Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

National Procedure

EVUSHELD 150 mg / 150 mg solution for injection
tixagevimab, cilgavimab

PLGB 17901/0360

ASTRAZENECA UK Limited

LAY SUMMARY

EVUSHELD 150 mg / 150 mg solution for injection
tixagevimab, cilgavimab

This is a summary of the Public Assessment Report (PAR) for EVUSHELD 150 mg / 150 mg solution for injection. It explains how this product was assessed and the authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as EVUSHELD in this lay summary for ease of reading.

For practical information about using EVUSHELD, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is EVUSHELD and what is it used for?
This application is a full-dossier application. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that this medicine is suitable for use in the specified indications.

EVUSHELD is used to help prevent COVID-19 infection in adults who are not currently infected with COVID-19 and who have not been recently in contact with someone who has COVID-19 (known as 'pre-exposure prophylaxis') when they:
- are unlikely to be protected by a COVID-19 vaccine
- or when vaccination is not recommended

EVUSHELD is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended.

How does EVUSHELD work?
EVUSHELD is made up of two active substances, tixagevimab and cilgavimab. These are both medicines called antiviral monoclonal antibodies. They work specifically against SARS-CoV-2, the virus that causes COVID-19. They prevent the virus from entering human cells.

How is EVUSHELD used?
The pharmaceutical form of this medicine is solution for injection and the route of administration is injection.

The recommended dosage is 300 mg of EVUSHELD, as 150 mg of tixagevimab and 150 mg of cilgavimab administered as separate sequential intramuscular injections.

A higher dose of 600 mg of EVUSHELD, as 300 mg of tixagevimab and 300 mg of cilgavimab, may be more appropriate for some SARS-CoV-2 variants based on *in vitro* neutralisation susceptibility data which show reduced susceptibility for EVUSHELD (see section 4.8 and 5.1 of the Summary of Product Characteristics, SmPC).

For further information on how EVUSHELD is used, refer to the PIL and SmPC available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning the medicine.

What benefits of EVUSHELD have been shown in studies?
EVUSHELD has been studied in an ongoing Phase III, randomised (2:1), double-blind, placebo-controlled clinical trial for the pre-exposure prophylaxis of COVID-19 in adults aged ≥18 years. In the study, participants who took EVUSHELD had a reduced risk of SARS-CoV-2 RT-PCR-positive symptomatic illness (COVID-19) when compared to placebo with a relative risk reduction (RRR) of 77% (95% CI: 46-90; p-value (two-sided) <0.001). Among participants who received EVUSHELD there were no severe/critical COVID 19 events compared to one event (0.1%) among participants who received placebo.

What are the possible side effects of EVUSHELD?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

The most common side effects with EVUSHELD (which may affect up to 1 in 10 people) are hypersensitivity reaction (rash or an itchy red rash or raised bumps) with 300 mg dose and injection site reaction (pain, redness, itching, swelling near where the injection was given).

Why was EVUSHELD approved?
EVUSHELD has been shown to be effective in the prevention of COVID-19 infection in adults who are not currently infected with COVID-19 and who have not been recently in contact with someone who has COVID-19 when they:
- are unlikely to be protected by a COVID-19 vaccine
- or when vaccination is not recommended

Furthermore, the side effects observed with use of this product are considered to be typical for this type of treatment. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that this medicine can be approved for use to prevent symptomatic COVID-19 infection.

EVUSHELD has been authorised with a Conditional Marketing Authorisation (CMA). CMAs are intended for medicinal products that address an unmet medical need, such as a lack of alternative therapy for a serious and life-threatening disease. CMAs may be granted where comprehensive clinical data are not yet complete, but it is judged that such data will become available soon.

What measures are being taken to ensure the safe and effective use of EVUSHELD?
As for all newly authorised medicines, a Risk Management Plan (RMP) has been developed to ensure that EVUSHELD is used as safely as possible. The RMP details the important risks of EVUSHELD, how these risks can be minimised, any uncertainties about EVUSHELD (missing information), and how more information will be obtained about the important risks and uncertainties.

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professional will be monitored and reviewed continuously.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about EVUSHELD
A Marketing Authorisation for EVUSHELD was granted in Great Britain (GB, consisting of England, Scotland and Wales) on 17 March 2022.

The full PAR for EVUSHELD follows this summary.

This summary was last updated in July 2022.

TABLE OF CONTENTS

I INTRODUCTION 6
II QUALITY ASPECTS 8
III NON-CLINICAL ASPECTS 16
IV CLINICAL ASPECTS 16
V USER CONSULTATION 83
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION 83
TABLE OF CONTENT OF THE PAR UPDATE 87

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for EVUSHELD 150 mg / 150 mg solution for injection (PLGB 17901/0360) could be approved.

The product is approved for the following indication: pre-exposure prophylaxis of COVID-19 in adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 and:

- Who are unlikely to mount an adequate immune response to COVID-19 vaccination or
- For whom COVID-19 vaccination is not recommended.

The active substances are tixagevimab and cilgavimab.

Tixagevimab and cilgavimab are recombinant human IgG1κ monoclonal antibodies, with amino acid substitutions in the Fc regions to extend antibody half-life (YTE) and to reduce antibody effector function and potential risk of antibody-dependent enhancement of disease (TM). Tixagevimab and cilgavimab can simultaneously bind to non-overlapping regions of the spike protein receptor binding domain (RBD) of SARS-CoV-2. Tixagevimab, cilgavimab and their combination bind to the spike protein RBD with equilibrium dissociation constant (KD) values of 2.76 pM, 13.0 pM and 13.7 pM, respectively, blocking its interaction with the human angiotensin-converting enzyme 2 (ACE2) receptor, the SARS-CoV-2 receptor, which is required for viral attachment to target cells. Tixagevimab, cilgavimab and their combination blocked RBD binding to the human ACE2 receptor with IC_{50} values of 0.32 nM (48 ng/mL), 0.53 nM (80 ng/mL) and 0.43 nM (65 ng/mL), respectively.

This application was approved under Regulation 50 of The Human Medicines Regulation 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended), a full-dossier application. All non-clinical safety data submitted were from studies conducted in accordance with Good Laboratory Practice (GLP). All clinical data submitted were from studies conducted in accordance with Good Clinical Practice (GCP).

This product has been authorised as a Conditional Marketing Authorisation (CMA). CMAs are granted in the interest of public health and are intended for medicinal products that fulfil an unmet medical need and the benefit of immediate availability outweighs the risk posed from less comprehensive data than normally required. Unmet medical needs include, for example, treatment or diagnosis of serious and life-threatening diseases where no satisfactory treatment methods are available. CMAs may be granted where comprehensive clinical data are not yet complete, but it is judged that such data will become available soon. Adequate evidence of safety and efficacy to enable the MHRA to conclude that the benefits are greater than the risks has been provided for EVUSHELD. The CMA for EVUSHELD, including the provision of any new information, will be reviewed every year and this report will be updated as necessary.

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a paediatric investigation plan (PIP) {P/0235/2021 and P/0236/2021}

At the time of the submission of the application the PIP was not yet completed as some measures were deferred.

The MHRA has been assured that acceptable standard of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) in January 2022 regarding data requirements for quality, efficacy, indications, dose and use in omicron/immunocompromised patients. These issues were resolved at the CHM meeting in March 2022.

A national marketing authorisation was granted in Great Britain (GB, consisting of England, Scotland and Wales) on 17th March 2022.

II QUALITY ASPECTS

II.1 Introduction

This product consists of a clear to opalescent, colourless to slightly yellow solution for injection presented in two vials: one containing 150 mg of tixagevimab in 1.5 mL (100 mg/mL); and one containing 150 mg of cilgavimab in 1.5 mL (100 mg/mL).

In addition to tixagevimab and cilgavimab, this product also contains the excipients histidine, histidine hydrochloride monohydrate, sucrose, polysorbate 80, and water for injections.

The finished product is packaged in two identical vials, one vial containing tixagevimab and one containing cilgavimab. The vials are composed of Type I clear glass closed with a chlorobutyl elastomeric stopper sealed with an aluminium flip-off top. The pack size is such that each carton of EVUSHELD contains 1 vial each of tixagevimab and cilgavimab.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCES

Tixagevimab
rINN: tixagevimab
Chemical Name: Not assigned

Structure: Tixagevimab is a human IgG1κ monoclonal antibody directed against the receptor binding domain (RBD) in spike (S) protein of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Tixagevimab is composed of two identical heavy chains and two identical light chains. The antibody was engineered to contain two sets of three amino acid substitutions that are referred to as TM (triple mutation) and YTE. The TM substitutions include: a leucine to a phenylalanine at residue 240, a leucine to a glutamic acid at residue 241, and a proline to a serine at residue 337. The YTE substitutions include: a methionine to a tyrosine at residue 258, a serine to a threonine at residue 260, and a threonine to a glutamic acid at residue 262. The YTE substitutions were introduced to enhance affinity to neonatal Fc receptor (FcRn) and therefore extend serum half-life. Tixagevimab has primarily N-linked biantennary complex-type glycans attached to each heavy chain.

Molecular weight: Approximately 149 kDa (including glycosylation).

Appearance: slightly opalescent and slightly yellow liquid

Tixagevimab is not the subject of a European Pharmacopoeia monograph.

Manufacturing process
A process flow diagram summarizing the manufacturing process, as well as the material inputs, critical and non-critical process parameters, and process outputs (in-process controls, microbial controls, and performance attributes) is provided and is acceptable. The manufacturing process has been well described; briefly, this consists of working cell bank (WCB) vial thaw, inoculum expansion in shake flasks and rocker bags, seed bioreactor(s) for further expansion of inoculum, before culture in production bioreactor(s) to generate tixagevimab, followed by harvest of the conditioned medium. The clarified conditioned medium containing tixagevimab is further processed through a series of purification steps,

designed to remove product-related and process-related impurities, with two dedicated virus clearance steps. The tixagevimab is then concentrated, formulated and sterile filtered to generate the Drug Substance.

Control of materials
The raw materials are purchased from Quality-approved suppliers according to approved procedures. Materials are inspected upon receipt, and supplier certificates of analysis are reviewed. These raw materials are tested and released according to approved specifications and require a minimum of appearance and identification testing. Specification changes follow quality change control procedures prior to implementation. Raw materials used in the manufacturing process for the master cell bank (MCB), working cell bank (WCB) and drug substance, including excipients, are described with the stages of the process in which they are used and quality standards. The quality standards listed are applicable for commercial drug substance and the generation of any future commercial cell bank.

No materials of human origin were used in host cell culture, cell line development, banking of the MCB and WCB, or in drug substance manufacturing.

Materials of animal origin used in cell line development, and materials of animal and other (non-animal) biological origins used in cell banking and the drug substance manufacturing process have been described. A TSE/BSE risk assessment and available certificates for relevant animal-derived materials (animal origin or biological origin manufactured using animal components) have been provided and are acceptable.

One material of animal origin (dialyzed foetal bovine serum, dFBS) was used in culturing the AstraZeneca CAT-S host cell line prior to cell line development. No material of animal origin was used in development of the manufacturing cell line after host cell culture.

No materials of animal origin were used in the preparation of the cell banks or in the manufacturing process. In addition, no animal-component-free materials that were manufactured using animal-derived material (material does not directly contain animal-derived material) were used in the preparation of the cell banks or in the manufacturing process.

The cell substrate has been adequately described and is satisfactory. Preparation of the cell banks has also been well described, as has their testing and stability.

Controls of critical steps and intermediates
Microbial controls (MCs) are in-process bioburden and endotoxin measurements used to demonstrate microbial control of the manufacturing process.

Bioburden and endotoxin action limits for process intermediates tested at the commercial manufacturing facilities have been provided and are acceptable.

Hold times for process intermediates have been validated and a commercial scale study has demonstrated effective microbial control during the hold times. All validation studies are complete. Justifications for the overall validated hold times have been provided and are acceptable.

Process validation and/or evaluation
The process is defined and validated through several stages: process design, process qualification (validation) and continued process verification. Validation has been performed

on several lots at the drug substance manufacturing sites and these were successfully validated through the entire process to drug substance.

Any deviations observed during process validation were evaluated and, upon resolution, determined to have no impact on the conclusions of the process validation. Details of deviations and qualification summary reports have been provided. In addition to the validation of the manufacturing process steps at the commercial scale, validation studies are being conducted at small scale and commercial scale to address a number of other manufacturing considerations.

Manufacturing process development
A summary of the manufacturing process development has been provided which describes the development of the process used to manufacture the drug substance and the rationale for the control strategy of the commercial process.

Two manufacturing processes were used during the development of tixagevimab: Process 1 (used for nonclinical toxicology and clinical manufacturing) and Process 2 (used for both clinical and commercial manufacturing). A comparison of the process flow diagrams for each process has been provided and is satisfactory. Each process has been adequately described. Lot release, characterization, and degradation trend and profile test results from the drug substance comparability testing demonstrate that Process 1 and 2 clinical lots are comparable to Process 2 commercial lots at the drug substance manufacturing sites.

Process characterisation has provided reassurance that the control strategy for tixagevimab is adequate to ensure that critical quality attributes (CQAs) of drug substance are within acceptable ranges, in order to maintain product consistency.

Characterisation
Adequate details have been provided to describe the physicochemical and biological properties of tixagevimab. This includes the primary structure (intact mass analysis and peptide mapping by LC/MS) to show consistency with the theoretical amino acid sequence, glycation level and site-specific modifications.

Impurities
Product-related and process-related impurities have been described and the ranges of impurities present are considered acceptable. Risk assessments have been performed as required. The impurity acceptance criteria in the drug substance are satisfactory.

Control of drug substance
An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Validation of analytical procedure
Validation of the analytical methods used for the control of the drug substance are satisfactory for ensuring compliance with the relevant specifications. In-house methods have been validated for specificity, linearity, accuracy, precision (repeatability and intermediate precision), quantitation limit, range (where applicable) and robustness. Compendial methods have been verified.

Batch analyses
Batch analysis data are provided and comply with the proposed specification.

Reference standard
A two-tiered (primary and working) reference standard (RS) system has been described including source material selection, preparation, storage, qualification and stability, as well as the history of reference standards and the plan for future replacement of reference standards.

Container closure system
The choice of container/closure is adequately described and justified. Stability testing has shown the primary container to be compatible with the drug substance. The primary packaging has been shown to comply with the quality standards of the Ph. Eur. and current regulations concerning materials in contact with food.

Stability
The stability data provided are sufficient to support the proposed shelf-life of 12 months for the drug substance stored at 2 - 8°C.

Cilgavimab
rINN: cilgavimab
Chemical Name: Not assigned

Structure: Cilgavimab is a human IgG1κ monoclonal antibody directed against the receptor binding domain (RBD) in spike (S) protein of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Cilgavimab is composed of two identical heavy chains and two identical light chains. The antibody was engineered to contain two sets of three amino acid substitutions that are referred to as TM (triple mutation) and YTE. The TM substitutions include: a leucine to a phenylalanine at residue 248, a leucine to a glutamic acid at residue 249, and a proline to a serine at residue 345. The TM sites were introduced to reduce Fc-mediated effector functions. The YTE substitutions include: a methionine to a tyrosine at residue 266, a serine to a threonine at residue 268, and a threonine to a glutamic acid at residue 270. The YTE substitutions were introduced to enhance affinity to neonatal Fc receptor (FcRn) and therefore extend serum half-life. Cilgavimab has primarily N-linked biantennary complex-type glycans attached to each heavy chain.

Molecular weight: Approximately 152 kDa (including glycosylation).

Appearance: slightly opalescent and slightly yellow liquid

Cilgavimab is not the subject of a European Pharmacopoeia monograph.

Manufacturing process
A process flow diagram summarizing the manufacturing process, as well as the material inputs, critical and non-critical process parameters, and process outputs (in-process controls, microbial controls, and performance attributes) is provided and is acceptable. The manufacturing process has been well described; briefly this consists of working cell bank (WCB) vial thaw, inoculum expansion in shake flasks and rocker bags, seed bioreactor(s) for further expansion of inoculum, culture in production bioreactor(s) to generate cilgavimab, followed by harvest of the conditioned medium. The clarified conditioned medium containing cilgavimab is further processed through a series of purification steps, designed to remove product-related and process-related impurities, with two dedicated virus clearance steps. The cilgavimab is then concentrated, formulated and sterile filtered to generate the Drug Substance.

Control of materials
The raw materials are purchased from Quality-approved suppliers according to approved procedures. Materials are inspected upon receipt, and supplier certificates of analysis are reviewed. These raw materials are tested and released according to approved specifications and require a minimum of appearance and identification testing. Specification changes follow quality change control procedures prior to implementation. Raw materials used in the manufacturing process for the master cell bank (MCB), working cell bank (WCB) and drug substance, including excipients, are described with the stages of the process in which they are used and quality standards. The quality standards listed are applicable for commercial drug substance and the generation of any future commercial cell bank.

No materials of human origin were used in host cell culture, cell line development, banking of the MCB and WCB, or in drug substance manufacturing.

Materials of animal origin used in cell line development, and materials of animal and other (non-animal) biological origins used in cell banking and drug substance manufacturing process have been described. A TSE/BSE risk assessment and available certificates for relevant animal-derived materials (animal origin or biological origin manufactured using animal components) have been provided and are acceptable.

One material of animal origin (dialyzed foetal bovine serum, dFBS) was used in culturing the AstraZeneca CAT-S host cell line prior to cell line development. No material of animal origin was used in development of the manufacturing cell line after host cell culture.

No materials of animal origin were used in the preparation of the cell banks or in the manufacturing process. In addition, no animal-component-free materials that were manufactured using animal-derived material (material does not directly contain animal-derived material) were used in the preparation of the cell banks or in the manufacturing process.

The cell substrate has been adequately described and is satisfactory. Preparation of the cell banks has also been well described as has their testing and stability.

Controls of critical steps and intermediates
Microbial controls (MCs) are in-process bioburden and endotoxin measurements used to demonstrate microbial control of the manufacturing process.

Bioburden and endotoxin action limits for process intermediates tested at the commercial manufacturing facilities have been provided and are acceptable.

Hold times for process intermediates have been validated and a commercial scale study has demonstrated effective microbial control during the hold times. All validation studies are complete. Justifications for the overall validated hold times have been provided and are acceptable.

Process validation and/or evaluation
The process is defined and validated through several stages: process design, process qualification (validation) and continued process verification. Validation has been performed on several lots at the drug substance manufacturing sites and these were successfully validated through the entire process to drug substance.

Any deviations observed during process validation were evaluated and, upon resolution, determined to have no impact on the conclusions of the process validation. Details of deviations and qualification summary reports have been provided. In addition to the validation of the manufacturing process steps at the commercial scale, validation studies are being conducted at small scale and commercial scale to address a number of other manufacturing considerations.

Manufacturing process development
A summary of the manufacturing process development has been provided which describes the development of the process used to manufacture the drug substance and the rationale for the control strategy of the commercial process.

Two manufacturing processes were used during the development of cilgavimab: Process 1 (used for nonclinical toxicology and clinical manufacturing) and Process 2 (used for both clinical and commercial manufacturing). A comparison of the process flow diagrams for each process has been provided and is satisfactory. Each process has been adequately described. Lot release, characterization, and degradation trend and profile test results from the drug substance comparability testing demonstrate that Process 1 and 2 clinical lots are comparable to Process 2 commercial lots at the drug substance manufacturing sites.

Process characterisation has provided reassurance that the control strategy for cilgavimab is adequate to ensure that critical quality attributes (CQAs) of drug substance are within acceptable ranges, in order to maintain product consistency.

Characterisation
Adequate details have been provided to describe the physicochemical and biological properties of cilgavimab. This includes the primary structure (intact mass analysis and peptide mapping by LC/MS) to show consistency with the theoretical amino acid sequence, glycation level and site-specific modifications.

Impurities
Product-related and process-related impurities have been described and the ranges of impurities present are considered acceptable. Risk assessments have been performed as required. The impurity acceptance criteria in the drug substance are satisfactory.

