15 September 2022
EMA/834036/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: EVUSHELD

International non-proprietary name: tixagevimab / cilgavimab

Procedure No. EMEA/H/C/005788/II/0001

Marketing authorisation holder (MAH) AstraZeneca AB

Note

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

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List of abbreviations

ADA	Antidrug antibodies
ADE	Antibody-dependent enhancement
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AUC(0-5 days)	Area under the serum concentration-time curve from time zero to 5 days post dose
AUC(0-28 days)	Area under the serum concentration-time curve from time zero to time 28 days post dose
AUCinf	Area under the serum concentration versus time curve extrapolated to infinity
AZD1061	cilgavimab
AZD8895	tixagevimab
AZD7442	EVUSHELD, combination of tixagevimab and cilgavimab
BMI	Body mass index
BP	Blood pressure
%CV	Percent coefficient of variation
CDS	Core data sheet
CI	Confidence interval
CL	Clearance
Cmax	Maximum serum concentration
CMH	Cochran-Mantel-Haenszel
CoV	Coronavirus
COVID-19	Coronavirus disease 2019
CSR	Clinical Study Report
D8850C00001	Phase I first time in human study
D8851C00001	TACKLE Phase III study
DCO	Data cut-off
ECG	Electrocardiogram
Fc	Fraction crystallizable
FTIH	First-time-in-human
GMT	Geometric mean titer
HIV	Human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IC50	Half-maximal inhibitory concentration or 50% inhibitory concentration
IC80	80% inhibitory concentration
IM	Intramuscular
IMP	Investigational medicinal product
IQR	Interquartile range
IV	Intravenous
IRT	Interactive Response Technology
KA	First-order absorption rate constant
KM	Kaplan-Meier
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LLOQ	Lower limit of quantification
LS	Least squares
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
nAb	Neutralizing antibody
NK	Natural killer
NGS	Next generation sequencing
NLF	Nasal lining fluid
PD	Pharmacodynamics

PK	Pharmacokinetics
PT	Preferred term
Q	Inter-compartmental clearance
RBD	Receptor binding domain
RNA	Ribonucleic acid
RR	Risk ratio
RRR	Relative risk reduction
RSV	Respiratory syncytial virus
RT-PCR	Reverse transcriptase polymerase
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SOC	System organ class
TM L234F/L235E/ P331S	Substitutions in the immunoglobulin heavy chain to reduce Fc receptor binding
t1/2	Terminal half-life
t1/2λz	Half-life associated with terminal slope of a semi-logarithmic concentration-time curve
tmax	Time to maximum serum concentration
V2	Central volume of distribution
V3	Peripheral volume of distribution

* This is a general list of abbreviations. Not all abbreviations will be used or are included.

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 14 April 2022 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adults and adolescents (aged 12 years and older weighing at least 40 kg) with COVID-19, who do not require supplemental oxygen, based on interim results from study D8851C00001 (TACKLE); this is an ongoing, randomized, double-blind, placebo-controlled, multicenter study assessing the safety and efficacy of a single 600 mg dose of AZD7442 (× 2 IM injections) compared with matching placebo for the treatment of mild to moderate COVID-19 in non-hospitalized adults. As a consequence, sections 4.1, 4.2, 4.8, 4.9, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Version 2 Succession 1 of the RMP has also been submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0048/2022 and P/0047/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0048/2022 and P/0047/2022 were not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Derogation(s) of market exclusivity

N/A

Scientific advice

The MAH received Scientific Advice from the CHMP on 20 November 2020 (EMA/SA/0000046190). The Scientific Advice pertained to clinical aspects and statistical methods of the dossier.

Key aspects are provided below. In general, the final design of the TACKLE study was aligned with the feedback received, and key considerations from the Agencies were addressed.

- CHMP recommended that the proportion of participants who develop hypoxemia (O2 saturation < 94% on room air on 2 occasions at least 8 hours apart) or hospitalization requiring non-invasive ventilation, high-flow oxygen devices, invasive mechanical ventilation, ECMO or death during the 28-day follow-up period could also be considered as primary endpoint. AstraZeneca's position was that this was already covered in the composite endpoint.

- CHMP recommended that hospitalization for COVID-19 complications or sequelae during the 168-day post-dose period should be added as a key secondary endpoint. However, this was already included as a secondary endpoint, which was considered appropriate.

- CHMP recommended that patients withdrawing/lost to follow-up should be counted as treatment failures. To address this, patients withdrawing/lost to follow-up were to be analyzed within a sensitivity analysis. Feedback received from FDA during the review of the protocol and during the study was incorporated, where possible.

