsky et al 2021a, Boyarsky et al 2021b), and dialysis patients (Broseta et al 2021).

Although the recent introduction of a third vaccine dose aims to better protect the immunocompromised, recent data shows that some populations still fail to mount an adequate response, among these, in solid organ transplant patients (Benotmane et al 2021, Schrezenmeier et al 2021), patients with hematological malignancies (Re et al 2021) and those individuals treated with rituximab (Bonelli et al 2021).

An additional unmet need continues for those contraindicated for vaccination, ie, those who have had a severe or immediate allergic reaction after a previous dose or component of the vaccine (CDC 2021b).As an example, anaphylaxis to the first dose is a contraindication to subsequent vaccination. Currently there is no option for some individuals to be fully protected against SARS-CoV-2 infection.

The recent emergence of the Omicron variant (B.1.1.529) in November 2021, which has a larger number of mutations (~30 substitutions, deletions, or insertions) in the spike protein (Torjesen 2021), raises concerns that this variant will escape the protection offered by both vaccines and anti-SARS-CoV-2 mAbs. Thus, an additional mAb product with neutralising activity against Omicron variant wouldbe needed and welcome.

3.1.3. Main clinical studies

Studies supporting the efficacy, safety, PK, and PD of Evusheld in this Application include Phase III Study D8850C00002 (PROVENT), Phase III Study D8850C00003 (STORM CHASER) as well as Phase I FTIH study (Study D8850C00001).

See also Section 2.3 for tabular overview.

Evidence of efficacy was investigated in 2 randomised, double-blind, placebo-controlled phase 3 trials PROVENT and STORM CHASER for the prevention of COVID-19 in pre- and post-exposure prophylaxis setting.

In PROVENT, included participants had a negative SARS-CoV-2 serology test at screening and were:

1. adults ≥ 18 years of age who were candidates expected to benefit from passive immunization with antibodies, defined as having an increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), OR
2. having an increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19, based on available risk assessment at time of enrollment.

STORM CHASER included participants who were SARS-CoV-2 PCR negative or positive at baseline, had a negative SARS-CoV-2 serology test at screening and were:

1. adults ≥ 18 years of age with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed symptomatic or asymptomatic SARS-CoV-2 infection, and who were therefore at appreciable risk of imminently developing COVID-19.

3.2. Favourable effects

The percentage of participants who experienced COVID-19 prior to Day 183 was reduced by Evusheld treatment compared to placebo in the pivotal study PROVENT:

1. Evusheld vs concurrent PBO: 0.2% vs 1.0%;
   RRR (95% CI): 76.73 (46.05, 89.96); p<0.001.

Results from the August 2021 DCO with longer follow-up were consistent with the primary estimand:

2. Evusheld vs concurrent PBO: 0.3% vs 1.8%;
   RRR (95% CI): 82.80 (65.79, 91.35); p<0.001.

The percentage of participants who had a Post-Treatment Response for SARS-CoV-2 Nucleocapsid Antibodies was reduced by Evusheld treatment compared to placebo in the pivotal study PROVENT:

3. Evusheld vs concurrent PBO: 0.7% vs 1.3%
   RRR (95% CI): 51.07 (10.57, 73.23); p=0.020

No cases of severe/critical COVID-19 or COVID-19 related deaths occurred under Evusheld treatment.

3.3. Uncertainties and limitations about favourable effects

As study STORM CHASER failed to meet its primary endpoint, efficacy of Evusheld in the post-exposure prophylaxis setting could not be demonstrated in the chosen population. No treatment effect could be demonstrated in already infected but asymptomatic subjects: SARS-CoV-2 RT-PCR positives at baseline were excluded from the analysis set of the primary endpoint in study PROVENT. No tendency of positive treatment effect in SARS-CoV-2 RT-PCR positives at baseline was seen in the formally failed study STORM CHASER.

The presented results are based on data snapshots from ongoing studies. With the chosen event-driven timing of the primary analysis in both studies, the number of overall COVID-19 cases was too low to allow any conclusion on Evusheld's effect on prevention of disease progression (severe/critical illness or death).

Efficacy result were obtained in non-pregnant, non-breast-feeding, unvaccinated and seronegative adults only. Participants with immunosuppressive disease/treatment were underrepresented.