Control of drug substance
An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Validation of analytical procedure
Validation of the analytical methods used for the control of the drug substance are satisfactory for ensuring compliance with the relevant specifications. In-house methods have been validated for specificity, linearity, accuracy, precision (repeatability and intermediate precision), quantitation limit, range (where applicable), and robustness. Compendial methods have been verified.

Batch analyses
Batch analysis data are provided and comply with the proposed specification.

Reference standard
A two-tiered (primary and working) reference standard (RS) system has been described including source material selection, preparation, storage, qualification and stability, as well as the history of reference standards and the plan for future replacement of reference standards.

Container closure system
The choice of container/closure is adequately described and justified. Stability testing has shown the primary container to be compatible with the drug substance. The primary packaging has been shown to comply with the quality standards of the Ph. Eur. and current regulations concerning materials in contact with food.

Stability
The stability data provided are sufficient to support the proposed shelf-life of 12 months for the drug substance stored at 2 - 8°C.

II.3 DRUG PRODUCT
Tixagevimab and cilgavimab

Pharmaceutical development
A satisfactory account of the pharmaceutical development has been provided. The two processes involved (Process 1 and Process 2: clinical and commercial) have been suitably described and compared.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

The finished drug product compositions are below:

Table 1: Finished product composition

Ingredient	Purpose	Quality Standard
	Active Ingredient	
Tixagevimab	Active	In-house Reference Standard
	Excipients	
L-Histidine	Formulation buffer	USP, Ph. Eur., JP
L-Histidine hydrochloride monohydrate	Formulation buffer	Ph. Eur., JP
Sucrose	Tonicity agent/stabilizer	NF, Ph. Eur., JP
Polysorbate 80	Surfactant/stabilizer	NF, Ph. Eur., JP
Water for Injection (WFI)	Aqueous vehicle	USP, Ph. Eur., JP

JP = Japanese Pharmacopeia; NF = National Formulary; Ph. Eur. = European Pharmacopoeia; USP = United States Pharmacopeia

Table 2: Finished product composition

Ingredient	Purpose	Quality Standard
Active Ingredient		
Cilgavimab	Active	In-house Reference Standard
Excipients		
L-Histidine	Formulation buffer	USP, Ph. Eur., JP
L-Histidine hydrochloride monohydrate	Formulation buffer	Ph. Eur., JP
Sucrose	Tonicity agent/stabilizer	NF, Ph. Eur., JP
Polysorbate 80	Surfactant/stabilizer	NF, Ph. Eur., JP
Water for Injection (WFI)	Aqueous vehicle	USP, Ph. Eur., JP

JP = Japanese Pharmacopeia; NF = National Formulary; Ph. Eur. = European Pharmacopoeia; USP = United States Pharmacopeia

Suitability of the proposed container closure system has been discussed and is acceptable. Compatibility with common materials used for intramuscular (IM) injection has been demonstrated.

No excipients of animal or human origin are used in the finished product.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process is described in sufficient detail, including the equipment and materials used, control of critical steps and process validation. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 18 months for the unopened vial, with the following storage conditions, is acceptable:
Store in a refrigerator (2°C – 8°C).
Store in the original package in order to protect from light.
Do not freeze.

Do not shake.

Shelf-life
Unopened vial
18 months

Storage of syringes for intramuscular administration
The solutions for injection do not contain a preservative. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not be longer than 4 hours at 2 to 8ºC or room temperature (up to 25ºC).

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
During development, the antibodies did not have names and codes were used to identify each antibody and also the use of the combination. Tixagevimab and cilgavimab were coded AZD8895 and AZD1061 respectively; in some testing they were used in combination and were coded AZD7442 (EVUSHELD).

The following non-clinical studies were submitted with this application:

Table 3: Nonclinical pharmacology studies of EVUSHELD (AZD7442)

Study Number	Study Title	GLP
In vitro		
MCBS7442-0001	AZD7442 Binding Kinetics and Mechanism of Action	Not required
MCBS7442-0002	AZD7442 Binds to Unique Epitopes on the Receptor Binding Domain of the SARS-CoV-2 Spike Protein	Not required
MCBS7442-0003	AZD7442 Potently Neutralises SARS-CoV-2	Not required
MCBS7442-0004	The Combination of AZD7442 is More Effective than Individual Monoclonal Antibodies for Neutralising SARS-CoV-2	Not required
MCBS7442-0005	AZD7442 Fc YTE and TM Substitutions Extend Half-Life and Mitigate Theoretical Risk of Antibody-Dependent Enhancement of Disease	Not required
MCBS7442-0007	In vitro Fc Effector Function Studies of AZD7442 and Composite Monoclonal Antibodies	Not required
MCBS7442-0010	Generation and Characterization of AZD7442 Monoclonal Antibody Escape Virus Variants	Not required
In vivo		
MCBS7442-0006	In vivo Activity of AZD7442 in Non-Human Primate Model of SARS-CoV-2 Infection	Not required
MCBS7442-0008	In vivo Prophylactic Activity of AZD7442-TM in the Syrian Hamster Model of SARS-CoV-2 Infection	Not required

Study Number	Study Title	GLP
MCBS7442-0009	Evaluation of Cellular and Humoral Immune Responses Elicited by SARS-CoV-2 Vaccination Subsequent to AZD7442-TM Administration in Mice	Not required
MCBS7442-0011	In vivo Therapeutic Efficacy of AZD7442-TM in the Syrian Hamster Model of SARS-CoV-2 Infection	Not required
MCBS7442-0012	Evaluation of Cellular and Humoral Immune Responses Elicited by SARS-CoV-2 Vaccination Subsequent to AZD7442 Administration in Non-Human Primates	Not required
MCBS7442-0013	In vivo Activity of AZD7442 in a Cynomolgus Macaque Model of SARS-CoV-2 Infection	Not required
Safety pharmacology		
20249158 *	AZD7442: Single Intravenous or Intramuscular Dose Toxicity Study in Cynomolgus Monkeys Followed by an 8-week treatment-Free Period.	Yes

Fc = fragment, crystallizable; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TM = L234F/L235E/P331S substitutions in the immunoglobulin heavy chain to reduce binding to Fc gamma receptor and C1q; YTE = M252Y/S254T/T256E substitutions in the immunoglobulin heavy chain to increase affinity for FcRn that results in the increased half-life of an antibody.

* No dedicated safety pharmacology study was conducted. Safety pharmacology was assessed as part of the single dose GLP toxicology study in cynomolgus monkeys (Study 20249158).

Table 4: Nonclinical pharmacokinetic studies of EVUSHELD (AZD7442)

Study Number[a]	Study Title	GLP
MCBS7442-PK-0001	PK Study of COVID-19 mAbs AZD7442 (AZD8895 + AZD1061) in Human FcRn Transgenic Mice	Not required
20249158	AZD7442: Single Intravenous or Intramuscular Dose Toxicity Study in Cynomolgus Monkeys Followed by an 8-Week Treatment-Free Period	Yes

Table 5: Nonclinical toxicology studies of EVUSHELD (AZD7442)

Study Number	Study Title	GLP
Single-dose studies		
20249158	AZD7442: Single Intravenous or Intramuscular Dose Toxicity Study in Cynomolgus Monkeys Followed by an 8-week treatment-Free Period.	Yes
Other toxicity studies		
20250022	A GLP Tissue Cross-Reactivity Study with the AZD7442 Antibody Combination, as well as the AZD8895 and AZD1061 Components, in Normal Human and Cynomolgus Monkey Tissues	Yes
20282218	A GLP Tissue Cross-Reactivity Study with the AZD7442 Antibody Combination, as well as AZD8895 and AZD1061 Components in Selected Foetal Human Tissues	Yes

Accordance of studies with current Good Laboratory Practice (GLP) is described in the tables above.

III.2 Pharmacology

In vitro studies

Study MCBS7442-0001 was carried out to characterise binding of AZD8895 and AZD1061 to spike protein from SARS-CoV-2 virus. AZD7442 is a mixture of AZD8895 and AZD1061 at 1:1 molar ratio. Results showed that AZD8895 and AZD1061 bind specifically and with high affinity to the receptor binding domain of SARS-CoV-2 spike protein. Neither antibody bound to other coronavirus proteins tested. Each had >3000-fold more potent interaction with the viral protein when compared with hACE2. This binding prevents SARS-CoV-2 virus binding to hACE2. Steric inhibition of SARS-CoV-2 spike protein interaction with hACE2 is the proposed mechanism of action as how AD7442 neutralises SARS-CoV-2.

Study MCBS7442-0002 was performed to determine the epitopes of AZD8865 and of AZD1061. AZD8895 has the same variable region amino acid sequence as an earlier antibody construct, called COV2-2196, and AZD1061 has the same variable region amino acid sequence as a different earlier construct, COV2-2130. A further antibody, CR3022 was also tested as a negative control: this is an IgG1 antibody that targets the receptor binding domain (RBD) but at a different site distal to the hACE2 binding interface. Results showed that AZD8895 and AZD1061 target unique, non-overlapping epitope on the SARS-CoV-2 receptor binding domain, although their binding sites had two residues in common: E484 and Q493. Key interactions were identified as residue F486 for AZD8895 and K444 and R346 for AZD1061. These epitopes and binding sites overlap with the hACE2 interface, supporting hACE2 blockade by steric hindrance as the mechanism of action for both AZD8895 and AZD1061.

Study MCBS7442-0003 reported on experiments on the ability of AZD8895, AZD1061 and AZD7442 to neutralise SARS-CoV-2. Testing was applied with use of SARS-CoV-2 virus (Wuhan strain) and using a recombinant lentiviral pseudovirus expressing the SARS-CoV-2 spike protein. Correlation between results from these two assays was investigated and confirmed that pseudovirus assays could be used in place of assays with live SARS-CoV-2 virus. Results showed that AZD7442, AZD8895 and AZD1061 each neutralise SARS-CoV-2. AZD8865 had higher neutralisation potency than AZD1061. AZD7442 potency was generally similar to that of AZD8895. Results with the pseudovirus support its use to evaluate SARS-CoV-2 neutralisation *in vitro*. AZD7442 was found to maintain neutralising activity against several pseudovirus variants as well as variants specifically engineered to render the virus resistant to each monotherapy component of AZD7442.

Study MCBS7442-0004 compared the potency of AZD7442 to neutralise SARS-CoV-2 with the potency of each antibody, AZD8895 and AZD1061 when tested alone. Synergistic activity of the combination was anticipated based on prior experience with antibodies targeting SARS-CoV as well as with antibodies to SARS-CoV-2. AZD8895 and AZD1061 were tested for neutralisation activity using SARS-CoV-2 pseudovirus. This was then compared with AZD7442 to determine if there was synergy against SARS-COV-2 pseudovirus. Results showed that AZD7442 was more potent than either of its constituent antibodies when they were tested alone and showed synergistic neutralising effects of AZD1061 and AZD8895.

Study MCBS7442-0005 looked at the effect of AZD7442 Fc YTE and TM substitutions on extension of half-life and mitigation of the theoretical risk of antibody-dependent enhancement of disease. Results found that incorporation of the YTE substitutions in AZD8895 and AZD1061 appeared to increase FcRn affinity and that incorporation of the TM substitutions reduced binding to FcγRs and C1q. The significance of this is that AZD7442 may, in humans, have (a) a longer elimination half-life and so a longer protective effect if

used as prophylaxis and (b) reduced propensity to elicit Fc-mediated effects which may reduce its risk of antibody-dependent disease enhancement.

Study MCBS7442-0007 examined the functional consequence of the Fc region modifications and activity of antibodies in AZD7442 compared against that of their wild-type (WT) versions that lack the TM and YTE substitutions. AZD8895 and AZD1061 were engineered with TM substitutions in the Fc to reduce antibody effector function and potential risk of antibody-dependent enhancement of disease. AZD8895, AZD1061 and AZD7442 displayed little or no activity in assays of Fc-mediated effects and did not permit pseudovirus entry and replication in human immune cell lines that do not express ACE2. The results suggest that AZD7442 poses minimal risk for causing enhancement of infection or disease.

***In vivo* studies**

Study MCBS7442-0006 evaluated the *in vivo* activity of AZD77442 in rhesus monkeys exposed to SARS-CoV-2 infection. Experiments were carried out that tested the effect of AZD7442 to prevent disease in monkeys first given the product and later given SARS-CoV-2 virus (prophylactic use) and also to treat disease where its use was started after monkeys had been exposed to SARS-CoV-2 virus (therapeutic use). To evaluate contributions of Fc effector function in viral clearance, one group received AZD7442-YTE (an antibody with YTE but not TM substitution) as prophylaxis. 3-4 rhesus monkeys were in each group and given a single intravenous bolus dose of AZD7442 at 4 or 40 mg/kg, or AZD7442-YTE at 4 mg/kg, or an isotype control antibody (R347-TM-YTE) at 40 mg/kg. Three days later the monkeys were exposed to SARS-CoV-2 infection. The monkeys were challenged with 100,000 pfu SARS-CoV-2 strain USA-WA1/2020 given as 1 ml delivered intratracheally and 0.5 ml into each nostril. AZD7442 given prior to exposure to SARS-CoV-2 virus resulted in protection. At 4 mg/kg, there was little or no virus replication and shedding detected in the lungs and nasal mucosae of infected monkeys. 40 mg/kg AZD7442 given 1 day after infection did not reduce peak viral load in lungs or nasal mucosae but was sufficient to reduce duration of virus shedding by several days. At 4 mg/kg, the serum antibody concentrations were similar to those in human patients given AZD7442. The activity of AZD7442 was not related to Fc-effector function.

In study MCBS7442-0013, the effect of AZD7442 in cynomolgus monkeys to prevent disease was assessed when monkeys were later given SARS-CoV-2 virus and also the effects when given after exposure to the virus. 3-4 cynomolgus monkeys were administered either a 40 mg/kg dose of 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 use) or a 40 mg/kg dose of AZD7442 24 hours after virus challenge (therapeutic use). Monkeys were dosed intravenously, once, with doses of AZD7442 of 0.04, 0.4 or 4 on one occasion, 3 days prior to infection (for prophylaxis analysis), or 40 mg/kg 24 hours after infection (for therapeutic analysis). Additional monkeys were given AZD7442-YTE (with the modified Fc region) at 40 mg/kg either prophylactically or as treatment. An additional group given an isotype control antibody at 40 mg/kg. The monkeys were challenged with 100,000 pfu SARS-CoV-2 strain USA-WA1/2020 given as 1 ml delivered intratracheally and 0.5 ml into each nostril. Results showed that prophylactic use of AZD7442 protected cynomolgus monkeys from SARS-CoV-2 infection and acted in both upper and lower respiratory tracts. AZD7442 was found to reduce pulmonary inflammation and damage and elicit dose-dependent protection of cynomolgus monkeys given SARS-CoV-2. It also limited viral shedding from the upper respiratory tract. Control monkeys showed histological changes in lungs consistent with SARS-CoV-2 infection but all monkeys given AZD7442, either as prophylaxis or as treatment, had reduced lung pathology, demonstrating that AZD7442 protects against virus-induced lung injury. As no difference was seen between different versions of antibodies, it

can be suggested that antibody effector function is not required for AZD7442 antiviral activity in monkeys. AZD7442 may provide clinical benefit in both prevention and treatment settings.

Study MCBS7442-0008 evaluated the effect in hamsters when test antibody was given prior to a challenge with SARS-CoV-2 virus. YTE modifications were introduced into AZD7442 with the intent to lengthen the elimination half-life in humans, but this change results in more rapid elimination in hamsters (and other rodent species); therefore the test antibody AZD7442-TM was used i.e. the antibody lacking YTE substitutions and which has reduced binding to Fc receptors and complement proteins. The study aimed to identify doses sufficient to reduce lung viral load and decrease pathological lesions associated with SARS-CoV-2 infection in hamsters. Results showed that AZD7442-TM protected hamsters against SARS-CoV-2 infection. A single dose of 2 mg protected hamsters from weight loss, pulmonary inflammation and alveolar damage and reduced viral burden in the lungs. Lower doses of 0.02 and 0.002 mg AZD7442-TM did not protect, but hamsters had equivalent pulmonary inflammation and alveolar damage, indicating no evidence of antibody-dependent enhancement of disease: the presence of AZD7442 did not result in worse lung damage. The concentration of AZD7442-TM in hamster serum was negatively correlated with the viral load in the lungs.

Study MCBS7442-0011 was also performed in hamsters and assessed the effect of AZD 7442 when given after exposure to SARS-CoV-2 virus. This study also used AZD-7442-TM, which lacks the YTE substitutions in AZD7442, to prolong exposure in hamsters. The study sought to define the timing and dosing of AZD7442-TM needed to reduce lung viral load and decrease pathological lesions in the lungs. A single dose of 0.5 or 5 mg AZD7442 protected hamsters against SARS-CoV-2 infection when given 24 or 48 hours after infection. Protection was shown in terms of reduced weight loss and reduced measures of pulmonary inflammation, alveolar damage and viral burden in lungs following SARS-CoV-2 infection. The concentration of AZD7442-TM in hamster serum was negatively correlated with the viral load in the lungs.

Study MCBS7442-009 tested if prior treatment with AZD7442-TM affected cellular and humoral responses to vaccination in mice. Mice were given AZD7442-TM, rather than AZD7442 as the YTE modification in AZD7442 causes rapid elimination of IgG in rodent species. Using AZD7442-TM, which incorporates TM but lacks YTE substitutions in the Fc region, therefore results in longer exposure. Mice were given AZD7442-TM by single intraperitoneal injection at doses of 0, 5, 25, 100 and 400 μg or were given an isotype control IgG at 400 μg or were given saline. A further group were given AZD7442-WT at 400 μg (AZD7442-WT does not have either TM or YTE substitutions in the Fc region). All mice were then given AZD1222, the company's own adenovirus-based COVID-19 vaccine, by intramuscular injection in a volume of 50 μl at a dose of 1x10(8) vp per mouse either once (cohort 1) or twice (cohort 2). Cohort 1 were dosed 1 day after being given test antibodies and cohort 2 were dosed 1 day and 4 weeks after being given test antibodies. Control mice received 400 μg AZD7442-TM but received saline only and therefore were not immunised. Results showed that all vaccinated mice demonstrated similar levels of CD8 T cell activation, regardless of treatment prior to vaccination. All vaccinated mice showed similar antibody titres for binding to spike or receptor binding domain.

Study MCBS7442-0012 was carried out in cynomolgus monkeys and its aim was to compare the immune response to vaccination with the company's own adenovirus-based vaccine, AZD1222, on activation of T cells and production of antibody to the SARS-CoV-2 spike proteins and receptor binding domain in monkeys given AZD7442 and those not given

AZD7442. Monkeys were randomly assigned to treatment groups and given an intravenous infusion of 0.2, 1, 4 or 12 mg/kg AZD7442 or were given an isotype control antibody at a dose of 12 mg/kg. Three days later, the monkeys were given 1 dose of AZD1222 vaccine by intramuscular injection; they were given a 2nd dose 4 weeks later. Results showed that AZD7442 did not alter either spike-specific CD8 or CD4 T cell responses, or spike- or RBD-specific antibody titres elicited by vaccination for COVID-19. Minimal impact of AZD7442 was observed on vaccine-elicited cellular or humoral immune responses, which suggests AZD7442 would not interfere with vaccine efficacy.

In viral passage studies in Vero E6 cells, to identify if the product would give rise to escape variants of the virus, escape variants were detected with use of AZD1061 alone but not with either of AZD8895 or the combination (AZD7442).

In studies using authentic SARS-CoV-2 isolates or pseudoviruses bearing spike substitutions identified in variants, AZD7442 retained full or 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 was active to inhibit the Omicron variant of this virus.

Safety pharmacology studies
No safety pharmacology studies have been carried out which is acceptable. Measures were evaluated in Study 20249158, a general toxicity study.