1.2. Steps taken for the assessment of the product

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

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

Timetable	Actual dates
Submission date	14 April 2022
Start of procedure:	23 May 2022
CHMP Rapporteur Assessment Report	8 June 2022
PRAC Rapporteur Assessment Report	23 May 2022
PRAC members comments	31 May 2022
PRAC Outcome	10 June 2022
PRAC RMP advice and assessment overview adopted by PRAC	1 September 2022
CHMP members comments	11 June 2022
Updated CHMP Rapporteur Assessment Report	17 June 2022
Request for supplementary information (RSI)	23 June 2022
CHMP Rapporteur Assessment Report	16 August 2022
CHMP members comments	5 September 2022
Updated CHMP Rapporteur Assessment Report	8 September 2022
CHMP Opinion	15 September 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

SARS-CoV-2 is a novel human coronavirus responsible for the Coronavirus disease 2019 (COVID-19) pandemic. SARS-CoV and SARS-CoV-2 are involved with the renin-angiotensin-aldosterone system (RAAS) through ACE2, the enzyme that functions as a receptor for both viruses and also physiologically counters RAAS activation. Clinical symptoms have been shown to occur most commonly between days 4 and 5 from exposure. The most common symptoms reported in the literature so far include fever, cough, fatigue and shortness of breath. Pneumonia and acute respiratory distress syndrome are the major complications of COVID-19. SARS-CoV-2 infection can activate innate and adaptive immune responses and result in massive inflammatory responses later in the disease. These uncontrolled inflammatory responses may lead to local and systemic tissue damage. COVID-19 severity hinges on the development of cytokine storm characterized by elevated serum levels of pro-inflammatory cytokines. Moreover, IgG-, IgM- and IgA-specific antibodies against SARS-CoV-2 can be detected in most patients, along with the viral RNA.

State the claimed the therapeutic indication

AstraZeneca is seeking approval for Evusheld for the treatment in adults and adolescents (12 years of age and older weighing at least 40 kg) with COVID-19 who do not require oxygen (see sections 4.2,5.1 and 5.2).

The recommended dosage is 600 mg of Evusheld, administered as two separate 3.0 mL, sequential, IM injections of 300 mg of tixagevimab and 300 mg of cilgavimab.

This indication is being sought based on Study D8851C00001 (TACKLE), an ongoing Phase III, randomized, double-blind, placebo-controlled, parallel-group study in the treatment of mild to moderate COVID-19.

Epidemiology and risk factors, screening tools/prevention

Globally, as of 7 September 2022, there have been 603,711,760 confirmed cases of COVID-19, including 6,484,136 deaths, reported to WHO. In Europe, 249,105,808 case were confirmed. {World Health Organization (WHO) 2022}.

With a basic reproduction number *R*0 value at the start of the pandemic estimated between 2.43 to 3.10 without medical intervention, SARS-CoV-2 is highly transmissible from person to person, which has contributed to its exponential dissemination worldwide (D'Arienzo and Coniglio 2020). The emergence of more virulent variants (e.g., Delta with an *R*0 of 3.2 to 8 [Liu and Rocklöv 2021] and Omicron [*R0* unknown at the time of writing]) has further increased the rate of spread globally. In March 2022, the Omicron BA.2 subvariant was the most prevalent variant globally, comprising 86% of all cases sequenced (as of 22 March 2022; WHO 2022b). As of 04 April 2022, 45% of all samples sequenced in the US were Omicron BA.2; in the UK the frequency of BA.2 was 95%, and in the majority of countries in Europe and Asia the frequency of BA.2 was > 70% and increasing (CoVariants 2022). Currently, globally, from 5 August to 5 September 2022, 118 028 SARS-CoV-2 sequences were shared through GISAID. Among

these, 117 317 sequences were the Omicron variant of concern (VOC), accounting for 99.4% of sequences reported globally in the past 30 days. A comparison of sequences submitted to GISAID in epidemiological week 34 (22 to 28 August 2022) and week 33 (15 to 21 August 2022) shows that BA.5 Omicron descendent lineages continue to be dominant globally, with an increase in weekly prevalence from 84.8% to 86.8%. The prevalence of BA.4 descendent lineages decreased from 6.8% in week 33 to 4.2% in week 34 including BA.4.6 descendent lineage, which decreased from 3.5% to 2% within the same time period. The prevalence of BA.2 descendent lineages (BA.2.X) remained stable in week 34 compared to week 33 (2.6% in week 33 and 2.5% in week 34). BA.2.75, an Omicron descendent lineage under monitoring, still shows a relatively low (0.9% and 1.2% in weeks 33 and 34 respectively) prevalence globally, but a number of countries have observed recent increasing trends. {taken from World Health Organization (WHO) 2022}. Many studies have shown that severe illness and death occur in patients with certain risk factors including older age and underlying medical comorbidities, such as hypertension, diabetes, coronary heart disease, chronic obstructive lung disease, immunocompromising conditions and obesity. (Chams et al, 2020)