Various design changes were conducted in the ongoing studies. Some of the participants were unblinded prior to primary endpoint analysis (1933 (36.8%) and 115 (10.2%) had been unblinded in PROVENT and STORM CHASER, respectively at the primary data cut-off).

As for these half-life extended antibodies long-term efficacy data are outstanding, considerations on duration of protection and potential re-dosing are based on modelling and simulations only. In addition, the extent/duration of protection against circulating and newly emerging strains of SARS-CoV-2 is not known. Viral sequencing from phase 3 studies is still ongoing, however, clinical trial data on viral variants are hampered by temporal and geographical limitations of an evolving viral landscape.

3.4. Unfavourable effects

In the pooled safety analysis set, the proportion of subjects with 1 or more TEAE was similar in both treatment groups (39.1% AZD7442 vs. 40.2% PBO). Most frequently reported TEAEs were headache, fatigue and cough; these were overall balanced.

More patients assigned to the verum group had AEs assessed possibly related to IMP by the investigator (7.8% AZD7442 vs. 6.7% PBO). The most frequently reported PTs considered possibly related to IMP by the Investigator were headache (1.6% AZD7442, 1.5% PBO), fatigue (1.1% AZD7442, 1.0% PBO), and injection site pain (0.7% AZD7442, 0.8% PBO).

A slightly higher SAE frequency was observed in the Evusheld group compared with the placebo group during PROVENT (2.7% vs. 2.4%). One related SAE was reported in the Evusheld group (Palpitations). Within the SOC 'Cardiac disorders', a slight imbalance was observed. Up to the latest DCO (August 2021) in PROVENT, 0.5% of the participants assigned to the AZD7442 group versus 0.2% in the placebo group experienced embolic or thrombotic events; the exposure-adjusted adverse event rate of cardiac disorder SAEs was 1.2 % in the AZD7442 group vs. 0.5% in the placebo group.

In PROVENT, a total of 12/6318 (0.2% in each treatment group) participants had an AE leading to death, none of the deaths were considered related to study drug. Death related to COVID-19 only occurred in the placebo group. In the verum group, reasons for death were myocardial infarction (1), arrhythmia (1), septic shock (1), overdose due to illicit drug use (1), overdose of an unknown substance (1), end renal stage disease (1), and unknown but most likely cause kidney failure (1). In the placebo group, patients died due to COVID-19 (2), dementia (1), hepatic cirrhosis (1), cancer of unknown primary site (1). In PROVENT at 2nd DCO 4 more cases with fatal outcome were recorded, thereof 2 in the AZD7442 group (congestive heart failure and cardiopulmonary arrest) and 2 in the placebo group (cancer and alcoholism). Additionally, 3 more patients deceased during STORM CHASER, 2 (0.3%) in the AZD7442 group (cerebral ischaemia, lung cancer) and 1 (0.3%) in the placebo group (unknown, report pending). No deaths occurred during Phase 1 study D8850C00001.

On PROVENT, AESI (anaphylaxis/ other serious hypersensitivity reactions and injection site reactions) occurred with a higher frequency in the Evusheld group compared to the placebo group (2.7% AZD7442 vs. 2.1% PBO) mainly due to injection site reactions. This phenomenon was not observed in the STORM CHASER study population.

More AEs leading to study discontinuation were reported in the Evusheld group of the PROVENT study

3.5. Uncertainties and limitations about unfavourable effects

The overall frequency of treatment-emergent adverse events was balanced between the treatment groups of PROVENT study, lower in the verum group of STORM CHASER when compared with placebo

and balanced regarding the pooled safety data. The majority of participants had AEs that were mild to moderate in intensity, with no major differences between PROVENT and STORM CHASER.

The most frequently reported PTs considered possibly related to IMP by the investigator were balanced between the treatment groups of the pooled safety data.

The majority of participants (77.5%) had pre-existing medical conditions and multiple comorbidities such as hypertension, cardiac diseases, obesity, diabetes etc. Since participants were allowed to take concomitant medications for the management of chronic medical conditions and/or for health maintenance, treatment effects are difficult to disentangle.

AESI were balanced between both studies (2.0% AZD7442 vs. 1.9% PBO). Medically attended adverse events were also balanced between treatment groups and studies (13% each).