III.3 Pharmacokinetics (PK)
Study MCBS7442-PK-0001 reviewed the kinetics of AZD7442 (AZD8895 and AZD1061) in human FcRn transgenic mice. The Fc modifications in each antibody has the potential to reduce the stability of the antibodies and this study sought to evaluate whether the *in vivo* kinetic profile was affected. The PK properties of AZD 8895 and AZD1061 were compared against a similar company-developed monoclonal antibody (mAb), MEDI8897 (nirsevimab) *in vivo*. The study was performed in human FcRn transgenic Tg32 mice which express human Fc receptors and which also have a knock-out of the mouse Fc receptor. As well as MEDI8897 (1G7 with YTE only), control antibodies included an anti-RSV IgG1 with YTE substitutions to prolong half-life, MEDI8897+TM (1G7 with YTE and TM), and 1G7 (no TM or YTE; WT Fc). AZD8895, AZD1061, or control antibodies were administered to Tg32 mice as a single IV dose of 5 mg/kg. Blood samples were collected up to day 28 post-dose for the determination of serum concentration of test articles. Results were that the serum concentrations of AZD8895, AZD1061, MEDI8897, MEDI8897+TM, and 1G7 IgG1 declined in a multi-phasic fashion with terminal half-life of 2-3 weeks. The PK of MEDI8897+TM was similar to that of MEDI8897, indicating TM did not significantly affect the PK of MEDI8897. The PK of AZD8895 and AZD1061 were similar to those of MEDI8897 and MEDI8897+TM.

III.4 Toxicology
Tissue cross reactivity studies
Study 20250022 was performed to determine the potential cross reactivity of AZD7442, as well as the potential cross reactivity of its individual antibody components, AZD1061 and AZD8895, with cryosections from a full panel of tissues from human and cynomolgus monkey donors. In addition, Study 20282218 was carried out in human fetal tissues. These studies determined whether test antibody bound to any of a wide panel of tissues. Such binding is not expected for antibodies that target a viral antigen, but if any specific binding is identified, this can influence safety testing to determine if there is any biological consequence or toxicity related to the binding. Both studies were carried out in compliance with Good

Laboratory Practice (GLP).

Results showed that staining to SARS-CoV-2 spike protein UV resin spot slides was confirmed for both of the concentrations of each of biotinylated antibodies, AZD7442, AZD8895 and AZD1061: this shows the methods were able to detect binding. The negative control material (human hypercalcemia of malignancy peptide, amino acid residues 1-34, UV-resin spot slides) did not show staining. The control human IgG antibody did not cross react with either positive or negative controls. All tissues from both humans and monkey showed staining with labelled rabbit antibody to β2-microglobulin which indicates that tissues used in the test did express epitopes that could be detected by immunohistochemical staining (β2-microglobulin antigen is expressed on many cell types and is strongly expressed on endothelium). Based on these findings, the methods applied were judged reliable. No staining was detected in either human or cynomolgus monkey tissues. In human fetal tissues, no staining was observed. No binding to mammalian tissues was identified in this testing.

Single dose toxicity

Study 20249158 was a single dose toxicity study in which monkeys were followed up to 8 weeks after dosing. The aim of this study was to evaluate potential toxicity and toxicokinetics of AZD7442. Monkeys were dosed with either AZD7442, at 600 mg/kg or at 150 mg/kg (given as 300 mg/kg or as 75 mg/kg of each of AZD8895 and AZD1061 as separate injections), or to a control group given vehicle (20 mM histidine/histidine-HCl, 240 mM sucrose, 0.04% PS80, pH 6.0). Dosing was either a single intravenous dose (600 mg/kg dose) given over up to ~15 minutes or as a single intramuscular dose (150 mg/kg dose). After dosing, the monkeys were followed to either study days 15 or 57 / 58. Results showed that AZD7442 was well tolerated and no treatment related adverse findings were reported in any of the evaluated endpoints at the week 2 and week 8 assessments.

III.5 Ecotoxicity/Environmental Risk Assessment

As both the components of EVUSHELD are antibodies they degrade to their constituent amino acids and are not expected to pose any risk to the environment.

III.6 Discussion on the non-clinical aspects

The data presented suffice to show how the two antibodies prevent viral attachment to cells with the resulting benefit of reduced disease on exposure to SARS-CoV-2 virus, shown in hamsters and monkeys. Effects were shown on both pre-exposure use and when used as a treatment, with dosing started after exposure to the virus. Although data suggest that use of a single antibody could give rise to escape variants, against which the drug no longer works, this did not occur with the combination of two antibodies, indicating the importance of use of both antibodies.

No concerns were identified from safety testing including tissue binding assays and an in vivo general toxicity study. This testing is in line with international guidelines for development of an antibody or antibodies that target a viral antigen.

The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The following clinical studies were submitted with this application. In this section EVUSHELD is also referred to as AZD7442.

Table 6: Clinical studies of EVUSHELD

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 (i.e., 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 enrolment (i.e., 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 enrolment (i.e., 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

All studies were conducted in line with current Good Clinical Practice (GCP).

The following additional reports were also provided.

Population PK Report	Interim pooled population pharmacokinetic analysis of EVUSHELD (tixagevimab and cilgavimab; AZD7442) in adult subjects
Exposure-response Memo	Correlation of PK and anti-SARS-CoV-2 neutralising antibody titer and exploratory analysis of the exposure-response relationship for prophylaxis of RT-PCR-positive symptomatic SARS-CoV-2 infection after a single dose of EVUSHELD
Viral Dynamic Modelling Report	AZD7442 viral dynamic modelling report supporting the prophylaxis indication

IV. 2 Pharmacokinetics

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

Pooled (phase I and phase III) population PK modelling

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.

TACKLE is a Phase III, double-blind, placebo-controlled clinical trial for the treatment of adult patients with mild to moderate COVID-19 (an indication for which EVUSHELD is not approved). TACKLE enrolled non-hospitalised adults (with the exception of those hospitalized for isolation purposes) with mild to moderate COVID-19 (within ≤7 days of symptom onset). Four-hundred and fifty-two (452) patients have received 600 mg IM EVUSHELD in TACKLE. The median duration for safety follow-up was 84 days.

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.

PK in healthy volunteers

Study D8850C00001 (Phase I)

Study design and objective

This was a Phase I, first time in human (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)
- Cohort 4 (EVUSHELD 3000 mg with the two mAbs co administered, or placebo IV).

In Cohorts 1a, 1b, 2, and 3, the two 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.

Study population

Overall, 60 participants were enrolled with a total of 10 participants randomised to EVUSHELD in each cohort, and 10 participants in total randomised to pooled placebo. At the time of the data cut off (DCO), all 60 participants had been randomised and received the IMP. One participant (in Cohort 2) withdrew consent and 59 participants were ongoing in the follow-up period.

The mean age of EVUSHELD participants was 39.4 years. Most EVUSHELD participants were male (32 [64.0%]) and white (34 [68.0%]).

Pharmacokinetic and PD (nAb) results are summarised below. Data are presented up to Day 271 for Cohort 1a (300 mg IM) and Cohort 1b (300 mg IV); and Day 211 for Cohort 2 (1000 mg IV), Cohort 3 (3000 mg IV sequential infusion) and Cohort 4 (3000 mg single infusion).

Methods

For participants who received the investigational medicinal product (IMP) via intramuscular (IM) injection, the investigational medicinal product (IMP) was administered as 2 sequential IM injections via the gluteal muscle. For participants who received the IMP via IV infusion (Cohorts 1b, 2, 3, and 4), the IMP was administered in 2 sequential IV infusions at a maximal rate of 20 mg/minute, starting with tixagevimab/placebo and followed by cilgavimab/placebo for Cohorts 1b, 2, and 3. For Cohort 4, tixagevimab/placebo and cilgavimab/placebo were combined as a single IV infusion at a maximal rate of 40 mg/minute.

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.

Descriptive summary and non-compartmental analysis of serum pharmacokinetics

Mean (standard deviation) serum concentration-time profiles are shown in Figure 7.

<u>300 mg IM dose</u>

After a single 300 mg IM dose, the geometric mean C_{max} was similar for tixagevimab and cilgavimab at 16.52 and 15.27 µg/mL, respectively, which was reached at a median t_{max} of 14 days for both antibodies. Between-participant variability (%CV) in tixagevimab AUC_{inf} and C_{max} after 300 mg IM administration was 30.22% and 35.56%, respectively, and 31.66% and 38.53%, respectively, for cilgavimab. The PK of tixagevimab and cilgavimab up to Day 271 were similar.

<u>300 mg IV dose</u>

After 300 mg IV administration, between-participant variability (%CV) in tixagevimab AUC_{inf} and C_{max} was 14.40% and 11.51%, respectively, and 14.40% and 15.31%, respectively, for cilgavimab. On Day 271, in the 300 mg IM arm, the bioavailability of EVUSHELD, calculated as the ratio of geometric mean AUC_{inf} after IM to IV, was 68.54% and 65.79% for tixagevimab and cilgavimab, respectively.

<u>1000 mg IV administration</u>

After 1000 mg IV administration, between participant variability (%CV) in tixagevimab AUC_{inf} and C_{max} was 14.17% and 11.31%, respectively, and 13.80% and 14.66%, respectively, for cilgavimab.

<u>3000 mg IV administration</u>

After 3000 mg IV administration, administered as 1500 mg of tixagevimab over 75 minutes followed by 1500 mg of cilgavimab over another 75 minutes (Cohort 3), the between participant variability (%CV) in tixagevimab AUC_{inf} and C_{max} was 10.73% and 10.54%, respectively, and 11.24% and 11.09%, respectively, for cilgavimab (Table 2).

After 3000 mg IV administration, with 1500 mg of tixagevimab and 1500 mg of cilgavimab administered at the same time over 60 minutes (Cohort 4), the between-participant variability (%CV) in tixagevimab AUC_{inf} and C_{max} was 11.65% and 8.980%, respectively, and 12.85% and 11.62%, respectively, for cilgavimab (Table 7). Overall, the C_{max} and AUC increased linearly with increasing IV dose. Administering tixagevimab and cilgavimab separately or together did not alter the PK of the mAbs as indicated by the overlapping serum drug

concentration-time curves. In addition, key exposure PK parameters such as AUC and C_{max} for tixagevimab and cilgavimab were similar between the two 3000 mg IV dosing regimens.

Half-lives ($t_{1/2\lambda z}$) of tixagevimab and cilgavimab were similar for all cohorts, routes of administration, and dose levels. The average of mean $t_{1/2\lambda z}$ calculated for both antibodies from all cohorts was approximately 90 days (range 87.93 to 94.60 days for tixagevimab and 82.90 to 91.24 days for cilgavimab).

Figure 1: Arithmetic mean (± SD) serum concentrations of tixagevimab [AZD8895], cilgavimab [AZD1061], and EVUSHELD [AZD7442] (tixagevimab + cilgavimab) following single dose IM or IV administration to healthy participants, through Day 271, PK analysis set, Study D8850C00001 (Phase I)

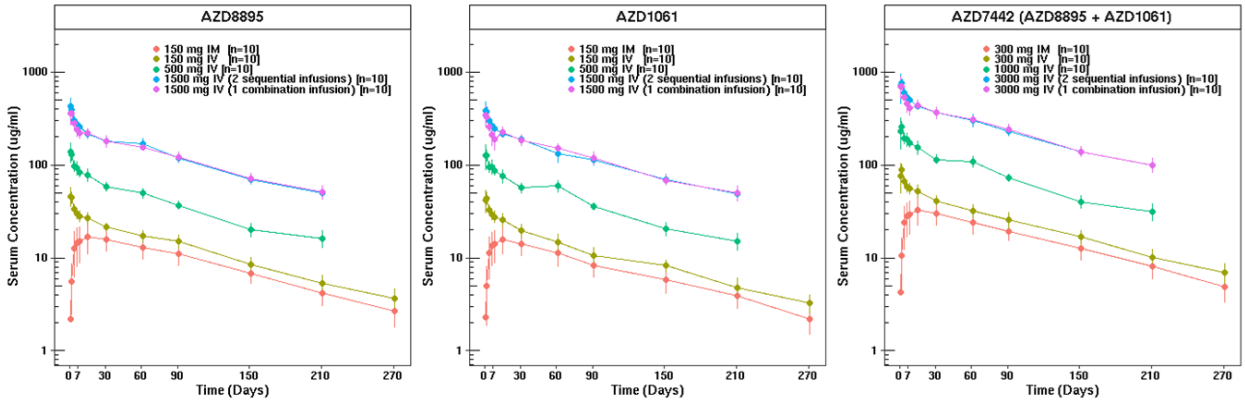


Table 7: Summary of PK parameters for tixagevimab and cilgavimab following single dose IM or IV administration of EVUSHELD – Day 211 PK analysis set, Study D8850C00001 (Phase I)

Analyte	Parameter (Units)	300 mg EVUSHELD IM[a] (N = 10)	300 mg EVUSHELD IV[a] (N = 10)	1000 mg EVUSHELD IV[b] (N = 10)	3000 mg EVUSHELD IV[c] (N = 10)	3000 mg EVUSHELD IV co-administration[c] (N = 10)
Tixagevimab	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
Cilgavimab	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 EVUSHELD (150 mg tixagevimab and 150 mg cilgavimab).
b 1000 mg EVUSHELD (500 mg tixagevimab and 500 mg cilgavimab).
c 3000 mg EVUSHELD (1500 mg tixagevimab and 1500 mg cilgavimab).
d Average concentration over 210 days post-dose, calculated as AUC_{0-210d}/210 days.
e Calculated as the single ratio of geometric mean AUC_{inf} after IM to IV, thus no %CV.
f n = 9, one participant had no samples beyond 1440 hours post-dose due to early termination; this participant's AUC_{0-210d} and Cavg210d were calculated via extrapolation.

Data are presented as geometric mean (geometric CV), except for t_{max} and t_{last} as median (min – max), and $t_{1/2\lambda z}$, CL(/F), V_z(/F), and V_{ss} as arithmetic mean (SD).

AUC_{0-210d}, area under the serum concentration-time curve from time zero to Day 211; AUC_{last}, area under the serum concentration-time curve from time zero to the last measurable time point; AUC_{inf}, area under the serum concentration-time curve from time zero to infinity; Cavg210d, average serum concentration over 210 days post-dose; C_{max}, 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; DCO, data cut-off; F210d, bioavailability at Day 211; IM, intramuscular; IV, intravenous; NA, not applicable; PK, pharmacokinetic; $t_{1/2\lambda z}$, half-life associated with terminal slope of a semi-logarithmic concentration-time curve; t_{last}, time to last serum concentration measurement; t_{max}, time to maximum serum concentration; V_{ss}, volume of distribution at steady state from an IV dose; V_z, volume of distribution following iv administration (based on terminal phase); V_z(/F), volume of distribution (apparent) following extravascular administration (based on terminal phase).

Absorption

After a single 300 mg IM dose (150 mg each mAb) in the Phase I study, the mean (%CV) C_{max} was 16.52 (35.56%) and 15.27 (38.53%) µg/mL for tixagevimab and cilgavimab, respectively, which was reached at a median t_{max} of 14 days. 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% and absorption rate (KA; 1/day) were similar for tixagevimab (0.109 1/day) and cilgavimab (0.106 1/day).

Based on PK modelling, 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
The estimated absolute bioavailability after a single 150 mg IM dose was 68.5% for tixagevimab and 65.8% for cilgavimab.

Bioequivalence - cell pools material versus clonal cell line material (PROVENT)
Serum EVUSHELD data were available for 68 of the 92 participants who had been dosed with the clonal cell line material and had PK results for both tixagevimab and cilgavimab at all sampling time points (Days 8, 29, 58, and 92). For the additional 24 participants that were dosed with clonal cell line material, scheduled PK samples were missing over the first 3 months. Corresponding data were used for 67 participants who were dosed with cell pools material for comparison.

Analysis performed on the partial dataset found that the C_{max} is comparable between the cell pools material and the clonal cell line material following administration of a single dose of EVUSHELD 300 mg IM, with a ratio of the geometric means of 97.1% with the 90% CI within the 80% to 125% comparability bounds for tixagevimab, cilgavimab, and EVUSHELD (86.8%, 109%). For $AUC_{(0\text{-}91)}$, the ratio of the geometric means (90% CI) was 83.8% (74.8%, 93.8%) for EVUSHELD. The results suggest that both cell pools material and the clonal cell line material result in serum EVUSHELD concentrations above the minimum protective concentration of 2.2 ug/mL in 100% of the participants.

Distribution
Distribution of immunoglobulin G and other recombinant proteins is usually restricted to the extracellular fluid. Based on the population PK model, the estimated V2 was 2.72 L for tixagevimab and 2.48 L for cilgavimab. The V3 was 2.64 L for tixagevimab and 2.57 L for cilgavimab.

Nasosorption samples for NLF PK analysis were collected at baseline (predose), Days 8, 31, 91, and 151 in Study D8850C00001. The NLF concentration data suggest that both tixagevimab and cilgavimab distribute significantly into the upper respiratory tract and that the mAb concentrations in NLF increase dose-proportionally in the range of 300 mg IV to 3000 mg IV. The range of the serum to NLF partition ratio was found to be dose-independent, mAb-independent, and in the same range up to D151. In the 300 mg IM dose cohort, the median tixagevimab, cilgavimab, and EVUSHELD (tixagevimab and cilgavimab) NLF concentrations were 171, 187, and 358 ng/mL, respectively, on Day 8 and 226, 205, and 431 ng/mL, respectively, on Day 31. For the prophylactic dose of 300 mg IM, the median partition from serum to NLF was calculated as 1.81% for EVUSHELD (the median of the individual Day 8 and Day 31 %NLF:serum ratios; individual ratios calculated as tixagevimab and cilgavimab in NLF divided by tixagevimab and cilgavimab in serum). The median value for the %partition ratio for EVUSHELD from serum to NLF was used for translating the targeted minimum protective level of 40 ng/mL (IC80 for inhibition of viral cell entry) in the upper respiratory tract to a targeted minimum protective level of 2.2 µg/mL in serum.

Metabolism
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.

Elimination
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. The estimated population median terminal elimination half-life of EVUSHLED was 90.6 days for EVUSHELD, 88.8 days for tixagevimab and 84.4 days for cilgavimab.

PK in target population

Descriptive summary of serum EVUSHELD concentrations - PROVENT

Blood samples for serum PK analysis were collected at pre dose (baseline), and at Study Days 8, 29, 58, 92, 183, 366, and 457.

Serum tixagevimab and cilgavimab concentration data were 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.

Serum PK samples were analysed by the same validated assay used for the Phase I serum PK samples.

Quantifiable amounts of either tixagevimab or cilgavimab were not detected in any baseline samples. The nominal geometric mean (%gCV) tixagevimab 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) cilgavimab concentrations at Study Days 8, 29, 58, 92, and 183 were numerically similar to tixagevimab 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) EVUSHELD 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. The observed PK profiles support an extended half-life for both antibodies.

Descriptive summary of the serum EVUSHELD concentrations – STORM CHASER

Blood samples for serum PK analysis were taken at pre dose (baseline), and at Study Days 8, 29, 58, 92, 183, 366, and 457.

Serum concentration data for tixagevimab and cilgavimab were 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 were 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.

Quantifiable amounts of either tixagevimab or cilgavimab were not detected in any baseline samples. The geometric mean (%gCV) tixagevimab 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) cilgavimab concentrations at Study Days 8, 29, and 58 were numerically similar to tixagevimab at 9.206 (85.700%), 11.056 (57.298%), and 11.663 (44.052%) µg/mL, respectively.

Dose proportionality and time dependency

The observed nominal median C_{max} in the PROVENT study at the 300 mg IM dose is 25 µg/mL and in the TACKLE study at 600 mg IM dose the C_{max} is 44.5 µg/mL, suggesting serum levels increased linearly from the 300 mg IM to the 600 mg IM dose.