Biologic features, Aetiology and pathogenesis

Three major outbreaks of the coronavirus, a zoonotic virus known to cause respiratory disease, have been reported since 2002, including SARS-CoV, MERS-CoV and the most recent 2019-nCoV, or more recently known as SARS-CoV-2. Bats are known to be the primary animal reservoir for coronaviruses. However, in the past few decades, the virus has been able to mutate and adapt to infect humans, resulting in an animal-to-human species barrier jump. The emergence of a novel coronavirus poses a serious global public health threat and possibly carries the potential of causing a major pandemic outbreak in the naïve human population (Sharma et al., 2021). SARS-CoV-2 is the coronavirus responsible for the current COVID-19 global pandemic. Coronavirus entry into host cells is mediated by the transmembrane S glycoprotein that binds to the cellular receptor hACE2 allowing the viral genome to enter and replicate in the cell (Tortorici and Veesler 2019). As the S protein is surface-exposed and mediates the entry into host cells, it is the main target of neutralizing antibodies and is the primary target for mAbs and vaccines. Unlike the majority of coronaviruses that mainly cause mild disease in humans and animals, SARS-CoV-2 can replicate in the lower respiratory tract to cause acute respiratory distress syndrome and fatal pneumonia. The uncontrolled pulmonary inflammation and increased secretion of pro-inflammatory cytokines associated with severe disease is suggestive of a cytokine storm, especially in patients who are critically ill (Huang et al 2020, CDC 2022, Guan et al 2020). These manifestations are also characteristic of SARS-CoV, to which SARS-CoV-2 bears 79% genetic similarity, and the more distantly related MERS-CoV, both of which were responsible for prior outbreaks in 2002 to 2003 and 2012, respectively (Gorbalenya et al 2020).

Clinical presentation, diagnosis and stage/prognosis

The estimated incubation period for COVID-19 is up to 14 days, with a median of 4 to 5 days from exposure to initial onset of symptoms (Zhou et al 2020b). The symptoms of COVID-19, if present, differ with severity of disease. The symptoms most frequently associated with symptomatic mild to moderate illness include fever, cough, fatigue, muscle or body aches, headache, sore throat, nasal congestion, shortness of breath or difficulty breathing, nausea, vomiting, diarrhea, and a loss in sense of taste or smell. COVID-19 is a systemic disease affecting not just the respiratory tract but also in myocardial, renal, neurologic, gastrointestinal, and pharyngeal tissues and where hACE2 receptors have been identified (Gupta et al 2020). Patients may progress to severe pneumonia or develop acute respiratory distress syndrome, which is the primary cause for respiratory failure, and direct organ damage by the virus likely contributes to multiorgan failure. Some people who recover from COVID-19 go on to suffer from symptoms long-term. Mortality risk factors associated with COVID 19 include age > 60

years (significantly greater for those 80 years and older), male sex, and chronic medical conditions including hypertension, diabetes, obesity, and cardiovascular disease. (Zhou et al 2020a).

Management

The ongoing COVID-19 pandemic, caused by SARS-CoV-2, has become a major threat to global health and economies (Di Fusco et al 2021, Zost et al 2020). As transmission continues and different variants of SARS-CoV-2 emerge, cases of severe disease and hospitalization, and in some countries, mortality, remain high. Breakthrough infections of fully vaccinated individuals continue to emerge both in the general population (Hacisuleyman et al 2021) and in high-risk populations (Agha et al 2021, ACIP 2021). The latest variant of concern, the highly mutated Omicron variant and its lineages, has increased transmissibility versus the original and Delta strains (Garcia-Beltran et al 2022).Early data suggests that vaccine effectiveness is reduced against Omicron B.1.1.529 (Dejnirattisai et al 2021; Regev-Yochay et al 2022) and therefore is likely leading to breakthrough disease in a COVID-19 vaccinated/recovered population as well as in those who remain unvaccinated or unresponsive to vaccines. Despite the reduced severity seen with Omicron infections (Lauring et al 2022), certain individuals remain at an increased risk of severe disease and includes, but is not limited to, the elderly, cancer patients as well as those with ongoing chronic health conditions. Globally, there is still a critical need to reduce hospitalizations and reduce the impact of COVID-19 on healthcare systems. Therefore, preventing progression of mild to moderate COVID-19 to severe disease remains a significant clinical need.