Very few AEs resulted in study discontinuation.

The available data (*in vitro*, non-clinical, clinical) do not raise a concern regarding antibody-dependent disease enhancement for the time being. Available clinical data on anti-drug antibody formation after Evusheld administration is currently limited.

No clinical data is available for adolescent participants.

3.6. Effects Table

Table 46: Effects Table for Evusheld in Prevention of COVID-19 (primary DCO).

Effect	Short Description	Unit	Evusheld	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
COVID-19 prior to day 183	Percentage of subjects meeting the endpoint definition	%	0.2	1.0	RRR (95% CI): 76.73 (46.05, 89.96) p< 0.001 Unknown transferability on emerging viral variants. This analysis excludes PCR-positive subjects	PROVENT Pre-exposure study
COVID-19 prior to day 183	Percentage of subjects meeting the endpoint definition	%	3.1	4.6	RRR (95% CI): 33.31 (-25.92, 64.68) p-value 0.212 Formally failed. No treatment effect in already infected subjects.	STORM CHASER Post-exposure study
Nucleo-capsid anti-bodies prior to day 183	Percentage of subjects meeting the endpoint definition	%	0.7	1.3	RRR (95% CI): 51.07 (10.57, 73.23) p-value 0.020 Unknown transferability on emerging viral variants.	PROVENT Pre-exposure study
Progressi on to severe/ critical illness	Number of subjects meeting the endpoint definition	n	0	2	Not interpretable	PROVENT and STORM CHASER

Effect	Short Description	Unit	Evusheld	Control	Uncertainties/ Strength of evidence	References
COVID19-related deaths	Number of subjects	n	0	0	Not interpretable	PROVENT and STORM CHASER
Unfavourable Effects						
TEAE frequency	Percentage of subjects with at least one treatment-emergent adverse events	%	39.1	40.2	Very limited or no data in adolescents, SARS-CoV2-vaccinated subjects, pregnant/lactating females; Limited data on immunogenicity	Pooled safety data PROVENT & STORM CHASER
SAE frequency	Percentage of subjects with at least one treatment-emergent serious adverse events	%	2.4	2.3	idem	Pooled safety data PROVENT & STORM CHASER
Related SAE frequency	Percentage of subjects with at least one treatment-related serious adverse events	%	0	0	idem	Pooled safety data PROVENT & STORM CHASER
AESI frequency	Percentage of subjects with at least one treatment-emergent adverse events of special interest	%	2.3	2.0	idem	Pooled safety data PROVENT & STORM CHASER
Anaphylaxis	Percentage of subjects with at least one of this treatment-emergent adverse event	%	0	0	idem	Pooled safety data PROVENT & STORM CHASER
Hypersensitivity reactions	Percentage of subjects with at least one of this treatment-emergent adverse event	%	1.0	0.9	idem	Pooled safety data PROVENT & STORM CHASER
Injection site reaction	Percentage of subjects with at least one of this treatment-emergent adverse event	%	2.0	1.9	idem	Pooled safety data PROVENT & STORM CHASER
Injection related reaction	Percentage of subjects with at least one of this treatment-emergent adverse event	%	0.2	0.3	idem	Pooled safety data PROVENT & STORM CHASER

Abbreviations: DCO=data cut-off; RRR=relative risk reduction, TEAE: treatment-emergent adverse event, SAE: serious adverse event, AESI: adverse event of special interest

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The chosen primary and secondary endpoints are considered appropriate to investigate the efficacy of Evusheld in the intended target population that is in a need of passive immunization with antibodies. Thus, obtained results are deemed clinically relevant in relation to the target disease.

Concerning the primary endpoint of PROVENT, Evusheld demonstrated a statistically significant effect with relevant effect size in a pre-exposure prophylaxis setting. The key supportive analyses confirmed the significance of the results related to the primary endpoint. The results of the key secondary endpoint, as a measure of prevention of SARS-CoV-2 infection (symptomatic and asymptomatic), can be considered confirmatory. In the analysed subgroups, including age, sex, race, ethnicity, COVID-19 co-morbidities at baseline, high risk for severe COVID-19 at baseline, and various individual risk factors for COVID-19, subjects assigned to the Evusheld group tended to experience fewer events compared to the PBO group.