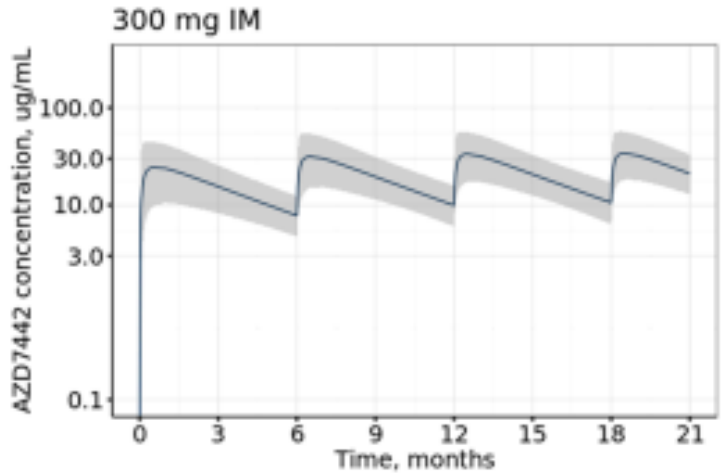
No PK data beyond Day 90 for the 600 mg dose is available to calculate a meaningful dose proportionality using AUC parameter between the 300 mg and 600 mg dose. Exposure to tixagevimab and cilgavimab, as reflected by AUC_{last}, following a single IM injection of EVUSHELD at doses of 300 mg and 600 mg, increased in an approximately dose proportional manner across this dose range in both mAbs.

Table 8: Geometric mean (%CV) of AUC following either single IM dose of 300 mg EVUSHELD (150 mg cilgavimab + 150 mg tixagevimab) or 600 mg EVUSHELD (300 mg cilgavimab + 3000 mg tixagevimab) using non-compartmental analysis or population-based PK model

Non-Compartmental Analysis AUC (0-31) days (µg·day/mL)		
Geometric Mean (%CV)	**Phase I (D8850C00001)**	**TACKLE Study**
Tixagevimab	421 (42)	877 (102)
Cilgavimab	389 (42)	821 (99)
Population Based PK model based on all studies (shown for EVUSHELD only)		
Median (90% PI) AUC (µg·day/mL)	**EVUSHELD 300 mg (n = 1870)**	**EVUSHELD 600 mg (n = 442)**
1 month	666 (261 to 1256)	1320 (517 to 2514)
3 months	1858 (851 to 3218)	3687 (1685 to 6409)
6 months	2880 (1469 to 4787)	5720 (2900 to 9517)

A long-term study is being planned to investigate repeat dosing of EVUSHELD post initial dose. The planned study is anticipated to start in Q1 2022. Based on the Population PK model, every 6 months dosing of 300 mg IM is predicted to result in 36% accumulation between first dose (AUC of 2830 µg*day/mL) versus third dose (AUC of 3843 µg*day/mL).

Figure 2: Pooled population-PK model predicted median (90% prediction interval) serum EVUSHELD concentration for a 6-month dosing interval following administration of EVUSHELD 300 mg IM, over 21 months



Special populations

Effect of intrinsic factors on the PK of EVUSHELD

Results from the population PK analysis found there was no clinically significant effect of age (< 65 years, ≥ 65 years), sex (female, male), race (black, white, other) and ethnicity (Hispanic/Latino, non-Hispanic/non-Latino), Study design (Phase I and III), body weight, body mass index, diabetes, renal or mild to moderate hepatic impairment, cardiovascular

disease, immunocompromised/immunosuppressed status. Therefore, no dose adjustment was required for these intrinsic factors.

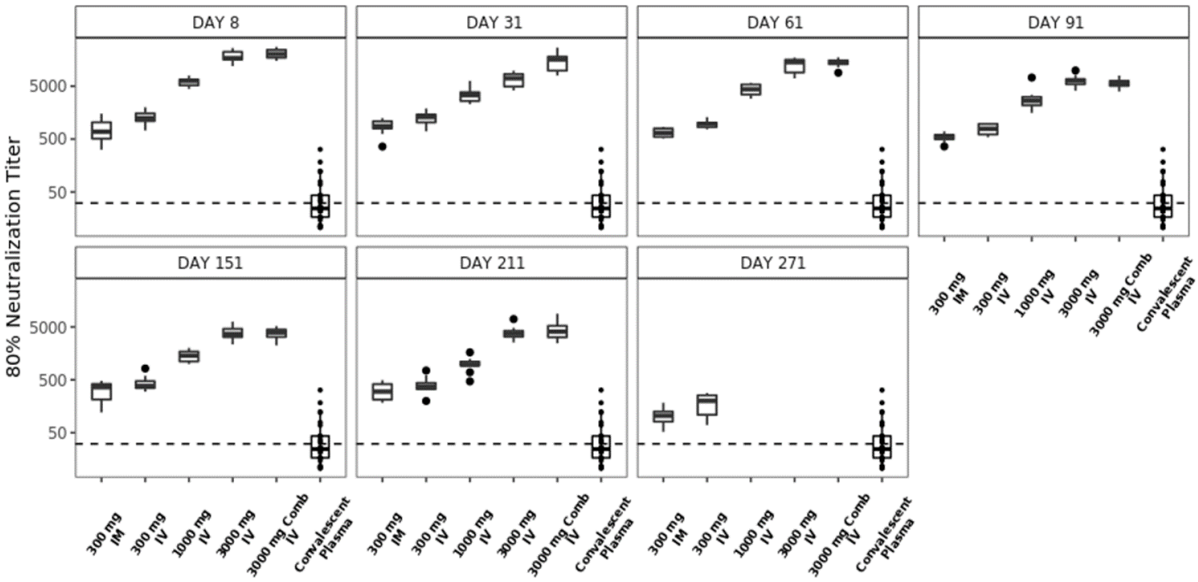
Effect of extrinsic factors on the PK of EVUSHELD
No specific studies have been conducted to examine the effects of extrinsic factors (e.g., food, ethanol, smoking, drug-drug interactions) on the PK of EVUSHELD. In the population PK analysis, immunosuppressant drugs, cell pools/clonal cell line material, and vaccination status post EVUSHELD dosing had

IV. 3 Pharmacodynamics

Tixagevimab and cilgavimab simultaneously bind to non-overlapping regions of the RBD of SARS-CoV-2 spike protein. Tixagevimab and cilgavimab and EVUSHELD 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. Tixagevimab and cilgavimab and EVUSHELD as combination product blocked RBD binding to the human ACE2 receptor with IC_{50} values of 47.7 ng/mL, 79.6 ng/mL, and 65.0 ng/mL, respectively. The virus-neutralising activity of EVUSHELD and the two mAbs that comprise it was assessed against SARS-CoV-2 strain USA-WA1/2020. EVUSHELD had a calculated IC_{50} value of 10 ng/mL. Data demonstrate that tixagevimab and cilgavimab can independently, or in combination (EVUSHELD), potently neutralise SARS-CoV-2 *in vitro*.

Pharmacodynamics - SARS-CoV-2 neutralising antibodies: D8850C00001 (Phase I)
Eighty percent 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 (i.e., 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 3: Box plot of neutralising antibody titres against SARS-CoV-2 on Day 8, Day 31, Day 61, Day 91, Day 151, Day 211, and Day 271 in comparison with plasma from convalescing patients (safety analysis set)

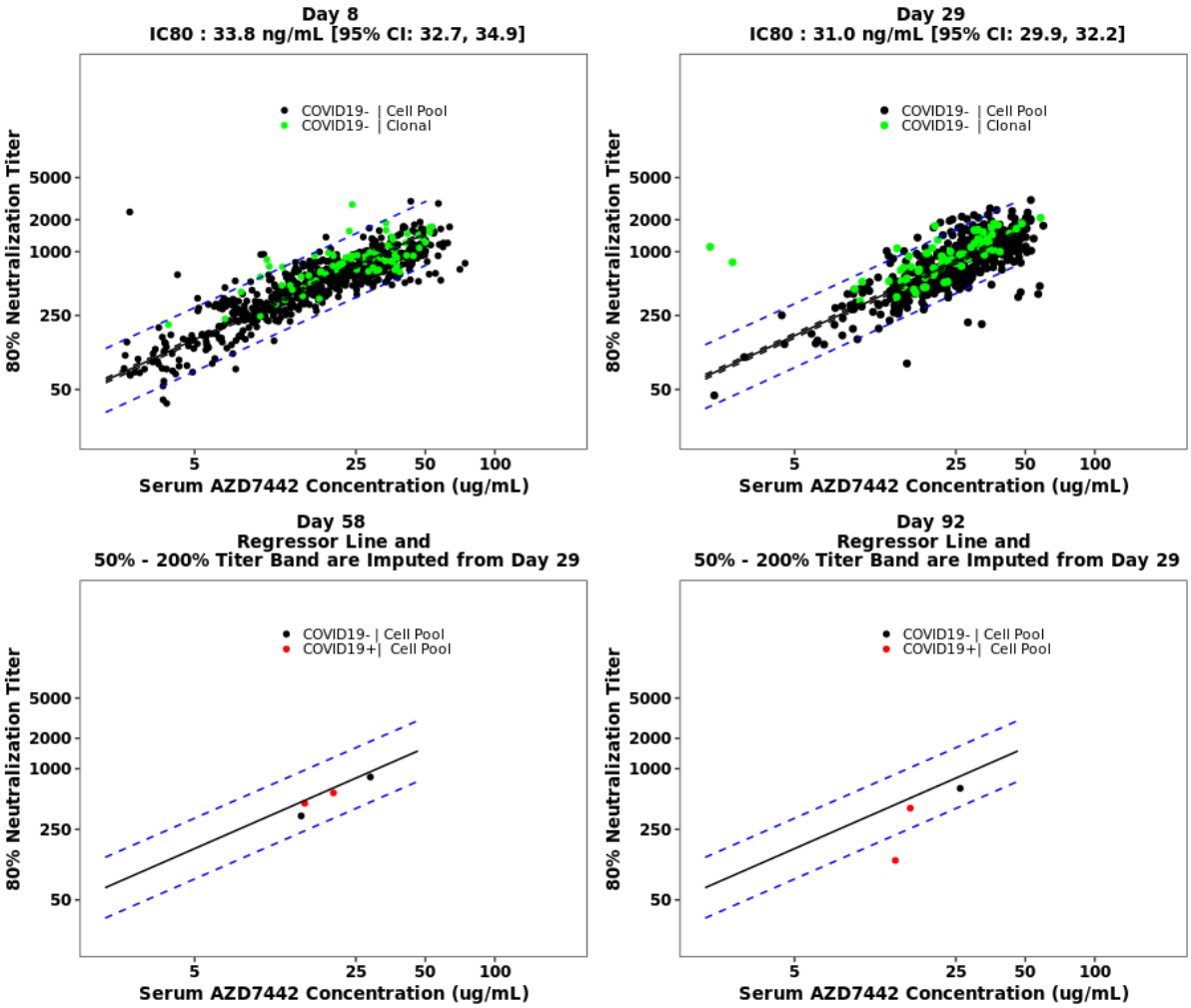


The dashed horizontal line represents GMT measured in plasma samples from convalescing COVID-19 patients. In the box, the dark black centre line denotes the median value (50th percentile), while the black box around median line contains the 25th to 75th percentiles of dataset. The black whiskers mark the 5th and 95th percentiles, and points beyond these upper and lower bounds are considered outliers, marked with black dots.
COVID-19, coronavirus disease 2019; DCO, data cut-off; IM, intramuscular; IV, intravenous, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Pharmacodynamics - SARS-CoV-2 neutralising antibodies: PROVENT (Phase III)
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 were available on Day 1 (IL D1), Day 14 (IL D14), Day 21 (IL D21), and Day 28 (IL D28) after symptom onset.

Similar to the Phase I data, the EVUSHELD concentration was strongly correlated to the nAb titre and was maintained over the first month. The inverse of the slope, which reflects the IC_{80} 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. The data are shown below.

Figure 4: 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; IC_{80}, 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; IC_{80}, 80% maximal inhibitory concentration; nAb, neutralising antibodies; SARS-CoV-2, Severe acute respiratory syndrome-coronavirus 2.

At all timepoints evaluated, the GMT in participants who received EVUSHELD exhibited > 4-fold increases in titre compared with baseline. 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.

Pharmacodynamics - SARS-CoV-2 neutralising antibodies: STORM CHASER (Phase III)
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, ILD14, 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).

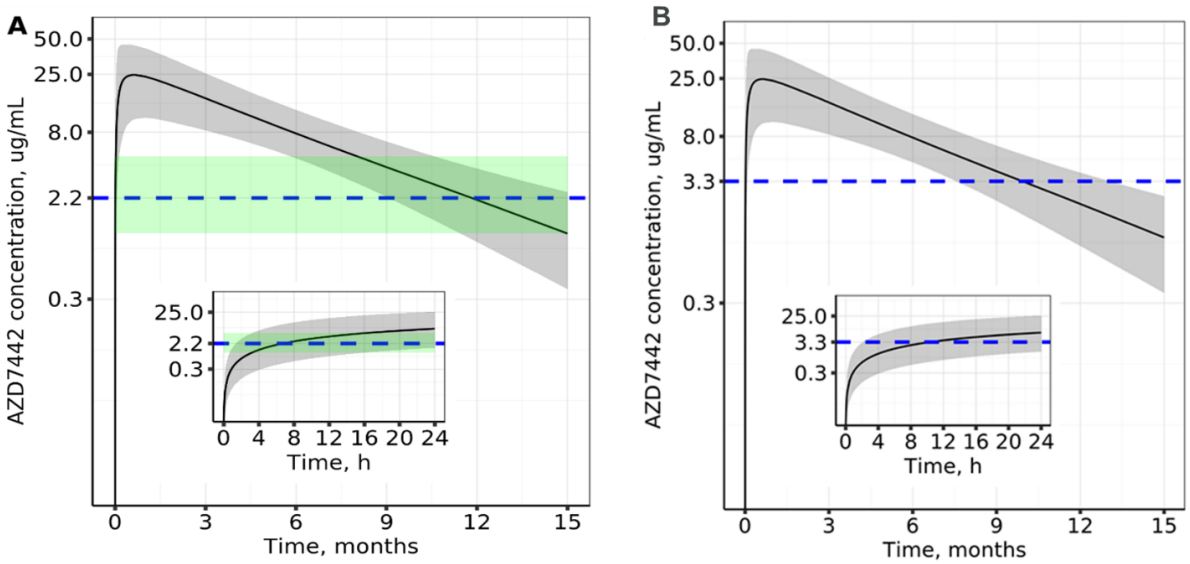
Exposure-response and PK/PD analysis of EVUSHELD
The exposure response relationship of EVUSHELD for the efficacy endpoint of incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness that occurs within 150 days after a 300 mg IM dose of EVUSHELD (i.e., by Day 151) was evaluated for PROVENT. The data 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 group (out of 663 actively treated participants), while there were 18 COVID-19 positive cases in the 1637 active plus placebo participants. For the exposure-response analysis, the population PK model individual predicted $AUC_{(0\text{-}150)}$ 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
Based on PK modelling and simulation, the time to achieve the minimum serum concentration of EVUSHELD to protect against the original SARS-CoV-2 strain in the upper respiratory tract (2.2 µg/mL [calculated based on the median partition from serum to NLF was calculated as 1.81% for EVUSHELD in combination with the measured EVUSHELD potency (IC_{50} of 10 ng/mL) and the VDM-derived minimal required viral entry inhibition for prophylaxis of 80%]) was estimated at 6 hours (IQR of 3.4 to 11.7 hours) in the typical participant following 300 mg IM administration, and by 28 hours in 90% of participants in the PROVENT population. Population PK modelling from available Phase I and Phase III data indicates that EVUSHELD concentrations are predicted to remain above the minimum protective serum concentration threshold of 2.2 µg/mL for at least 6 months in 100% of patients, 9 months in 96% of patients, and for 12 months in 46% of patients.

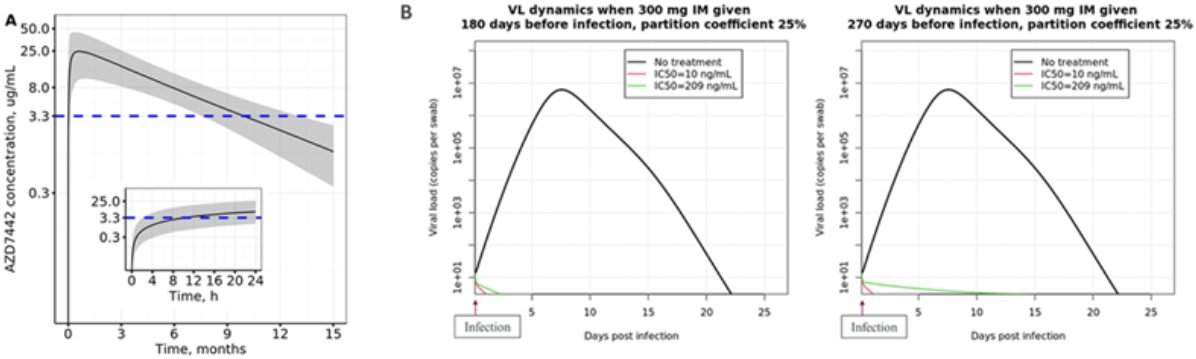
To assess the impact of the lower potency or higher IC_{50} on the duration of protection by EVUSHELD against the Omicron variant, the geometric mean IC_{50} of 209 ng/mL across 4 available different IC_{50} values (FNIH 2022, Dejnirattisai et al 2021, VanBlargan et al 2021) was used. The potency loss of EVUSHELD against the Omicron variant (i.e., 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 an assumption based on the highest value of available data with other biologics that the serum to lower respiratory tract transfer is ~25% and VDM modelling.

Figure 5: PK model predicted median (90% prediction intervals) serum EVUSHELD concentration for Wuhan Strain (A) and Omicron Variant (B) following administration of 300 mg IM EVUSHELD, over 15 months based on PK modelling using pooled data of Phase I and Phase III Studies



Using the IC_{50} of 209 ng/mL, a required minimal inhibition of 80%, and an optimistic assumed 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.

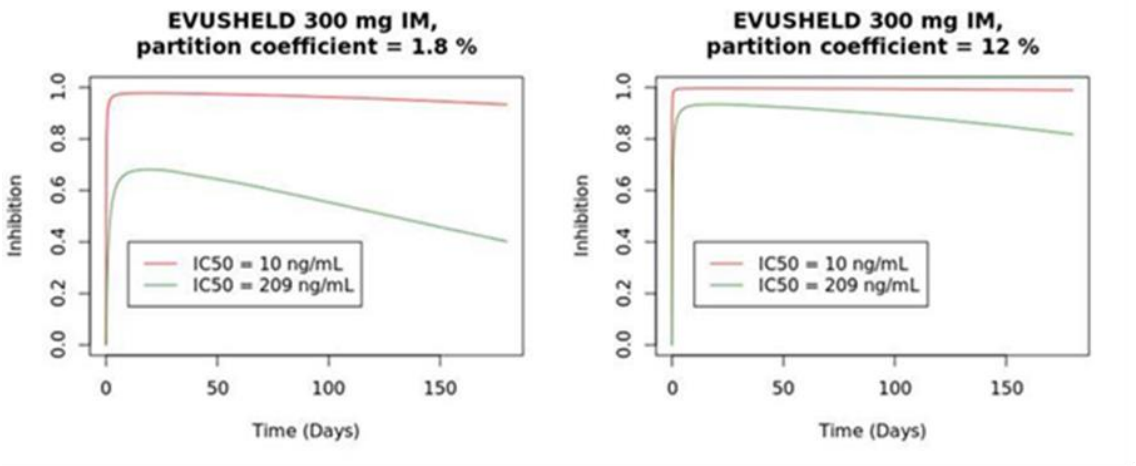
Figure 6: Predicted duration of protection against omicron SARS-CoV-2 strain post a single dose of 300 mg IM A) PK B) viral load dynamics for original and omicron variant IC_{50} values



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.

Efficacy predictions for variants is very dependent on the value used for lung partitioning. Using an alternative literature value of 12% or the value of 1.8% measured in NLF suggests efficacy could be limited against the omicron variant

Figure 7: Time course of %viral cell entry inhibition with EVUSHELD 300 mg IM over 6 months



SPECIAL STUDIES

Immunogenicity

The EVUSHELD antibodies were developed from B cells from SARS-CoV-2 convalescent patients, and fully human mAbs are expected to have a low immunogenicity risk.