Clinical management of COVID-19 is based on supportive care and there are limited approved/authorized effective treatment or prevention interventions, which include antivirals as well as mAbs (e.g., in some markets: remdesivir [VELKURY], PF07321332/ritonavir [PAXLOVID], regdanvimab [REGKIRONA], casirivimab and imdevimab [RONAPREVE], and sotrovimab [XEVUDY]), and finally EVUSHELD which results in healthcare resources being stretched (Tangcharoensathien et al 2021). Recent in vitro antiviral resistance studies have demonstrated that some of the mAbs in late clinical development, do not offer significant neutralization of the emergent SARS-CoV-2 Omicron subvariants and as a consequence are no longer available in some markets. Evusheld remains one of the only mAb products to retain neutralizing activity against the Omicron variant authentic virus in vitro, with comparable activity against Omicron BA.2 to the original strain (Case et al 2022) and also some residual activity against BA.4/5 although this seems to be more limited (Takashita et al 2022).

As the pandemic continues, and new variants emerge, there is a need for additional effective therapeutic antibodies that target different epitopes on the spike protein, and for people ineligible for antivirals, to prevent COVID-19 disease progression and its serious complications (Kim et al 2020).

Clinical benefit is likely to be achieved by treating patients early in their disease course while the disease is primarily driven by replication of SARS-CoV-2, before the innate immune/inflammatory response is triggered, and the disease progresses to severe illness requiring hospitalization. However, treatments available specifically in the outpatient setting are limited. Overall, despite effective vaccination programs, COVID-19 remains a global threat with significant numbers of patients contracting the disease. Early intervention is critical to prevent progression to severe disease, especially for those who are at high risk of severe COVID-19. There are limited treatment options available and, as variants emerge, there is a risk that treatments that are currently effective may not remain so, therefore further options that are effective against current variants are needed, including those available in the outpatient setting.

2.1.2. About the product

Evusheld is a combination of two severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-specific antiviral monoclonal antibodies (mAbs) (tixagevimab and cilgavimab) that bind to non-overlapping

epitopes on the receptor binding domain of the spike protein and block its interaction with the human angiotensin-converting enzyme 2 host cellular receptor, resulting in a blockade of virus entry, neutralizing the SARS-CoV-2 virus. Each mAb is engineered with YTE and TM substitutions to extend half-life and reduce the potential risk of antibody-dependent enhancement of disease, respectively, which is a key theoretical concern with mAbs, Evusheld is administered by IM injection.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The clinical development program evaluated the safety and efficacy of EVUSHELD in the treatment of mild to moderate COVID-19 in accordance with regulatory guidance and advice received from Regulatory Authorities.

Study D8851C00001 (TACKLE), an ongoing Phase III, randomized, double-blind, placebo-controlled, parallel-group, AstraZeneca-sponsored study in the treatment of mild to moderate COVID-19 provides key data supporting the efficacy and safety of Evusheld in this application. Approximately 90% of participants met the protocol definition of being at high risk of progression to severe COVID-19.

This Application also provides the final CSR for the AstraZeneca-sponsored Phase I FTIH study (Study D8850C00001). An overview of these studies is provided in Section 2.3.1.

The safety profile of Evusheld has been assessed in 4210 participants in the prophylaxis Phase III studies PROVENT and STORM CHASER (300 mg IM), and 50 participants in the interim Phase I study analysis (to Day 211 for all cohorts/Day 271 for 300 mg IM and 300 mg IV cohorts) (300 mg IM, 300 mg IV, 1000 mg IV, and 3000 mg IV), submitted previously. The TACKLE study included in this Application adds safety data from a further 452 participants with mild to moderate COVID-19 at 600 mg IM with median safety follow-up of 84 days (DCO 21 August 2021). The final analysis of the Phase I study provides safety data up to 12 months.