Potential bias resulting from inadequate planning and partial unblinding could not all entirely be ruled out but did not have the potential to impact study results to an extent that would make the entire conclusion on efficacy questionable.

As STORM CHASER study did not meet its primary endpoint, efficacy of Evusheld in the post-exposure prophylaxis setting could not be demonstrated in the chosen population. Results do not support the general prophylactic administration of Evusheld irrespective of exposure. Furthermore, due to inconclusive data obtained in the small amount of PCR positive subjects in studies PROVENT and STORM CHASER there remains a minor residual risk for already SARS-CoV-2 infected asymptomatic patients. Considering results of both confirmatory studies, no databased statement can be made on Evusheld's effect on prevention of disease progression, as the number of overall COVID-19 cases was too low to allow any conclusion. Otherwise, considering the totality of available information that might support efficacy results of the confirmatory studies, it is acknowledged that a broad indication statement might also be appropriate in the given context. Such considerations might consider the theoretical assumption that viral load reduction may be beneficial for both, clinical outcome and transmission rates, as well as knowledge gained with other anti-SARS-CoV-2 mAbs.

Lacking efficacy data in adolescents ≥40 kg may be compensated by available popPK modelling: based on PK extrapolation, a dose of 300 mg Evusheld IM is expected to achieve similar exposure (AUC) as in adults. Based on theoretical considerations, adolescents are expected to profit from prophylactic treatment in a similar way like adult patients. Currently available data and theoretical considerations did not identify specific safety issues.

As clinical trial data for previously SARS-CoV-2 vaccinated and/or seropositive individuals are lacking, treatment decisions or timing of such decisions will need to be based on local/national guidelines. No specific safety issues are expected in the groups of vaccinated and/or seropositive patients.

Although immunosuppressed participants (by disease or treatment) were underrepresented in the study population, a safety profile comparable to overall population is expected.

Treatment of pregnant women was currently not investigated in the clinical trial setting. Lack of cross-reactivity in human foetal tissues suggests low risk to developing foetuses in pregnant women administered Evusheld. Nevertheless, currently available information without any clinical data is too limited to make a general treatment recommendation. Use in pregnancy is subject to Additional Pharmacovigilance Activities.

Based on biological plausibility no risk for the breastfed infant is anticipated. Treatment in breast feeding women may be considered when clinically indicated.

A single dose of Evusheld was well tolerated, with a safety profile mainly comparable to placebo. The risk of hypersensitivity is adequately addressed in the product information and is supposed to be manageable with the given precautionary measures. Although the knowledge about ADA formation and potentially associated risks is limited at present, the safety risk due to clinically relevant ADA response is assumed to be low based on the mechanism of action and dosing schedule. The data of *in vitro* and *in vivo* studies pose minimal theoretical risk for mediating ADE.

Overall, the safety profile of Evusheld appears favourable and in line with what is expected from a monoclonal antibody with an exogenous target i.e. viral target and thus without intrinsic activity.

An overall suitable popPK model was used to predict long-term PK. Predictions were confirmed by 1-year PK data available from the phase I study. However, dose justification and predicted duration of protection were based on SARS-CoV-2 original strain. As no clinical efficacy data will be obtained for recent/upcoming viral variants, estimates on efficacy will need to rely on *in vitro* information and modelling/simulations. Post authorisation, the applicant will gain latest information on Evusheld antiviral activity against circulating virus strains in the EU by monitoring of viral sequence data bases followed by prompt testing of variants of interest in established *in vitro* systems. As part of Routine Pharmacovigilance Activities, the applicant will be evaluating available data on breakthrough infections due to emerging variants from spontaneous cases, clinical trial data, and literature. Thus, potential loss of efficacy due to emerging spike variants will be manageable post authorisation.

3.7.2. Balance of benefits and risks

The demonstrated effect of a single Evusheld dose in the prevention of COVID-19 in a pre-exposure prophylaxis setting is considered clinically relevant.

A single dose administration of Evusheld demonstrated a good safety profile with a manageable risk of hypersensitivity that does not raise a specific concern.