At the time of the Day 211 data cut-off in Study D8850C00001, none of the participants (n = 50) in any of the 5 dose cohorts who received EVUSHELD had tested positive for ADA to either tixagevimab or cilgavimab. Thus, based on the available data, both ADA prevalence (percentage of ADA-positive participants in the study) and ADA incidence (percentage of treatment-emergent ADA-positive participants in the study) were 0%.

At the time of the primary analysis DCO in PROVENT, ADA incidence (the percentage of participants who were evaluable for ADA and were treatment-emergent ADA positive) was 0% for tixagevimab, cilgavimab, and EVUSHELD in the 46 ADA evaluable subjects with ADA data available through Day 58. Antidrug antibody data were not available at the time of completion of the primary STORM CHASER CSR.

For PROVENT, ADA data were available up to Day 58 for a subset of 36 participants who were ADA evaluable for tixagevimab (all participants in the safety analysis set with a baseline and at least one post baseline tixagevimab ADA result), 36 participants were ADA evaluable for cilgavimab, and 46 participants for EVUSHELD (all participants in the safety analysis set who are tixagevimab ADA evaluable and/or cilgavimab ADA evaluable). In the placebo arm, the number of ADA-evaluable participants were 19, 19, and 24, for tixagevimab, cilgavimab, and EVUSHELD, respectively.

Antidrug antibody prevalence (the percentage of ADA-evaluable participants with positive ADA results at any visit) were 0% (0/36), 2.8% (1/36), and 2.2% (1/46) for tixagevimab, cilgavimab, and EVUSHELD, respectively. The corresponding values for participants in the placebo group were 0% (0/19), 5.3% (1/19), and 4.2% (1/24) for tixagevimab, cilgavimab, and EVUSHELD, respectively. The percentage of ADA positive participants in the placebo groups is consistent with the targeted 1% false positive rate in the confirmatory assays.

Table 9: Summary of ADA responses to EVUSHELD following administration of 300 mg IM EVUSHELD through study Day 58 (ADA-Evaluable Analysis Set) in PROVENT

ADA Category	Statistics	EVUSHELD	
		Treatment (N = 46)	Placebo (N = 24)
ADA positive at any visit (ADA prevalence) [a]	n (%)	1 (2.2)	1 (4.2)
	Median of maximum titre	640.0	320.0
TE-ADA positive [b] (ADA incidence)	n (%)	0	1 (4.2)
	Median of maximum titre	0	320.0

a ADA positive to EVUSHELD is defined as having positive ADA result to tixagevimab and/or cilgavimab at any time, baseline or post-baseline. ADA prevalence is the proportion of ADA-positive participants in the EVUSHELD ADA-evaluable population.
b For tixagevimab and cilgavimab, TE-ADA positive is defined as either treatment-induced (ADA negative at baseline and ADA positive at ≥ 1 post-baseline assessments with ADA titre ≥ 2 times higher than the minimum required dilution of 80 and 40, for tixagevimab and cilgavimab, respectively) or treatment-boosted (baseline ADA titre that was boosted to ≥ 4-fold during the study period). A participant is TE-ADA positive for EVUSHELD if either tixagevimab and/or cilgavimab is TE-ADA positive. ADA incidence is the proportion of treatment-emergent participants in the EVUSHELD ADA-evaluable population.
The EVUSHELD ADA evaluable analysis set consists of participants in the safety analysis set who are tixagevimab ADA evaluable and/or cilgavimab ADA evaluable.
ADA, anti-drug antibody; DCO, data cut-off; IM, intramuscular; n, number of participants who were ADA positive; N, Number of participants in the ADA evaluable analysis set; TE-ADA, treatment-emergent ADA.

Overall, no treatment-emergent ADAs were observed in any study; the Phase III studies are ongoing and ADAs will continue to be assessed until the end of the studies.

Antiviral resistance
A similar proportion of PROVENT and STORM CHASER participants in EVUSHELD and placebo groups were infected with SARS-CoV-2 variants of concern and variants of interest circulating at the time of the studies. EVUSHELD retained *in vitro* neutralisation activity against available pseudoviruses expressing the entire SARS-CoV-2 spike protein (Alpha [B.1.1.7], Beta [B.1.351], Delta [B.1.617.2], Epsilon [B.1.427/B.1.429], B.1.375, B.1.1.519, and A_1), individual characteristic spike RBD substitutions (K417N, L452R, T478K, E484K, S494P, N501Y, Q675H, Q677H, P681H, and V1176F), and EVUSHELD binding site substitutions (L452R, T478K, E484K, and S494P) identified among variants within participants who received EVUSHELD.

IV.4 Clinical efficacy

In support of the application, the following Phase III, randomised, double-blind, placebo-controlled, parallel-group, prophylaxis studies were submitted:

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

The PROVENT (pre-exposure prophylaxis study) and STORM CHASER (post-exposure prophylaxis study) studies were initiated with cell pool derived EVUSHELD material. Once clonal cell line material (the intended commercial formulation) became available, an additional cohort in the PROVENT Phase III study was set up to allow for the assessment of clonal cell line material; 150 participants at 3 sites in the US received the clonal cell line material or placebo in a 2:1 ratio. The participants were recruited according to the current inclusion and exclusion criteria and were followed as per the schedule of activities.

The 300 mg IM dose was selected for both Phase III prophylaxis studies.

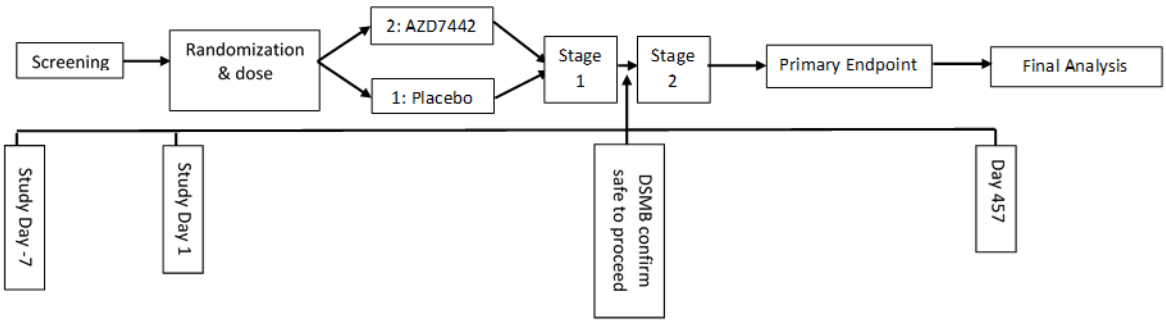
The data cut-off dates for the Phase III studies are given below

Study	Data cut-off (DCO)	Endpoints
D8850C00002 (PROVENT)	05 May 2021 (Primary analysis)	Efficacy (primary analysis), PK, nAbs
	29 August 2021 (August 2021 DCO)	High level results for key efficacy and safety only (median 6 months analysis; all ongoing participants had a minimum of 5 months' data)
D8850C00003 (STORM CHASER)	07 April 2021 (Primary analysis)	Efficacy (primary analysis), PK
	19 August 2021 (August 2021 DCO)	High level results for key efficacy and safety only (median 6 months analysis; all ongoing participants had a minimum of 5 months' data)

Study D8850C00002 (PROVENT)

PROVENT is an ongoing Phase III, randomised, double blind, placebo controlled, multicountry, multicentre study assessing the safety and efficacy of a single dose of EVUSHELD (× 2 sequential IM injections) compared to placebo for the prevention of COVID-19.

Figure 8: PROVENT, study schematic



Following screening (-7 to 0 days), randomization occurred in 2 stages and was contingent on safety. The primary analysis was planned to occur when approximately 24 primary endpoint events had been confirmed or 30% of study participants had become unblinded, whichever occurred first. A final analysis is planned when all participants complete the study (Day 457) and will be reported separately.
The DSMB evaluated the 7-day safety data from participants dosed in Stage 1 and advised the Sponsor on whether it was appropriate to proceed into Stage 2 of the study. The DSMB also regularly reviews study progress monthly and monitors for evidence of harm resulting from EVUSHELD.
Study Day was calculated from the reference start date which is defined as the day of the dose of IMP i.e., Day 1.
DSMB, Data Safety Monitoring Board; IMP, investigational medicinal product.

Participants were enrolled into one of 2 cohorts:

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

Study Participants

Main inclusion criteria:

- Participant must be ≥ 18 years of age at the time of signing the informed consent.
- Negative result from point of care SARS-CoV-2 serology (anti-nucleocapsid) testing at screening.

- Medically stable defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 1 month prior to enrolment, with no acute change in condition at the time of study enrolment as judged by the Investigator.
- Candidate for benefit from passive immunization with antibodies, defined as:

a. Increased risk for inadequate response to active immunization (predicted poor responders to vaccines) defined as:
   - Elderly ≥ 60 years old
   - Obese BMI ≥ 30
   - Congestive heart failure
   - Chronic obstructive pulmonary disease
   - Chronic kidney disease, i.e., GFR < 30 mL/min/1.73 m2
   - 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 (SAE) after receiving any approved vaccine.

b. 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 enrolment. Examples included:
   - 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
   - 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

- Female participants of childbearing potential must use one highly effective form of birth control. All male participants must use a condom from Day 1 and agree to continue through 365 days following administration of the IMP.

Main exclusion criteria:

- Significant infection or other acute illness, including fever > 100°F (> 37.8°C) on the day prior to or day of randomization.
- 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 SARS or 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 (e.g., 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.

Study treatment
Participants were randomised in a 2:1 ratio to receive a single IM dose of either 300 mg of EVUSHELD or saline placebo given as 2 sequential IM injections, one in each gluteal region, on Day 1. After administration of the dose of IMP on Day 1, participants underwent follow-up until Day 457.

The PROVENT study was initiated with cell pools material. Once clonal cell line material (the proposed commercial material) became available, an additional cohort in the PROVENT Phase III study was established to gain use experience in the clinic.

To allow for the assessment of clonal cell line material, 150 participants in the US were randomised to the clonal material or placebo in ratio 2:1. A PK analysis was planned for pooled versus clonal material.

Objectives and endpoints
Primary objectives:
- To estimate the efficacy of a single intramuscular (IM) dose of EVUSHELD 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 EVUSHELD compared to placebo.

Secondary objectives:
- To estimate the efficacy of a single IM dose of EVUSHELD compared to placebo for the prevention of SARS-CoV- 2 infection.
- To estimate the efficacy of a single IM dose of EVUSHELD compared to placebo for the prevention of severe or critical symptomatic COVID-19
- To estimate the efficacy of a single IM dose of EVUSHELD compared to placebo for the prevention of COVID-19-related Emergency Department visits
- To assess the pharmacokinetics (PK) of EVUSHELD administered as a single dose of 300 mg IM
- To evaluate anti-drug antibody (ADA) responses to EVUSHELD in serum

Exploratory objectives:
- To estimate the efficacy of a single IM dose of EVUSHELD compared to placebo for the prevention of COVID-19 through Day 366
- To evaluate the single dose pharmacokinetic concentrations of EVUSHELD in nasal fluid
- To determine anti-SARS-CoV-2 neutralising antibody (nAb) levels in serum following a single IM dose of EVUSHELD or placebo
- To quantify SARS-CoV-2 viral loads in infected participants treated with a single IM dose of EVUSHELD or placebo (illness visits)
- To quantify duration of viral shedding in participants with symptomatic COVID-19 treated with a single IM dose of EVUSHELD or placebo (illness visits)
- To characterize resistance to EVUSHELD (illness visits) – not covered by this SAP
- To assess the biometric profiles associated with COVID-19 using a biosensor in participants treated with a single IM dose of EVUSHELD or placebo (illness visits)

- To assess symptoms associated with COVID-19 using an e-Diary in participants treated with a single IM dose of EVUSHELD or placebo (illness visits only)
- To assess additional immune responses following a single IM dose of EVUSHELD or placebo

Objectives and endpoints are given in the table below.

Table 10: Objectives and endpoints PROVENT

Primary objectives	**Primary endpoints**
To estimate the efficacy of a single IM dose of EVUSHELD 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 EVUSHELD 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 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
Secondary objectives	**Secondary endpoints**
To estimate the efficacy of a single IM dose of EVUSHELD 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 EVUSHELD 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 EVUSHELD administered as a single dose of 300 mg IM	Serum AZD7442 concentrations
To evaluate ADA responses to EVUSHELD in serum	Incidence of ADA to AZD7442 in serum

ADA, anti-drug antibody; AE, adverse event; AESI, adverse event of special interest; AZD7442, EVUSHELD; COVID-19, coronavirus disease 2019; IM, intramuscular; IMP, investigational medicinal product; MAAE, medically attended adverse event; SAE, serious adverse event; RT PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

Randomisation and blinding

Participants were randomised in a 2:1 ratio to receive a single dose (× 2 IM injections) of either 300 mg of EVUSHELD or saline on Day 1. All participants were centrally assigned to a randomised IMP using an interactive Response Technology (IRT). Randomisation was stratified within each of the 2 cohorts (Cohort 1 and Cohort 2).

- Cohort 1: Adults ≥ 60 years of age. 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.

Participants were enrolled into the study in 2 stages, contingent upon safety.

This was a double-blind study. 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. As EVUSHELD and placebo are 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 was responsible for documenting and reporting 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 were unexpected and suspected to be causally related to the IMP and that potentially required 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

General methods

Categorical variables were summarised using frequency and percentages, where the denominator for calculation is the underlying analysis set population, unless otherwise stated. Continuous variables were summarised with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate. All point estimates were presented with a 95% CI, unless otherwise stated. p-values, corresponding to a 2-sided test, were presented for comparisons between treatments.

Primary analysis

The pre-planned primary efficacy endpoint was formally assessed at the primary analysis, which was conducted after approximately 24 primary endpoint events had been confirmed or 30% of study participants had become unblinded, whichever occurred first. A final efficacy analysis was to be conducted at the end of the study, i.e., when the last participant dosed had completed the Day 457 visit.

The primary efficacy endpoint 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 occurred post dose of IMP and prior to Day 183. Participants were included in the primary endpoint if they had RT-PCR-confirmed SARS-CoV-2 and met the qualifying symptoms.

The primary analysis was 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, analysed according to their randomised treatment.

A Poisson regression model with robust variance (Zou 2004) adjusting for follow-up time, was 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 EVUSHELD and the placebo groups. Efficacy was calculated as 1-relative risk,

which is the incidence of infection in the EVUSHELD group relative to the incidence of infection in the control group.

No missing data imputation method was used for primary efficacy analysis. Missing data due to early withdrawal from the study were counted as non-events in the primary analysis.

Supportive analyses
Two key supportive analyses of the primary endpoint were conducted. These key supportive analyses were included in the multiple testing hierarchy.

Estimands
The efficacy objectives, endpoints, and description of target estimation (estimand) including the chosen strategy for handling specific post-randomisation events (referred to as intercurrent events) and population level summary are further described in the table below (see Table 11).

The set of intercurrent events consisted 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 criteria for the relevant endpoint.

For the primary estimand, the intercurrent events were handled using a while on treatment strategy, where participants who experienced an intercurrent event were censored at the date of unblinding/receipt of first dose of COVID-19 product, whichever was earlier. The use of "while on treatment strategy" for handling intercurrent events was considered acceptable since data after unblinding and or vaccination is likely to bias treatment effect (this strategy was also applied to the key secondary estimand). Deaths that were caused by COVID-19 and all hospitalisations due to COVID-19 were handled using composite strategy and were counted as events in the primary analysis. Only adjudicated deaths were included in the efficacy analysis.

An estimand using the treatment policy strategy, which included all data for the primary endpoint, irrespective of unblinding and/or vaccination, was used for the two key supportive estimands. The primary analysis was repeated as follows:

- First key supportive estimand: First case of SARS-CoV-2 RT-PCR-positive symptomatic illness (regardless of unblinding/receipt of COVID-19 preventive product) post dose of IMP and prior to Day 183.

- Second key supportive estimand: First case of SARS-CoV-2 RT-PCR-positive symptomatic illness including all deaths post dose of IMP and prior to Day 183.

Table 11: Efficacy objectives and endpoints - PROVENT

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 prior to Day 183	**Population:** Full pre-exposure 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: Participants who become unblinded to treatment assignment and/or take a COVID-19 vaccine or other COVID-19 preventive product but, in both cases prior to having met the criteria for the primary efficacy endpoint, will be censored at the date of unblinding/receipt of first dose of COVID-19 preventive product, whichever is earlier (i.e., intercurrent events will be handled using a while on treatment strategy).
	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 SARS-CoV-2 infection	**Population:** Full pre-exposure analysis set
	Endpoint: 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.
	Intercurrent events: Participants who become unblinded to treatment assignment and/or take a COVID-19 vaccine or other COVID-19 preventive product, in both cases prior to having met the criteria for this endpoint, will be censored at the date of unblinding/receipt of first dose of COVID-19 preventive product, whichever is earlier (i.e., intercurrent events will be handled using a while on treatment strategy).
Other 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	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 EVUSHELD 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.

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.

The hierarchical testing strategy was carried out as follows:
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)

Additional sensitivity analyses to explore different methods for handling intercurrent events and different assumptions for missing data were also performed for the primary endpoint.

Results

Participant flow

As of the primary analysis data cut-off of 5th May 2021, 5254 participants (ratio 3500:1754) had been randomised, and 5197 (99%) had received the IMP. A total 5109 (97.2%) (3409 [97.4%] EVUSHELD and 1700 [96.9%] placebo) were ongoing in the study, and 145 (2.8%) participants (91 [2.6%] EVUSHELD and 54 [3.1%] placebo) had discontinued the study.

The discontinuations rate in the >=60 years group was higher in the placebo group compared to EVUSHELD group (35.2% vs 28.6%), whereas in the <60 years old group the discontinuation rate was higher in the EVUSHELD group compared to the placebo group (71.4% vs 64.8%).

The most common reasons for early discontinuation from the study were withdrawal by subject (60.7%), other reasons (19.3%), loss to follow up (13.1%) and death (5.5%). A higher proportion of deaths (7.4% vs 4.4%) and lost to follow-up (14.8% vs 12.1%) were noted in the placebo group compared to the EVUSHELD group.

At the 29th August 2021 DCO, 4991 (95.0%) participants (ratio 3334:1657) were ongoing in the study. A total of 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 EVUSHELD group (853 [48.6%] participants versus 1161 [33.2%] participants, respectively), there were no notable differences between the treatment groups.

Table 12: Participant flow, PROVENT (data cut-off: 5th May 2021)

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.

Baseline data

The demographic and other baseline characteristics in the two treatment groups of study PROVENT from the full analysis set are provided in the table below:

Table 13: Demographic characteristics, full analysis set, primary analysis, PROVENT (data cut-off: 5th May 2021)

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/m²)			
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/m²	43 (1.2)	18 (1.0)	61 (1.2)
≥ 18.5 to < 25 kg/m²	885 (25.6)	460 (26.5)	1345 (25.9)
≥ 25 to < 30 kg/m²	1067 (30.8)	538 (31.0)	1605 (30.9)
≥ 30 to < 40 kg/m²	1187 (34.3)	571 (32.9)	1758 (33.8)
≥ 40 kg/m²	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.

Participants who were at high-risk for severe COVID-19 were identified using the US Centres 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. At baseline 4028 (77.5%) participants were considered to have a high-risk for severe COVID-19, the most frequently reported high-risk categories for severe COVID-19 for this study population were obesity ≥ 30 kg/m2 (2168 [41.7%] participants), hypertension (1866 [35.9%]), and smoking 1090 [21.0%]).

Table 14: COVID-19 Comorbidities at baseline, full analysis set, primary analysis PROVENT (data cut-off: 5th May 2021)

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.

Numbers analysed
A total of 5172 (98.4%) randomised participants were included in the full pre-exposure analysis set. The reasons for exclusion from the full pre-exposure analysis set were balanced between the groups.

Table 15: Analysis sets, all randomised participants, primary analysis, PROVENT (data cut-off: 5th May 2021)

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 estimations

Primary endpoint

The primary analysis was conducted after 30% of study participants had become unblinded. All primary endpoint events (25 events) accrued up until the DCO (5th May 2021) were included in the primary analysis (see Table 16). The full pre-exposure analysis set is the primary analysis population.