2.1.4. General comments on compliance with GCP

AstraZeneca procedures, internal quality control measures and audit programs provide reassurance that the clinical study program was carried out in accordance with Good Clinical Practice, as documented by the ICH.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

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

- Tabular overview of clinical studies (Studies with Evusheld included in this application):

Study/Sponsor/Status	Phase	Population	Success Criteria	Dose/Route of EVUSHELD and Number of Participants Exposed	Countries
D8851C00001 (TACKLE)/ AstraZeneca/ Ongoing (recruitment complete)[a]	III	Adults with mild to moderate COVID-19[b]	Statistically significantly lower incidence of the composite endpoint of either severe COVID-19 or death from any cause through Study Day 29 for EVUSHELD 600 mg IM than placebo	600 mg IM (N = 452), placebo (N = 451)	Argentina, Brazil, Czech Republic, Germany, Hungary, Italy, Japan, Mexico, Poland, Russian Federation, Spain, UK, Ukraine, and US
D8850C00001/ AstraZeneca/ Complete[c]	I	Healthy adult volunteers	Not applicable	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] First participant randomized 29 January 2021

[b] Mild to moderate COVID-19 population (TACKLE): outpatient adults (≥ 18 years) with a documented positive SARS-CoV-2 molecular test (antigen or nucleic acid) from a sample collected ≤ 3 days prior to study entry and with ≤ 7 days of symptoms of COVID-19 at study entry ('Day 1' symptom count starts from the first day of symptoms), plus the presence of select symptoms within 24 hours prior to Day 1. At least 60% of participants were to meet the protocol definition of being at high risk of progression to severe COVID-19 as defined in Section 4.1.

[c] First participant enrolled 18 August 2020

COVID-19, coronavirus disease 2019; IM, intramuscular; IV, intravenous; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; UK, United Kingdom; US, United States

2.3.2. Pharmacokinetics

PK data for the following studies were submitted:

- Study D8850C00001 (Phase I FTIH) – final CSR (interim PK data were available with prophylaxis application)
- Study D8851C00001 (TACKLE), phase 3 study for treatment indication – interim CSR (with the first submission package, PK results were presented with DCO 21 August 2021; with submission of responses results were presented with DCO 14 January 2022)

The TACKLE Phase III study utilized clonal cell line material (commercial material).

TACKLE serum PK samples were analysed by the same validated assay used for the Phase I and prophylaxis Phase III (STORM CHASER [D8850C00003] and PROVENT [D8850C00002]) PK samples (PPD Laboratories, Richmond, Virginia using a LC-MS/MS method LCMSF 1024.1 Version 1.00). Bioanalytical reports for the determination of AZD8895 and AZD1061 human serum concentrations in TACKLE are currently outstanding and will be available by the end of Q4 2022. The bioanalytical reports for study D8850C00001 for the quantitation of AZD8895 and AZD1061 in human serum (report RQHJ) and in human nasal lining fluid (report RRFI) are provided. For analysis of Study D8850C00001 serum samples, a maximum of 391 days passed between sample collection and analysis, which is slightly exceeding the currently validated long term stability period of 358 days. Stability experiments are, however, still ongoing. Overall mean accuracy and precision of QC samples was below 15%. Reasons for reanalysis are reported and considered acceptable. Incurred sample reanalysis of approximately 10% of study samples met the acceptance criteria. The population PK model submitted previously as part of the prophylaxis application included final data from Phase I Study D8850C00001 and primary DCO data from TACKLE; therefore, the model has not been updated. In addition, one exploratory exposure-response analysis and a viral dynamic modelling report were submitted to support the treatment indication.

Table 1: Overview of EVUSHELD Clinical Studies with Pharmacokinetic, Pharmacodynamic, and Antidrug Antibody Assessments