Although most of the pregnant women with COVID -19 infection will recover without complications, some studies have shown an increased risk of severe COVID-19 in pregnant women when compared with nonpregnant women (Zambrano et al, 2020). However, the overall data presented are not sufficient to make a general recommendation for use of Evusheld in this population. An individual benefit-risk appraisal appears appropriate.

Overall, the favourable effects outweigh the unfavourable effects.

3.8. Conclusions

The overall benefit/risk balance of Evusheld is positive, post authorisation measures are defined as recommendations

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Evusheld is favourable in the following indication(s):

EVUSHELD is indicated for the pre-exposure prophylaxis of COVID-19 in adults and adolescents aged

12 years and older weighing at least 40 kg (see sections 4.2, 5.1 and 5.2).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that tixagevimab and cilgavimab are to be qualified as new active substances in themselves as they are not constituents of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0235/2021 and P/0236/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. Appendix

List of Recommendations

Recommendations:

Description	Recommended within Proc. No
1. The applicant is recommended to provide biochemical hold time stability data for cilgavimab intermediates once the study is completed	EMEA/H/C/5788/RR/001
2. The applicant is recommended to provide the results of the chromatography resin lifetime studies once they are available. This recommendation applies to both active substances	EMEA/H/C/5788/RR/001
3. The applicant is recommended to provide the results of the reprocessing of the virus filtration and 0.2 micron filtration studies when they become available. This recommendation applies to both active substances.	EMEA/H/C/5788/RR/001
4. The applicant is recommended to provide degradation profiles for the ongoing comparability study for the LB Process 2 material as they become available. This recommendation applies to both active substances	EMEA/H/C/5788/RR/001
5. Regarding the potency assay, the applicant is recommended to recalculate the tolerance intervals used to assess process variability for the Stability Limits Approach and Non-Stability Limits Approach once 30 DS batches are available. This recommendation applies to both active substances.	EMEA/H/C/5788/RR/001
6. The applicant is recommended to recalculate the acceptance criteria for Target Binding Potency Assay once 30 DS batches are available. This recommendation applies to both active substances.	EMEA/H/C/5788/RR/001
7. The applicant is recommended provide the final results of the elemental impurities risk assessment as soon as they become available. This recommendation applies to both active substances	EMEA/H/C/5788/RR/001
8. Revision of DS HCP acceptance limits on the basis of batch results is recommended for both cilgavimab and tixagevimab. .	EMEA/H/C/5788/RR/001
9. The applicant is recommended to provide the updated analysis for the multivariate DP formulation characterisation study by June 2022. This recommendation applies to both finished products	EMEA/H/C/5788/RR/001
10. As the robustness study was conducted during method development and not with the analytical validation, the applicant will not incorporate the robustness data into the validation section. This does not stand in contradiction to the guidance of ICHQ2. However, robustness study data are recommended to be inserted	EMEA/H/C/5788/RR/001

Description	Recommended within Proc. No
into an appropriate section of the dossier, e.g. S.2.6 by Q3 2022. This recommendation applies to both active substances.	
11. The applicant is recommended to list the reference IDs of the in-house method documents in Sections 3.2.S.4.1 and 3.2.P.5.1. .	EMEA/H/C/5788/RR/001
12. For the simulated leachables study on the active substance container, results beyond 6 months for the 2–8°C and 23–27°C conditions are recommended to be submitted as soon as they are available, This recommendation applies to both active substances.	EMEA/H/C/5788/RR/001
13. Information about the area of the sterilising filter should be stated in Module 3.2.P.3.3 of the dossier according to the Guideline on the sterilisation (EMA/CHMP/CVMP/QWP/850374/2015). This recommendation applies to both finished products	EMEA/H/C/5788/RR/001
14. From the data provided it is concluded that the method seems suitable to quantify AZD8895 and AZD1061 in human serum. Summary information on sample storage, dilutions, performance of analytical runs and incurred sample re-analysis for PROVENT and STORM CHASER should be provided when available. .	EMEA/H/C/5788/RR/001
15. During the covariate exploratory analysis, scatter plots highlighting possible relationships between continuous covariates is shown as well as some box plots displaying possible relationships between selected categorical and continuous covariates. However, the latter is incomplete. Of particular interest is the correlation between diabetes and bodyweight because the 2 covariates are retained on the same PK parameter in the final model. The box plot shows a correlation between diabetes and body weight with higher body weight in diabetes patients compared to non-diabetes. Both body weight and diabetes were statistically significant covariates on CL. However, no dose adaptations was proposed for diabetes and the allometric exponent were fixed for bodyweight effect on CL. Hence, the inclusion of both body weight and diabetes as covariates on CL is not an issue for the current popPK model. Issue will be followed in updated versions of the popPK model. .	EMEA/H/C/5788/RR/001
16. In some figure provided it has been shown a correlation between bodyweight and sex. Given this the applicant should discuss the appropriateness of retaining both sex and bodyweight as covariates on the CL and V in the final model. However, no dose adaptations was proposed for sex and the allometric exponent were fixed for bodyweight effect on CL. Hence, the inclusion of both body weight and sex as covariates on CL and V is not an issue for the current popPK model. However, the issue will be followed in updated versions of the popPK model that should be provided. .	EMEA/H/C/5788/RR/001
17. The applicant was asked to provide a sensitivity analysis excluding these subjects from study PROVENT that are showing so far unexplained "up and down PK profiles" low concentrations followed by an increase at later time points) from popPK model. As there are remaining issues to be addressed with updated versions of pop PK modelling, and the bioanalytical final reports from PROVENT are	EMEA/H/C/5788/RR/001