Table 16: First SARS-CoV-2 RT-PCR-positive symptomatic illness – primary estimand, full pre-exposure analysis set, primary analysis, PROVENT (data cut-off: 5th May 2021)

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.
Percentages are based on the number of participants in the analysis by arm (N).
DCO: 05 May 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

A summary of qualifying symptoms for the primary endpoint is shown in Table 17 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 17: Summary of qualifying symptoms for definition of primary efficacy endpoint, full pre-exposure analysis set, primary analysis, PROVENT (data cut-off: 5th May 2021)

Events occurring post-dose	Number (%) of participants	
	AZD7442 (N = 3441)	Placebo (N = 1731)
All participants with SARS-CoV-2 RT-PCR-positive symptomatic illness[a]	10 (0.3)	20 (1.2)
No minimum duration		
Fever	0	9 (0.5)
Shortness of breath	2 (0.1)	6 (0.3)
Difficulty breathing	0	3 (0.2)
New onset confusion (participants ≥ 60 years)	0	0
Appetite loss or decrease food intake (participants ≥ 60 years)	0	0
Increased supplemental oxygen requirement (participants ≥ 60 years on baseline supplemental oxygen)	0	0
Present for ≥ 2 days		
Chills	2 (0.1)	9 (0.5)
Cough	4 (0.1)	15 (0.9)
Fatigue	5 (0.1)	16 (0.9)
Muscle aches	3 (0.1)	9 (0.5)
Body aches	1 (0.0)	7 (0.4)
Headache	4 (0.1)	9 (0.5)
New loss of taste	1 (0.0)	6 (0.3)
New loss of smell	1 (0.0)	8 (0.5)
Sore throat	5 (0.1)	4 (0.2)
Congestion	7 (0.2)	7 (0.4)
Runny nose	3 (0.1)	11 (0.6)
Nausea	3 (0.1)	3 (0.2)
Vomiting	0	1 (0.1)
Diarrhea	0	3 (0.2)
Participants with SARS-CoV-2 RT-PCR-positive collected > 5 days prior to symptom illness	0	0
Participants with SARS-CoV-2 RT-PCR-positive collected > 10 days post symptom illness	0	1 (0.1)
Present for ≥ 2 days		
Chills	0	1 (0.1)
Headache	0	1 (0.1)
Vomiting	0	1 (0.1)
Diarrhea	0	1 (0.1)

[a] Events presented are not censored at time of unblinding and/or COVID-19 vaccination.
Presented event categories are mutually exclusive and participants are only counted once across the event categories.
DCO: 05 May 2021

Events occurring post-dose	Number (%) of participants	
	AZD7442 (N = 3441)	Placebo (N = 1731)
Participants with symptomatic illness only	227 (6.6)	89 (5.1)
No minimum duration		
Fever	21 (0.6)	15 (0.9)
Shortness of breath	29 (0.8)	17 (1.0)
Difficulty breathing	14 (0.4)	14 (0.8)
New onset confusion (participants ≥ 60 years)	0	0
Appetite loss or decrease food intake (participants ≥ 60 years)	5 (0.1)	1 (0.1)
Increased supplemental oxygen requirement (participants ≥ 60 years on baseline supplemental oxygen)	0	1 (0.1)
Present for ≥ 2 days		
Chills	29 (0.8)	12 (0.7)
Cough	86 (2.5)	38 (2.2)
Fatigue	86 (2.5)	32 (1.8)
Muscle aches	36 (1.0)	14 (0.8)
Body aches	37 (1.1)	14 (0.8)
Headache	71 (2.1)	36 (2.1)
New loss of taste	12 (0.3)	4 (0.2)
New loss of smell	9 (0.3)	4 (0.2)
Sore throat	60 (1.7)	25 (1.4)
Congestion	73 (2.1)	33 (1.9)
Runny nose	68 (2.0)	29 (1.7)
Nausea	29 (0.8)	9 (0.5)
Vomiting	14 (0.4)	3 (0.2)
Diarrhea	28 (0.8)	10 (0.6)

Presented event categories are mutually exclusive and participants are only counted once across the event categories.
DCO: 05 May 2021

The study met its primary endpoint. The estimated Relative risk reduction (RRR) and corresponding 95% confidence interval (95% CI) for first SARS-CoV-2 RT-PCR-positive while on treatment was 76.73% (46.05, 89.96), p-value <0.001.

Key supportive analyses
The key supportive estimands were supportive of the primary analysis (see Table 18).

Fist key supportive estimand: The estimated RRR (95% CI) regardless of unblinding and vaccination status for first SARS-CoV-2 RT-PCR-positive was 77.29% (52.01, 89.25), p-value <0.001.

Second key supportive estimand: A reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness or death from any cause was observed in EVUSHELD group with relative risk reduction of 68.78% (95% CI: 35.64,84.86; p-value = 0.002) compared to the placebo group.

Table 18: Primary endpoint - key supportive estimands, full pre-exposure analysis set, primary analysis, PROVENT (data cut-off: 5th May 2021)

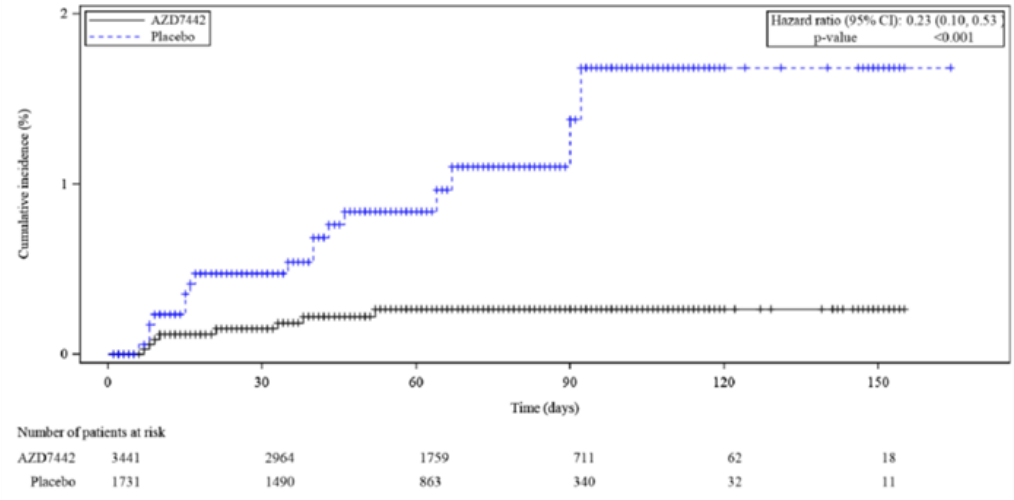
Endpoint	AZD7442 300 mg IM (N = 3441)	Placebo (N = 1731)
First case of SARS-CoV-2 RT-PCR-positive symptomatic illness (regardless of unblinding/receipt of COVID-19 preventive product)		
n (%)	10 (0.3)	22 (1.3)
RRR	77.29	
(95% CI)	(52.01, 89.25)	
p-value	< 0.001	
First case of SARS-CoV-2 RT-PCR-positive 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; IM, intramuscular; RRR, relative risk reduction; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Key supplementary analyses of primary efficacy endpoint
Time to SARS-CoV-2 RT-PCR positive symptomatic illness was longer in the EVUSHELD group compared to placebo. The hazard ratio (95% CI) was 0.23 (0.10, 0.53); p-value < 0.001 (see Figure 15).

The estimated absolute risk reduction (ARR) (95% CI) for first SARS-CoV-2 RT-PCR-positive while on treatment was 0.75% (0.33%, 1.35%); p-value <0.001. The number of events in the EVUSHELD group and placebo group were 8/3441 (0.2%) and 17/1731 (1.0%) respectively. The number needed to treat was 134 (95% CI: 75, 304).

Figure 9: Time to first SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post-dose of IMP Kaplan-Meier curves by group, supplementary analysis, full pre-exposure analysis set, primary analysis, PROVENT (data cut-off: 5th May 2021)



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).
DCO: 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

Key secondary endpoint

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 those who had received placebo, with an RRR (95% CI) of 51.07 (10.57, 73.23); p-value 0.020. The corresponding number of events in the EVUSHELD group and the placebo group were 21/3123 (0.7%) and 21/1564 (1.3%) respectively (see Table 19).

Table 19: Incidence of participants who had a post-treatment response for SARS-Cov-2 nucleocapsid antibodies, full pre-exposure analysis set, primary analysis, PROVENT (data cut-off: 5th May 2021)

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).
DCO: 05 May 2021
CI, confidence interval; DCO, data cut-off; RRR, relative risk ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Secondary endpoint
There were 0 participants with SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness in the EVUSHELD group compared to 1 (0.1%) participant in the placebo arm.

There were 6 (0.2%) participants in the EVUSHELD group who attended the emergency department due to COVID-19-related symptoms, as determined by the Investigator, compared to 0 in the placebo arm.

Subgroup analysis
Subgroup analyses for the key secondary endpoint (incidence of first SARS-CoV-2 RT-PCR positive symptomatic illness occurring at any time post baseline) 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, region and various individual risk factors for COVID-19. The RRR of EVUSHELD compared to placebo and corresponding 95% CI were derived using a Poisson Regression with robust variance. Estimates of RRR were generally consistent across the pre-defined subgroups and supportive of EVUSHELD.

Results from data provided at the data cut-off 29th August 2021
Results based on additionally provided data at the 29th August 2021 DCO, conducted 5 months after last participant dosed with a median follow up of 6-months are supportive of EVUSHELD. p-values are nominal.

Primary endpoint

Table 20: First SARS-CoV-2 RT-PCR-positive symptomatic illness – primary estimand, full pre-exposure analysis set, PROVENT (data cut-off: 29th August 2021)

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 (%)	11 (0.3)	31 (1.8)
RRR	82.80	
(95% CI)	65.79, 91.35	
p-value	< 0.001	

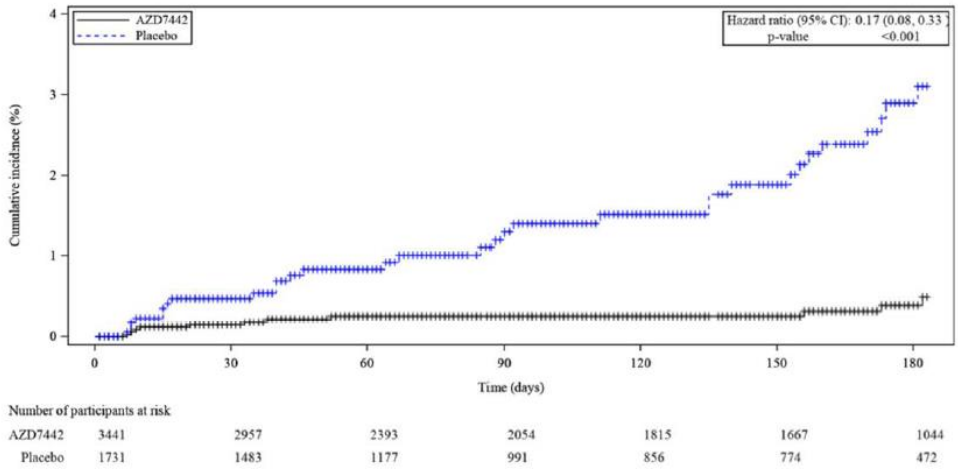
Estimates are based on a Poisson regression with robust variance. The model includes covariate for treatment (AZD7442 versus placebo), and age at informed consent (≥ 60 years versus < 60 years), with the log of the follow-up time as an offset. Estimated RRR greater than 0% provides evidence in favor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

Table 21: Key supportive analyses of primary efficacy endpoint PROVENT (data cut-off: 29th August 2021)

Endpoint	AZD7442 300 mg IM (N = 3441)	Placebo (N = 1731)
First case of SARS-CoV-2 RT-PCR-positive symptomatic illness (regardless of unblinding/receipt of COVID-19 preventive product)		
n (%)	20 (0.6)	44 (2.5)
RRR	77.43	
(95% CI)	61.72, 86.69	
p-value	< 0.001	
First case of SARS-CoV-2 RT-PCR-positive symptomatic illness including all deaths		
n (%)	18 (0.5)	36 (2.1)
RRR	75.77	
(95% CI)	57.33, 86.23	
p-value	< 0.001	

Key supplementary analyses of primary efficacy endpoint

Figure 10: 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, PROVENT (data cut-off: 29th August 2021)



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.

Key secondary endpoint

Table 22: Incidence of participants who had a post-treatment response for SARS-Cov-2 nucleocapsid antibodies, full pre-exposure analysis set, PROVENT (data cut-off: 29th August 2021)

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

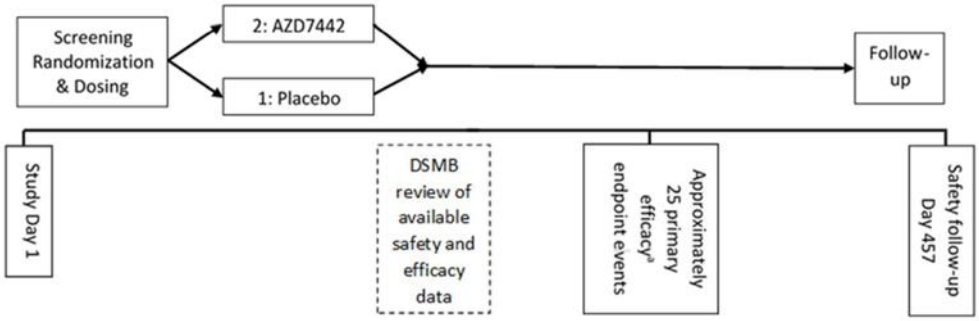
CI, confidence interval; DCO, data cut-off; IM, intramuscular; N, number of participants in the full pre-exposure analysis set; n, Number of participants included in analysis; RRR, relative risk ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Study D8850C00003 (STORM CHASER)

STORM CHASER is an ongoing Phase III, randomised, double-blind, placebo-controlled, multicentre study assessing the safety and efficacy of a single dose of EVUSHELD (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 11: STORM CHASER, study schematic



[a] Primary analysis to be conducted 30 days after the 25th event is observed.

Note: An independent DSMB will review available safety and efficacy data after the first 100 participants have been dosed, or after 4 weeks from first participant dosed, whichever comes first. Enrollment will not be paused pending the DSMB's review.

Participants were stratified into one of 2 cohorts:

- Cohort 1: Adults ≥ 60 years of age, living in long-term care facilities. In this context, long term care facilities include 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" 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.

- 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 may include, but are 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.

Study Participants

Main inclusion criteria:

- Participant must be ≥ 18 years of age at the time of signing the informed consent.
- Prior to enrolment, participants must not have had COVID-19 symptoms within 10 days of dosing.
- Negative result from point of care SARS-CoV-2 serology testing at screening.

- Participants will be 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:
  i. Long-term care facilities, including skilled nursing homes, assisted living homes, independent living residences for the elderly. Residents, health care workers in such 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.
  ii. 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 are eligible under this criterion.
  iii. Military settings including but not limited to barracks, ships, or other close-quarters working environments. Military and civilian personnel exposed in such settings are eligible.
  iv. Health care facilities. Health care workers and other staff exposed in such setting are eligible under this criterion.
  v. University or college dormitories. Students exposed in such setting are eligible.
  vi. Household contacts. Any adult living in the same household as an index case are 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.
- Participants were required to use suitable contraception

Main exclusion criteria:

- History of laboratory-confirmed SARS-CoV-2 infection or SARS-CoV-2 seropositivity at screening
- History of infection with SARS or 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 (e.g., 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, in the judgement 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
- 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 EVUSHELD program, 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 enrolment of participants who lack capacity to provide their own informed consent, such participants are excluded.

Study treatment
Participants were randomised in a 2:1 ratio to receive a single dose (2 sequential IM injections) of either 300 mg of EVUSHELD (n = 756) or saline placebo (n = 375), given as two sequential IM injections of tixagevimab and cilgavimab, (one in each gluteal region), or corresponding placebo on Day 1.

Objectives and endpoints
Primary objectives:
- To estimate the efficacy of a single IM dose of EVUSHELD compared to placebo for the prevention of COVID-19
- To assess the safety and tolerability of a single IM dose of EVUSHELD compared to placebo

Secondary objective:
- To estimate the efficacy of a single IM dose of EVUSHELD compared to placebo for the prevention of severe or critical symptomatic COVID-19

Other secondary objectives:
- To estimate the efficacy of a single IM dose of EVUSHELD compared to placebo for the prevention of SARS-CoV-2 infection
- To estimate the efficacy of a single IM dose of EVUSHELD compared to placebo for the prevention of COVID-19-related death
- To estimate the efficacy of a single IM dose of EVUSHELD compared to placebo for the prevention of all-cause mortality

Table 23: 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).
	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 (i.e., intercurrent events will be handled using treatment policy strategy).
Secondary	
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.
To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19-related death	The incidence of COVID-19-related death occurring after dosing with IMP.
To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of all-cause mortality	The incidence of all-cause mortality occurring after dosing with IMP.
To assess the pharmacokinetics of AZD7442 administered as a single dose of 300 mg IM	Serum AZD7442 concentrations. PK parameters if data permit.
To evaluate ADA responses to AZD7442 in serum	Incidence of ADA to AZD7442 in serum.

ADA, antidrug antibody; AE, adverse event; AESI, adverse event of special interest; COVID-19, coronavirus disease 2019; PK, pharmacokinetic; IM, intramuscular; IMP, investigational medicinal product; MAAE, medically attended adverse event; RT-PCR, reverse transcriptase polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.
AZD7442, EVUSHELD

Randomisation and blinding
Eligible participants were randomised in a 2:1 ratio to receive a single IM dose of EVUSHELD (divided in 2 sequential injections, one for each mAb component) (the active group, n = approximately 750) or saline placebo (the control group, n = approximately 375) on Day 1.

All participants were centrally assigned to a randomised IMP using an interactive remote technology (IRT).

Randomisation was 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 include skilled nursing facilities, assisted living facilities, and independent living facilities for senior adults.
- Cohort 2: Other adults ≥ 18 years of age with who have been exposed to a specific identified individual with laboratory-confirmed SARS-COV-2 infection. Such individuals may include, but are 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.

Neither the participant nor any of the investigators or Sponsor staff involved in the treatment or clinical evaluation and monitoring of the participants were aware of the IMP received. Since EVUSHELD and placebo are visually distinct prior to dose preparation, IMP was handled by an unblinded pharmacist at the study site. Syringe masking was required in order to maintain the blind. The IRT provided the investigator(s) or pharmacists with 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 broken except in medical emergencies when the appropriate management of the participant required knowledge of the treatment randomisation. The investigator was responsible for documenting and reporting 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 were unexpected and that were suspected to be causally related to the IMP and that potentially required 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. The IRT was programmed with blind-breaking instructions.

Statistical methods
General methods
For continuous data, descriptive statistics (i.e., n [number of participants with available data], mean, standard deviation [SD], median, minimum, maximum, and quartile values) were presented by treatment group and visit, when applicable. For concentration data and log-transformed data, descriptive statistics (i.e., n [number of participants with available data], n < lower limit of quantification (LLOQ) [number of participants with results below the limit of quantification], geometric mean, arithmetic mean, SD, co-efficient of variation, median, min and max) were presented by treatment group and visit, when applicable. For categorical data, the number and percentages of participants in each category were presented by treatment group and visit, when applicable. The denominator for percentage calculations was the underlying analysis set population N values unless otherwise stated.

Primary 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.

For the primary analysis, relative risk reduction (RRR) and its corresponding 95% CI were estimated from a Poisson regression model with robust variance, adjusting for follow-up time. The RRR was expressed as 100% x (1- relative risk). If a participant's first case of SARS-CoV-2 RT-PCR positive symptomatic illness occurs on or after Day 183, the participant was considered as not having met the primary endpoint.

No missing data imputation method was used for primary efficacy analysis. For participants who withdraw from the study prior to having met the criteria for the primary efficacy endpoint, absence of data following these participants' withdrawal (or lost to follow-up, death not caused by SARS-CoV-2) was treated as missing. Participants were considered as not having the event through the time of their last observation.

Efficacy summaries were presented with a 2-sided 95% CI. Statistical significance was achieved if the lower bound of the 2-sided 95% CI was > 0.

If the primary endpoint achieves statistical significance a hierarchical approach was planned to be used to control for multiplicity of the primary and key secondary efficacy endpoints at 5% two-sided significance level.

Subgroup analyses were performed in pre-specified subgroups including age at informed consent, sex, race, ethnicity, COVID-19 co-morbidities at baseline, SARS-CoV-2 RT-PCR status at baseline, and High Risk for severe COVID-19 at baseline. The subgroup analyses were designed to be exploratory.

Estimands

The efficacy objectives, endpoints, and description of target estimation (estimand) including the chosen strategy for handling specific post-randomisation events (referred to as intercurrent events), and population level summary are further described in the table above (see Table 23).

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, analysed 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 primary estimand uses a treatment policy strategy for handling intercurrent events. Data 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, are collected and analysed regardless of the intercurrent event. There is a concern that unblinding of participants may introduce bias. Additional estimands for the primary efficacy were planned using a while on treatment strategy for handling the intercurrent events in the FAS and treatment policy strategy based on the per-protocol population (PP).

Participants with deaths that are caused by SARS-CoV-2 (death related to COVID marked on the death eCRF page) or hospitalizations that are characterised to be severe COVID-19 were considered as having the event i.e. using a composite strategy.

Sensitivity analyses were used to assess the robustness of treatment effects for the primary efficacy endpoint, where different missing data mechanisms were explored using multiple imputation approaches.

Results

Participant flow

At the time of the primary efficacy analysis (7th April 2021 data cut-off date), a total of 1131 participants were randomised (756:375) and 1121 (749:372) were dosed.
A total of 21 (1.9%) participants discontinued from the study. Discontinuation rates overall were low but the discontinuation rate was higher in the EVUSHELD group compared to the placebo group (2.0% vs 1.6%).

The most common reasons for discontinuations were withdrawal by subject (n=10), other (n=7), lost to follow up (n=2), physician decision (n=1), and protocol deviation (n=1). There were no deaths.

A higher proportion of participants in the placebo group compared to the EVUSHELD group were unblinded (14.1% vs 8.2%). Similarly, the rate of vaccination was higher in the placebo group compared to the EVUSHELD group (12.5% vs 3.4%).

The median follow-up times were similar between the groups. The median time from IMP to primary analysis was 48 days in the placebo group and 49 days in the EVUSHELD group.

Table 24: Participant disposition, all participants analysis set; STORM CHASER (data cut-off: 7th April 2021)

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

Category	Number (%) of Participants		
Sub category	AZD7442 300 mg IM	Placebo	Total
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.

Baseline data

A total of 548 (48.9%) participants had potential COVID-19 comorbidities identified from their medical history at baseline.

Table 25: Key demographic characteristics, full analysis set, primary analysis, STORM CHASER (data cut-off: 7th April 2021)

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/m²)	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.

Table 26: High risk for severe COVID-19 at baseline, full analysis set, STORM CHASER (data cut-off: 7th April 2021)

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.

Numbers analysed

As of the primary efficacy analysis based on the 07 April 2021 DCO, 1131 participants had been randomised (ratio 756: 375). A total of 1121 had received the IMP (ratio 749:372), and 1110 (ratio 741: 369) 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 FAS.

Table 27: Analysis sets – all randomised participants, primary analysis STORM CHASER (data cut-off: 7th April 2021)

Analysis Set	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)
Reason for exclusion			
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)
Reason for exclusion			
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)
Reason for exclusion			
Not dosed	7 (0.9)	3 (0.8)	10 (0.9)
No data available	579 (76.6)	368 (98.1)	947 (83.7)
Blood samples 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)
Reason for exclusion			
Not dosed with AZD7442	7 (0.9)	375 (100)	382 (33.8)
At data cut off did not have serum concentration data available	551 (72.9)	0	551 (48.7)
Had an exclusionary protocol deviation	0	0	0

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

[b] The safety analysis set included all participants who received at least one injection of IMP. Participants were classified according to actual treatment.

[c] The SARS-CoV-2 nAb evaluable analysis set included all participants who received at least one injection of IMP from whom blood samples were assumed to be unaffected by factors such as protocol violations, and who had at least one quantifiable serum observation post-dose. Participants were classified according to actual treatment. A participant who has received one injection of active IMP will be classified as active.

[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 to be unaffected 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.

DCO: 07 April 2021

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

DCO, data cut-off; IM, intramuscular; IMP, investigational medicinal product; nAb, neutralizing antibody; PK, pharmacokinetic; SARS-CoV-2, severe acute respiratory

Outcomes and estimations

Primary endpoint

The primary endpoint failed to achieve statistical significance. The relative risk reduction (95% CI) was 33.31% (-25.92, 64.68); p-value=0.212, based on the FAS.

The results of the key secondary endpoint are consistent with the primary analysis showing lack of significant treatment effect in terms of SARS-COV-2 RT-PCR-positive with severe

critical symptoms. There was 0/749 case in the EVUSHELD group and 1/372 case in the placebo group.

Table 28: First SARS-CoV-2 RT-PCR-positive symptomatic illness, full analysis set, primary analysis, STORM CHASER (data cut-off: 7th April 2021)

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.

Key supplementary analyses of primary efficacy endpoint

Key secondary endpoint:
There were no participants with SARS-CoV-2 RT PCR positive severe or critical symptomatic illness in the EVUSHELD group compared to one (0.3%) participant in the placebo group.

Other secondary endpoints:
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 not statistically significantly lower for participants who had received EVUSHELD compared to placebo, consistent with the primary result

No COVID-19-related deaths occurred after dosing in the EVUSHELD group or placebo group.

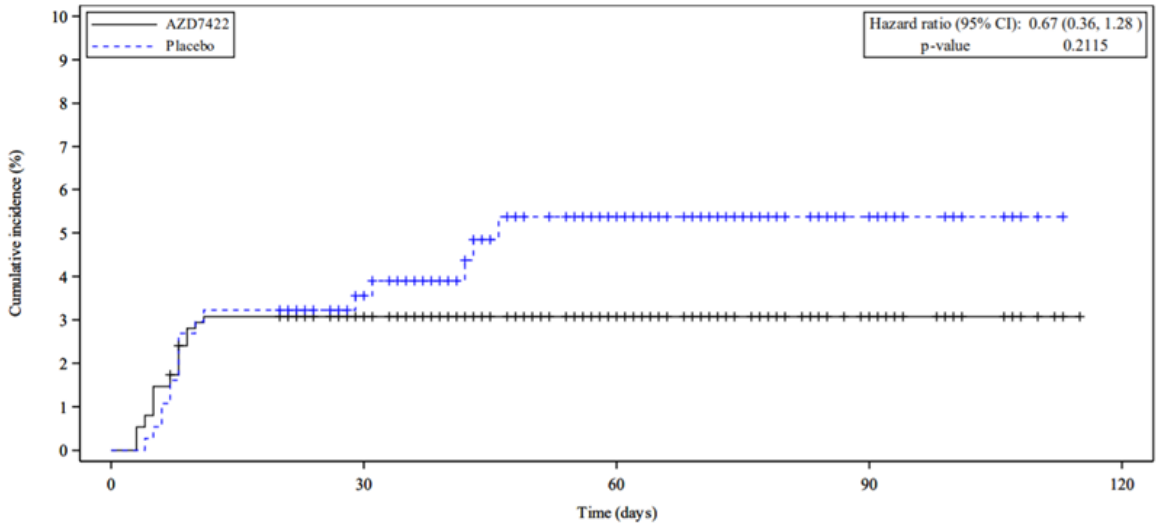
There were no all-cause mortality events in the EVUSHELD or placebo groups.

Supplementary analyses
The supplementary analyses for absolute risk reduction (ARR) and hazard ratio, based on the FAS, found no statistical difference between EVUSHELD and placebo in the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness in line with the primary analysis. The ARR (95% CI) was 1.50 (-0.76, 4.32); p-value =0.231. The number of participants with events was 23/749 (3.1%) and 17/372 (4.6%) in the EVUSHELD group and placebo group, respectively.

The hazard ratio for the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness in the EVUSHELD group was 0.67 (95% CI 0.36, 1.28); p-value = 0.215. The Kaplan-Meier plot showed that there were no cases of SARS-CoV-2 RT-PCR-positive symptomatic

illnesses in the EVUSHELD group after Day 11 compared with the placebo group where there were 5 cases.

Figure 12: Time to first SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose of IMP, Kaplan-Meier Curves by group, supplementary analysis, full analysis set, primary supplementary analysis STORM CHASER (data cut-off: 7th April 2021)



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.

Subgroup analysis
Analyses were conducted in pre-specified subgroups for the incidence of first SARS-CoV-2 RT-PCR-positive symptomatic illness and these were generally consistent with the primary analysis.

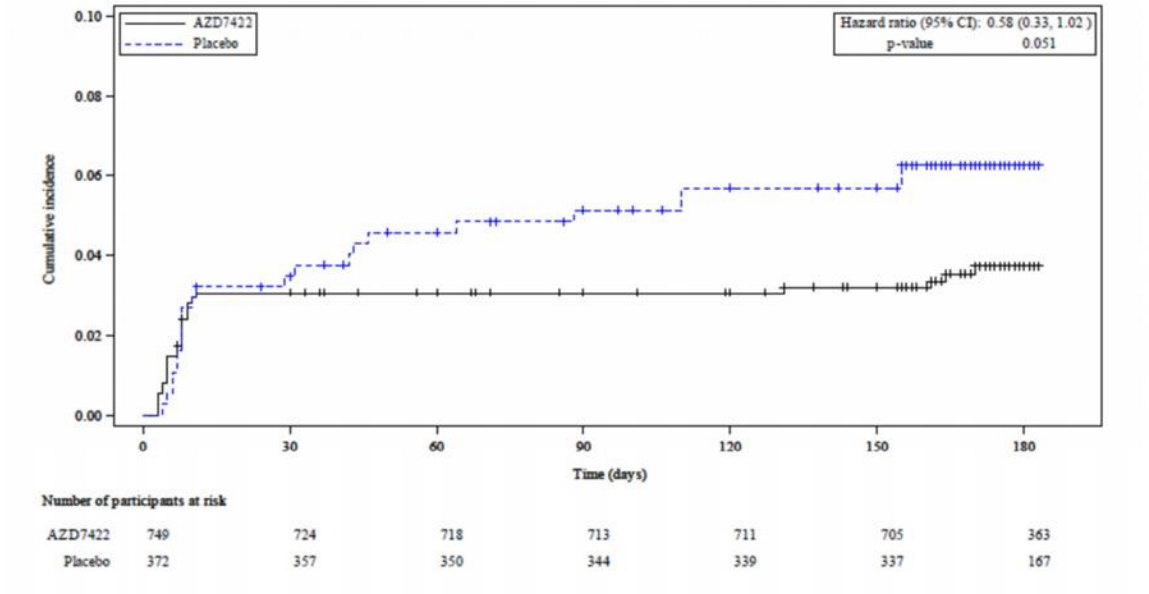
Results from data provided at the DCO 19th August 2021
Additionally provided 6-months data at the 19th August 2021 DCO is presented below.

Table 29: Participant disposition (all participants analysis set), STORM CHASER (data cut-off: 19th August 2021)

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

Figure 13: Time to first SARS-CoV-2 RT PCR positive symptomatic illness occurring post-dose of IMP, Kaplan Meier Curves by group, supplementary analysis, full analysis set, STORM CHASER (data cut-off: 19th August 2021)



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.
6-month DCO: 19 August 2021
CI, confidence interval; DCO, data cut-off; 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.

The additionally provided 6-months data at the 19th August 2021 DCO for the primary endpoint are shown below (see Table 30). The updated results for the primary endpoint are

border line significant (p=0.049). It is noted that the number of events increased in both group with more events in the placebo group.

Table 30: Primary endpoint, full analysis set, STORM CHASER (data cut-off: 19th August 2021)

Statistic	AZD7442 300 mg IM (N = 749)	Placebo (N = 372)
Primary endpoint - first SARS-CoV-2 RT-PCR-positive symptomatic illness		
n (%)	27 (3.6)	23 (6.2)
RRR	43.21	
(95% CI)	0.14, 67.70	
P-value	0.049	

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

IV.5 Clinical safety

Safety data are available for 5197 participants in PROVENT (3461 of whom received EVUSHELD 300 mg IM),1121 participants in STORM CHASER (749 of whom received EVUSHELD 300 mg IM) and 903 participants in TACKLE (452 of whom received EVUSHELD 600 IM). In addition, there are safety data from the Phase 1 PK study in 60 healthy volunteers, 50 of whom received EVUSHELD. Pooled safety data were provided for PROVENT and STORM CHASER. The PROVENT and STORM CHASER studies were initiated with cell pool material. Once clonal cell line material (the proposed commercial material) became available, this DP supplied an additional cohort in the PROVENT Phase III study to gain use experience in the clinic. To allow for the assessment of clonal cell line material, 150 participants were planned to be randomised 2:1 in PROVENT.

The data cut off dates for each study are given in the table below.

Table 31: Data cut-off dates for safety data for studies included in this application

Study	DCO (Term Used in Text)	Endpoints
D8850C00002, PROVENT	29 June 2021 (June 2021 DCO)	Safety (minimum of 3 months' data on all participants) PK for cell pools material versus clonal cell line material
	29 August 2021 (August 2021 DCO)	High-level results for key efficacy and safety (median 6 months analysis; all ongoing participants had a minimum of 5 months' data)
D8850C00003, STORM CHASER	19 June 2021 (June 2021 DCO)	Safety (minimum of 3◦months' data on all participants)
	19 August 2021 (August 2021 DCO)	High-level results for key efficacy and safety only (median 6 months analysis; all ongoing participants had a minimum of 5 months' data)

D8850C00001, Phase I	06 June 2021	Safety, PK, nAbs (Day 271 for Cohorts 1a and 1b; Day 211 for Cohorts 2, 3, and 4)

Additionally, safety data in support of 600 mg dose of EVUSHELD (300 mg tixagevimab and 300 mg cilgavimab) were obtained from the clinical trial TACKLE, a Phase III, double-blind, placebo-controlled clinical trial for the treatment of adult patients (≥18 years of age) with mild to moderate COVID-19 (an indication for which EVUSHELD is not approved). TACKLE enrolled non-hospitalised adults (with the exception of those hospitalized for isolation purposes) with mild to moderate COVID-19 (within ≤7 days of symptom onset). Four-hundred and fifty-two (452) patients have received 600 mg IM EVUSHELD in TACKLE. The median duration for safety follow-up was 84 days.

The overall safety profile in patients who received 600 mg IM EVUSHELD was generally similar to that reported in participants who received 300 mg IM EVUSHELD. The most frequently reported adverse reaction in TACKLE was injection site reaction (2.4%). All SAEs observed in this study are described below.

Phase 1 (D8850C00001)
Study D8850C00001 was an ongoing Phase I, FTIH, dose escalation study to evaluate the safety, tolerability, and PK of EVUSHELD in healthy adults aged 18 to 55 years of age. Sixty participants in 5 cohorts (randomised 10:2 to either EVUSHELD or placebo) were administered doses of either 300 mg IV, 300 mg IM, 1000 mg IV or 3000 mg IV. At the data cut-off date in June 2021 all participants in Cohort 1a and Cohort 1b had completed their Day 271 visit and all participants in Cohorts 2, 3, and 4 had completed their Day 211 visit. Overall AEs were similar across treatment groups. All AEs were either mild or moderate in intensity with no AEs of severe intensity. The only AEs reported in more than one participant in any group were: headache, abdominal distension, abdominal pain, toothache, fatigue, and oropharyngeal pain. There were no dose-related trends observed. AEs of special interest were anaphylaxis and other serious hypersensitivity reactions, including immune complex disease. No participants reported an AE of special interest. There were no apparent differences between treatment groups in mean clinical chemistry parameters, haematology or coagulation parameters over time, or in shifts from normal to high/low in individual parameters. There were also no apparent differences between treatment groups in relation to 12-lead safety ECG or vital parameters. No participants reported injection site reactions.

Pooled safety data from prophylaxis studies: PROVENT & STORM CHASER
Pooled safety data are available at the data cut offs given in the above table. Participants in each study (PROVENT and STORM CHASER) received the same 300 mg IM dose and had similar study procedures and schedule of activity/assessments.

Patient exposure
A total of 4210 adult participants received 300 mg IM EVUSHELD in Phase III prophylaxis studies. In addition, 50 adult participants (10 in each dose group) received EVUSHELD 300 mg IM, 300 mg IV, 1000 mg IV, 3000 mg IV (all administered as sequential injections or infusions), or 3000 mg IV co-administered in a single infusion in a Phase I study. In total, 4260 participants were exposed to EVUSHELD in the clinical trials included in the application. Due to the nature of the drug product, exposure for all participants included in the safety analysis set in each study was 100%. Median (min, max) duration of follow-up was 137 (3, 221) days in PROVENT and 121 (5, 188) days in STORM CHASER.

Baseline demographics

Across both prophylaxis 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%). For each study, the COVID-19 co-morbidities of the study populations were balanced between treatment groups. 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-CoV2 RT-PCR negative at baseline (96.3% vs 87.1%).

Table 32: Selected demographic and other baseline characteristics – PROVENT, STORM CHASER, and POOLED (data cut-off: June 2021)

	PROVENT			**STORM CHASER**			**POOLED**		
Characteristic	300mg (N = 3460)	PCB (N = 1737)	Total (N = 5197)	300mg (N = 749)	PCB (N = 372)	Total (N = 1121)	300mg (N = 4210)	PCB (N = 2108)	Total (N = 6318)
Age (years)									
Median	57.0	57.0	57.0	48.0	47.0	48.0	55.0	55.0	55.0
Missing	2 (0.1)	2 (0.1)	4 (0.1)	0	0	0	2 (0.0)	2 (0.1)	4 (0.1)
High risk for severe COVID-19 at baseline, n (%)									
Any high risk for severe COVID-19 at baseline, n (%)	2667 (77.1)	1362 (78.4)	4029 (77.5)	486 (64.9)	240 (64.5)	726 (64.8)	3154 (74.9)	1601 (75.9)	4755 (75.3)
Obesity (> = 30 kg/m2)	1456 (42.1)	712 (41.0)	2168 (41.7)	287 (38.3)	158 (42.5)	445 (39.7)	1743 (41.4)	870 (41.3)	2613 (41.4)
Chronic kidney disease	184 (5.3)	86 (5.0)	270 (5.2)	16 (2.1)	7 (1.9)	23 (2.1)	200 (4.8)	93 (4.4)	293 (4.6)
Diabetes	492 (14.2)	242 (13.9)	734 (14.1)	91 (12.1)	38 (10.2)	129 (11.5)	583 (13.8)	280 (13.3)	863 (13.7)
Immunosuppressive disease	15 (0.4)	9 (0.5)	24 (0.5)	0	0	0	15 (0.4)	9 (0.4)	24 (0.4)
Immunosuppressive treatment	110 (3.2)	64 (3.7)	174 (3.3)	6 (0.8)	2 (0.5)	8 (0.7)	116 (2.8)	66 (3.1)	182 (2.9)
CV disease	**272 (7.9)**	**151 (8.7)**	**423 (8.1)**	**19 (2.5)**	**14 (3.8)**	**33 (2.9)**	**291 (6.9)**	**165 (7.8)**	**456 (7.2)**
COPD	179 (5.2)	95 (5.5)	274 (5.3)	7 (0.9)	12 (3.2)	19 (1.7)	186 (4.4)	107 (5.1)	293 (4.6)
Chronic liver disease	149 (4.3)	91 (5.2)	240 (4.6)	8 (1.1)	2 (0.5)	10 (0.9)	157 (3.7)	93 (4.4)	250 (4.0)
Hypertension	1231 (35.6)	637 (36.7)	1868 (35.9)	184 (24.6)	84 (22.6)	268 (23.9)	1416 (33.6)	720 (34.2)	2136 (33.8)
Asthma	378 (10.9)	198 (11.4)	576 (11.1)	50 (6.7)	27 (7.3)	77 (6.9)	428 (10.2)	225 (10.7)	653 (10.3)
Cancer	251 (7.3)	133 (7.7)	384 (7.4)	25 (3.3)	11 (3.0)	36 (3.2)	276 (6.6)	144 (6.8)	420 (6.6)
Smoking	721 (20.8)	370 (21.3)	1091 (21.0)	144 (19.2)	71 (19.1)	215 (19.2)	865 (20.5)	441 (20.9)	1306 (20.7)
Sickle cell disease	1 (0.0)	1 (0.1)	2 (0.0)	1 (0.1)	0	1 (0.1)	2 (0.0)	1 (0.0)	3 (0.0)

Adverse events

The overall incidences of AEs, SAEs, AEs with outcome of death, AEs leading to discontinuation, medically attended adverse events (MAAEs), and adverse events of special interest (AESIs) in the EVUSHELD group were similar to the placebo group, which is consistent with the data reported for the individual studies (PROVENT and STORM CHASER).