Description	Recommended within Proc. No
still pending, this issue should also be readdressed with respect to PK data inclusion and final conclusions on covariates, in particular weight effects.	
18. Viral load/viral shedding results from infected subjects in PROVENT are pending and once available, AstraZeneca will update the VDM with these viral load data and try to correlate viral dynamics with clinical outcomes. The updated VDM and outcomes should be provided.	EMEA/H/C/5788/RR/001
19. The applicant is asked to provide results from PRNT50 pseudovirus assays development and validation (expected Q2 2022), when available. In this line, evaluation of relevant clinical trial samples should be provided as well. .	EMEA/H/C/5788/RR/001
20. Due to the indicated reduced time of protection regarding Omicron BA.1, BA.1.1 and BA.2, a need to adapt the posology either in terms of dose strength or more frequent dosing might be necessary. The applicant is asked to still provide results of probability of target attainment (PTA) and simulations of the following (worst case) scenarios for all three Omicron variants: a. Target serum concentration needed to reach IC80 and IC90 should be documented, together with % of subjects above MPC following a single dose 300 mg and 600 mg Evusheld IM at 1, 2, 3, 4, 5 and 6 months post dose. IC90 should be used as PD target, unless an updated version of the viral dynamic model is provided with acceptable fitting performances on data from the PROVENT and STORM CHASER studies. This should be simulated based on the following assumptions for sensitivity considerations: Lung partition coefficients: 6.5% and 12%; mean and highest IC50 value per strain, reflecting inter-experiment variability. Of note, similar simulations may become relevant in case new VOCs needs to be considered. In this case, this should be provided. Data to be provided once this situation applies. b. The results of PTA should be provided separately for the different quartiles of body weights, with clear indication of % of persons remaining above the minimum protective concentrations (IC90 and 6.5% partition coefficient should be used. Simulations focussing on bodyweight quartiles have not been conducted with the highest MPC (4.8 µg/ml) for the BA.2 strain. Thus, it could not be precluded that the duration of protection patients at high weight (>95 kg) is reduced to a clinically relevant level (also for original strains). This issue thus remains to be addressed (with potential consequences for SmPC statement, Section 5.2).	EMEA/H/C/5788/RR/001
21. The updated Version of the popPK model together with the outstanding issues on PK modelling and data inclusion are expected in Q3 2022 (REC15-REC17). Depending on the data and re-analysis of covariates, the inclusion of weight effect on PK might be relevant to be re-addressed.	EMEA/H/C/5788/RR/001

Description	Recommended within Proc. No
22. Data from interim analysis on the first 50 participants from a PROVENT sub-study (multiple dosing) should be provided.	EMEA/H/C/5788/RR/001
23. Final PROVENT, STORM CHASER and Phase I FTIH study (D8850C00001) CSRs should be provided as soon as available.	EMEA/H/C/5788/RR/001