Table 33: Overall summary of adverse events in any category –PROVENT, STORM CHASER, and POOLED (data cut-off: June 2021)

	Number (%) of Participants					
	PROVENT		STORM CHASER		POOLED	
Number of participants with at Least One	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.

Common adverse events

A total of 1646 (39.1%) subjects assigned to EVUSHELD group and 848 (40.2%) participants in the placebo group reported treatment-emergent AEs.

Of 468 participants- 327 (7.8%) and 141 (6.7%) in the EVUSHELD and placebo group, respectively, 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. Individual AE preferred terms were balanced across the treatment groups, which was consistent with the AEs reported in each individual study. Furthermore, there was no clinically meaningful difference in the frequency of AEs when adjusted by duration of follow-up.

Table 34: Number of participants with adverse events, most common (frequency of ≥= 1%), by preferred term– safety analysis set, PROVENT, STORM CHASER, and POOLED (data cut-off: June 2021)

	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

Serious adverse events

Overall, the incidence of SAEs was similar between treatment groups (EVUSHELD: 2.4%, placebo: 2.3%). However, in PROVENT a higher proportion of subjects who received EVUSHELD versus placebo reported myocardial infarction and cardiac failure serious adverse events (SAEs), including one fatal SAE (Table below). All of the subjects with events had cardiac risk factors and/or a prior history of cardiovascular disease, and there was no clear temporal pattern.

Table 35: Exposure adjusted incidence rate (EAIR) of cardiac SAEs regardless of causality in PROVENT, (data cut-off: 29th August 2021)

System Organ Class Preferred term	**EVUSHELD 300 mg IM** **N = 3461** **Events (EAIR† (person years))**	**Placebo** **N = 1736** **Events (EAIR† (person years))**
Cardiac disorders‡	23 (1.2)	5 (0.5)
Acute myocardial infarction	4 (0.2)	2 (0.2)
Myocardial infarction	5 (0.3)	0
Acute left ventricular failure	0	1 (0.1)
Paroxysmal atrioventricular block	1 (0.1)	0
Cardiac failure congestive	4 (0.2)	0
Atrial fibrillation	1 (0.1)	2 (0.2)
Angina pectoris	1 (0.1)	0
Arrhythmia	1 (0.1)	0
Arteriosclerosis coronary artery	1 (0.1)	0
Cardiac failure	1 (0.1)	0
Cardiac failure acute	1 (0.1)	0
Cardio-respiratory arrest	1 (0.1)	0
Cardiomegaly	1 (0.1)	0
Cardiomyopathy	1 (0.1)	0
Coronary artery disease	1 (0.1)	0

* Date Cut Off date: 29 August 2021
† EAIR is calculated by the number of participants with the events divided by the duration of exposure (in years) x 100. 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.
‡ One EVUSHELD recipient had two cardiac SAEs

In PROVENT a higher proportion of subjects who received EVUSHELD versus placebo reported thromboembolic SAEs (Table below).

Table 36: Exposure adjusted incidence rate (EAIR) of thromboembolic event SAEs regardless of causality in PROVENT (data cut-off: 29th August 2021)

System Organ Class Preferred term	**EVUSHELD 300 mg IM** **N = 3461** **Events (EAIR† (person years))**	**Placebo** **N = 1736** **Events (EAIR† (person years))**
Thromboembolic SAEs	**17 (0.9)**	**4 (0.4)**
Cardiac disorders		
Acute myocardial infarction	4 (0.2)	2 (0.2)
Myocardial infarction	5 (0.3)	0
Gastrointestinal disorders		
Mesenteric artery thrombosis	1 (0.1)	0

System Organ Class Preferred term	EVUSHELD 300 mg IM N = 3461 Events (EAIR† (person years))	Placebo N = 1736 Events (EAIR† (person years))
Nervous system disorders		
Cerebral infarction	1 (0.1)	0
Transient ischaemic attack	2 (0.1)	0
Lacunar infarction	0	1 (0.1)
Cerebrovascular accident	2 (0.1)	1 (0.1)
Respiratory, thoracic and mediastinal disorders		
Pulmonary embolism	2 (0.1)	0

* Date Cut Off date: 29 August 2021
† EAIR is calculated by the number of participants with the events divided by the duration of exposure (in years) x 100. 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

No cardiac SAE occurred in STORM CHASER, where patients had a lower baseline prevalence of cardiac disease.

In TACKLE (N= 903), four subjects reported cardiac SAEs. Acute myocardial infarction was reported for two subjects who received EVUSHELD (one of whom also experienced cardiac failure leading to death) and sudden cardiac death was reported for one subject who received EVUSHELD. One subject who received placebo reported arrhythmia. All subjects who experienced cardiac SAEs had cardiac risk factors and/or a prior history of cardiovascular disease at baseline.

In TACKLE in the EVUSHELD group, four subjects reported thromboembolic SAEs, including two events of acute myocardial infarction, one event of pulmonary embolism and one event of peripheral artery thrombosis. In the placebo group, two subjects reported SAEs of portal vein thrombosis and superior sagittal sinus thrombosis.

Deaths
In PROVENT trial, June 2021 DCO a total of 12/6318 (0.2% in each treatment group) participants had an AE leading to death. There were no cases of severe COVID-19 or COVID-19-related deaths in the EVUSHELD group. In the placebo group, 2 (0.1%) participants died due to COVID-19 (PTs COVID-19 pneumonia and acute respiratory distress syndrome). In the EVUSHELD group, 2 deaths due to cardiac events occurred (1 arrythmia, 1 myocardial infarction). There were no deaths due to cardiac causes in the placebo group. 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 37: Deaths and adverse events with an outcome of death, by preferred term – safety analysis set, PROVENT, STORM CHASER, and POOLED (data cut-off: June 2021)

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.

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) in the PROVENT clinical study.

In STORM CHASER, there were no AEs with the outcome death.

In the clinical study TACKLE, overall, 12 (1.3%) participants (6 [1.3%] in the AZD7442 group and 6 [1.3%] in the placebo group) had an AE with an outcome of death (Table below).

Table 38: Number of participants with adverse events with outcome of death, by system organ class and preferred term (safety analysis set) TACKLE study data cut-off 21 August 2021

System Organ Class / Preferred Term	Number (%) of Participants[a]		
	AZD7442 (N=452)	Placebo (N=451)	Total (N=903)
Participants with AE with outcome of death	6 (1.3)	6 (1.3)	12 (1.3)
Cardiac disorders	1 (0.2)	0	1 (0.1)
Acute left ventricular failure	1 (0.2)	0	1 (0.1)
General disorders and administration site conditions	1 (0.2)	0	1 (0.1)
Sudden cardiac death	1 (0.2)	0	1 (0.1)
Infections and infestations	3 (0.7)	6 (1.3)	9 (1.0)
COVID-19 pneumonia	2 (0.4)	4 (0.9)	6 (0.7)
COVID-19	1 (0.2)	1 (0.2)	2 (0.2)
Septic shock	0	1 (0.2)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.2)	0	1 (0.1)
Malignant neoplasm progression	1 (0.2)	0	1 (0.1)

[a] Number (%) of participants with AE with outcome of death, sorted alphabetically by SOC, and within each SOC, PTs sorted by decreasing order of total frequency.

Participants with multiple events of the same preferred term are counted only once in that preferred term.

Participants with events in more than 1 preferred term within the same SOC will be counted only once in that SOC row.

Includes adverse events that occurred during through end of study.

Percentages are based on the total numbers of participants in the treatment group (N).

MedDRA version 24.0.

AE, adverse event; COVID-19, coronavirus disease 2019; DCO, data cut-off; PT, preferred term; SOC, system organ class.

Discontinuation due to adverse events

Overall, 5 (0.1%) participants were recorded as having discontinued the study; however, 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 (EVUSHELD group) and Alcoholism (placebo group). None of the AEs leading to study discontinuation were assessed as possibly related to IMP by the Investigator. All AEs leading to study discontinuation were reported in PROVENT. There were no AEs leading to study discontinuation in STORM CHASER.

Adverse events of special interest

Adverse events of special interest are anaphylaxis and other serious hypersensitivity reactions (including immune complex disease) and injection site reactions; an option of ‘other’ was also available that the Investigator could select according to his or her judgement.

Table 39: Number of participants with adverse events of special interest, by category and preferred term – PROVENT, STORM CHASER, and POOLED (data cut-off: June 2021)

AESI category/ 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)
Participants with at least one AESI	92 (2.7)	37 (2.1)	5 (0.7)	5 (1.3)	97 (2.3)	42 (2.0)
Anaphylaxis	1 (0.0)	0	0	0	1 (0.0)	0
Anaphylactic reaction	1 (0.0)	0	0	0	1 (0.0)	0
Dyspnoea	1 (0.0)	0	0	0	1 (0.0)	0
Injection site reaction	82 (2.4)	36 (2.1)	4 (0.5)	4 (1.1)	86 (2.0)	40 (1.9)
Other	9 (0.3)	2 (0.1)	1 (0.1)	1 (0.3)	10 (0.2)	3 (0.1)

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.

Adverse drug reactions

Hypersensitivity, injection-related reaction, and injection site reaction are considered to have a reasonable possibility of having casual association with EVUSHELD.

Table 40: Summary n (%) of hypersensitivity and injection site reaction

Preferred Term[a]	Number (%) of Participants	
	EVUSHELD (N = 4210)	Placebo (N = 2108)
Hypersensitivity[b]	43 (1.0)	18 (0.9)
Rash	34 (0.8)	15 (0.7)
Urticaria	9 (0.2)	3 (0.1)
Injection site reaction[b]	55 (1.3)	26 (1.2)
Injection site erythema	8 (0.2)	2 (0.1)
Injection site induration	4 (0.1)	1 (0.0)
Injection site pain	33 (0.8)	18 (0.9)
Injection site pruritus	6 (0.1)	3 (0.1)
Injection site reaction	4 (0.1)	5 (0.2)
Injection related reaction	9 (0.2)	7 (0.3)

[b] Including AEs not checked as AESI in the eCRF

[c] grouped terms.

Safety in special groups and situations

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 $AUC_{(0\text{-}60)}$ and C_{max}, respectively, based on PK data from the Phase I study.

Extrinsic factors
Based on the mechanism of action, PK/PD results, and AEs presented, it seems unlikely that the safety profile of EVUSHELD will be affected by diet, concomitant medication use or other extrinsic factors.

Fertility, pregnancy and lactation
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. There are no data on the effects of tixagevimab and cilgavimab on human fertility.

Drug interactions
No interaction studies have been conducted. EVUSHELD is not expected to undergo metabolism by hepatic enzymes or renal elimination. EVUSHELD is not renally excreted or metabolized 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. There is a theoretical risk that EVUSHELD may interfere with COVID-19 vaccines by neutralising antibodies to SARS-CoV-2 that are produced in response to vaccination.

EVUSHELD interaction with COVID-19 vaccination
Data from animal studies and 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 expected to interfere with vaccine safety. There are no clinical data available on the use of EVUSHELD following COVID-19 vaccination.

Laboratory findings
There were no notable observations in haematology, clinical chemistry, or urine parameters.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The safety concerns are as follows:

Summary of safety concerns	
Important Identified risk	None
Important potential risk	Emergence of viral variants
Missing information	Use in pregnant and breastfeeding women* Use in immunocompromised patients Use in adolescents

* in core RMP

In addition to the routine pharmacovigilance and risk minimisation measures proposed by the company, specific targeted follow-up questionnaires are proposed for the following adverse events of special interest in GB: emergence of viral variants/lack of efficacy, cardiac serious adverse events, hypersensitivity reactions, injection site reactions, immunogenicity and immunogenicity-related adverse drug reactions and hepatotoxicity. The following additional

pharmacovigilance activity has also been proposed to address the safety concerns for EVUSHELD in GB:

Study Name	Summary of Objective	Safety Concern	Milestone	Due Date
Category 2 Study				
To be confirmed	• To investigate safety of EVUSHELD in immunocompromised patients	• Use of EVUSHELD in immunocompromised patients	*Study Synopsis*	*Within one month of MA approval*
			Protocol Submission	*31-Jul-2022*
To be confirmed	• To investigate how EVUSHELD is used clinically with focus on immunocompromised patients • To study the emergence of viral variants in EVUSHELD patients	• Use of EVUSHELD in immunocompromised patients • Emergence of viral variants	*Study synopsis*	*Within one month of MA approval*
			Protocol submission	*31-May-2022*
Category 3 Study				
Study Name	**Summary of Objective**	**Safety Concern**	**Milestone**	**Due Date**
D8850R00006	• To investigate the safety of EVUSHELD in pregnancy	• Use of EVUSHELD in pregnancy	*Study Synopsis*	*Within one month of MA approval*

This is acceptable.

IV.7 Discussion on the clinical aspects

A brief discussion of the benefit-risk conclusions is given below.

The overall benefit-risk of EVUSHELD is considered to be positive for the pre-exposure prophylaxis of COVID-19 in adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 and:

- Who are unlikely to mount an adequate immune response to COVID-19 vaccination

or

- For whom COVID-19 vaccination is not recommended.

Based on PK simulations a higher dose of 600 mg is likely to have better efficacy against the Omicron variant as target minimum protective concentration are expected to be achieved, even based on more cautious estimates of lung partitioning, but the duration of any effect presently is not known. This is reflected in the product information where a higher dose of 600 mg is recommended for some SARS-CoV-2 variants (for example, Omicron BA.1, Omicron BA.1.1).

In Phase III studies, a total of 4210 adult participants received 300 mg EVUSHELD and 452 patients received 600 mg EVUSHELD via intramuscular injections and the most frequently reported adverse reaction was injection site reaction (1.3% and 2.4% in the 300 mg dose and 600 mg dose group, respectively).

V USER CONSULTATION

Evaluation of the patient information for readability via a user consultation study is currently deferred. The provision of user testing is a condition of the licence as set out below.

The applicant will provide results from user testing when available and update the Patient Information Leaflet (PIL) as required.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable. The non-clinical and clinical data submitted have shown the positive benefit/risk of this product in the pre-exposure prophylaxis of COVID-19 in adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 and:

- who are unlikely to mount an adequate immune response to COVID-19 vaccination

Or

- for whom COVID-19 vaccination is not recommended.

EVUSHELD has been authorised with a Conditional Marketing Authorisation (CMA). The Marketing Authorisation Holder shall complete, within the stated timeframe, the following measures:

Description	**Due date**
Quality	
Submissions of ongoing stability data (all available data including 12 months of real-time data on commercial lots)	May 2022
Submission of completed column lifetime studies	31 July 2022
Addition of new Drug Substance manufacturing site to be submitted via a Type II variation once comparability studies completed, including degradation trends and minimum 3 months stability data.	No date
Drug Substance and Drug Product specifications to be reviewed once a total of 20 batches across all manufacturing sites for each of tixagevimab and cilgavimab are available.	31 July 2022
Quality dossier to be updated in line with commitments for post-approval data made with the responses.	Q3 2022
Clinical	
Submission of final CSR for Phase I study	30 April 2022
Submission of primary CSR for TACKLE	31 May 2022

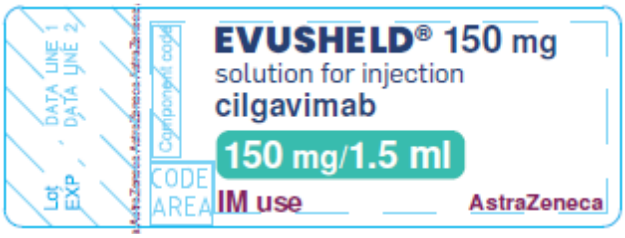
Description	Due date
Submission of final CSRs for PROVENT and STORM CHASER	30 December 2022
Submission of final CSR for TACKLE	30 April 2023
Final data from the PK comparability study	Q4 2023
Final data from the PROVENT sub-study	Q1 2024
Final TFLs for the safety data from ACTIV-2	Q2 2023
Final TFLs for the safety data from ACTIV-3	Q3 2023
Final TFLs for the safety data from DISCOVERY	Q2 2025
Submission of interim analysis results from the paediatric PK/safety study	31 May 2023
Ongoing monitoring of activity against emerging viral variants of SARS-CoV-2	Monthly reports
Submission of updated Population PK model containing final PK data from the PROVENT and STORM CHASER studies	30 December 2022
The Company (and its contracted parties) must accept MHRA GPvP and GCP inspections to assess the compliance of any and all pharmacovigilance obligations and of the clinical trials and applicable data attached to the authorisation of the CMA. The powers of inspection will be the same as those outlined in regulations 325, 326 and 327.	
AstraZeneca must ensure timely impact assessment and Corrective and Preventative Action (CAPA) implementation in response to any MHRA GxP Inspection findings reported in relation to any data submitted to support this application. AstraZeneca must promptly provide to MHRA any GxP non-compliance impact assessment outcomes that is generated by them, or which otherwise come into their possession, which concludes that the clinical trial or pharmacovigilance data integrity may have been adversely impacted.	
Good Laboratory Practice studies must be performed to standards in accordance with national regulations, relevant guidelines and the OECD Principles of Good Laboratory Practice. Astra Zeneca (and its contracted parties) must accept GLP inspections by national competent authorities should such inspections take place.	
The Company must ensure that clinical trials are performed to national regulations and relevant guidelines including ICH GCP E6 R2	

Description	Due date
The Company will develop a study protocol for a Post Authorisation Study to further characterise the emergence of viral variants in patients treated with EVUSHELD. The study should be broadly reflective of how the product is used clinically and mainly focused on use in immunocompromised patients. The company will submit an acceptable study synopsis within 1 month of approval and a protocol by 31st May 2022.	31 May 2022 (for study protocol)
The Company will develop a study protocol for a Post Authorisation Study to investigate the safety of EVUSHELD in immunocompromised patients. The company will submit an acceptable study synopsis for an observational study to evaluate the safety of EVUSHELD in immunocompromised patients within 1 month of approval and a protocol by 31st July 2022.	31 July 2022 (for study protocol)
The Company will commit to providing real-world data on clinical effectiveness (from the UK and the US) as soon as it is available. This should include the planned US real-world study of effectiveness in vaccinated individuals.	
The company will submit an updated TFUQ for "lack of efficacy due to emerging viral variants/antibody dependent enhancement of disease" for agreement within 1 month of approval.	10 March 2022
The applicant will provide the data from the PROVENT study for vaccinated individuals.	
Final data for PK comparison of cell pools versus clonal cell line material.	
Efficacy based minimum protective concentration derivation analysis	30 July 2022
Product information	
User testing of finally agreed PIL to be provided	31 March 2022

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved GB versions of the SmPC and PILs for these products are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.



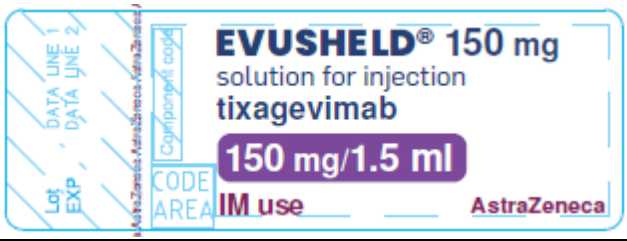


TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**