Study Number (Acronym)/ Sponsor/ Countries	Study Type and Design	Study Population	Treatments. Doses, and Number of Participants Exposed	PK, PD, and ADA Sampling Days	DCO (Endpoints)
D8850C00001/ AstraZeneca/ UK EudraCT No 2020-003076-40 NCT04507256	Phase I, first-time-in-human, double-blind, placebo-controlled, dose escalation, single center	Healthy adults 18 to 55 years of age	**Cohorts with the 2 mAbs administered sequentially:** **Cohort 1a:** EVUSHELD 300 mg IM (n = 10); placebo (n = 2) **Cohort 1b:** EVUSHELD 300 mg IV (n = 10); placebo (n = 2) **Cohort 2**: EVUSHELD 1000 mg IV (n = 10); placebo (n = 2) **Cohort 3:** EVUSHELD 3000 mg IV (n = 10); placebo (n = 2) **Cohort with the 2 mAbs co-administered:** **Cohort 4:** EVUSHELD 3000 mg IV (n = 10) co-administered; placebo (n = 2)	Serum PK: predose (baseline), mid-infusion (IV), end of dosing (IV), 8 hours post-dose, Day 2 (discharge) and at post-dose Follow-up Days 4, 6, 8, 15, 31 61, 91, 151, 211, 271, and 361 NLF PK: predose (baseline), and at post-dose Follow-up Days 8, 31, 91, and 151 PD (nAbs): predose (baseline), and at post-dose Follow-up Days 8, 31, 61, 91, 151, 211, and 271 ADA: predose (baseline), and at post-dose Follow-up Days 8, 15, 31, 91, 151, 211, and 361.	27 Jan 2022 Study complete.
D8851C00001 (TACKLE)/ AstraZeneca/ Argentina, Brazil, Czech Republic, Germany, Hungary, Italy, Japan, Mexico, Poland, Russian Federation, Spain, UK, Ukraine, and US EudraCT Number: 2020-005315-44 NCT04723394	Phase III, randomized, double-blind, placebo-controlled, multicenter	Outpatient adults (≥ 18 years) with a documented positive SARS-CoV-2 molecular test (antigen or nucleic acid) from a sample collected ≤ 3 days prior to study entry and with ≤ 7 days of symptoms of COVID-19 at study entry ('Day 1' symptom count starts from the first day of symptoms), plus the presence of select symptoms within 24 hours prior to Day 1.	EVUSHELD 600 mg IM (N = 452); placebo (N = 451) Enrolled into one of 2 independent cohorts: - Cohort 1 – underwent more intensive testing to characterize their virological and immunological status, and to correlate that status with clinical outcomes. - Cohort 2 –is being followed for clinical outcomes.	Serum PK: predose (baseline), and at Study Days 3, 6, 15, 29, 85, 169, 366, and 457 in Cohort 1; predose (baseline), and at Study Days 6, 29, 85, 169, 366, and 457 in Cohort 2[a] PD (nAbs): predose (baseline), and at Study Days 6, 15, 29, 85, 169, and 366 in Cohort 1; predose (baseline), and at Study Days 6, 29, 85, 169, and 366 in Cohort 2 ADA: predose (baseline), and at Study Days 29, 85, 169, 366, and 457 in Cohort 1[b]	21 Aug 2021 (PK, nAbs, ADA) Ongoing, primary analysis complete

[a] At the time of DCO (21 Aug 2021), PK data up to Day 85 were available for both cohorts.

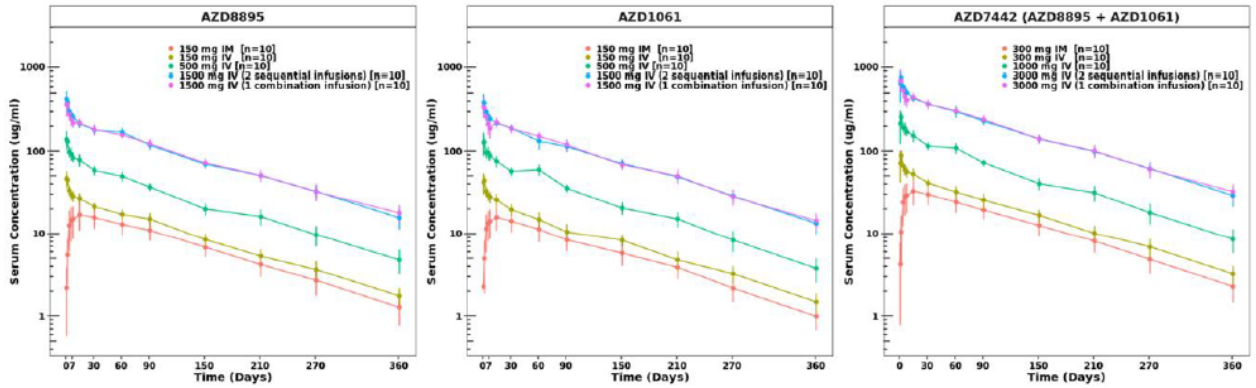
[b] The ADA analysis for assessing the presence of ADA against either tixagevimab or cilgavimab is ongoing. ADA data to tixagevimab up to 84 days post-dose are available for a subset of 112 and 154 participants in the EVUSHELD and placebo groups, respectively; ADA data to cilgavimab up to 84 days post-dose are available for a subset of 121 and 147 participants in the EVUSHELD and placebo groups, respectively; ADA data to EVUSHELD up to 84 days post-dose are available for a subset of 134 and 163 participants in the EVUSHELD and placebo groups, respectively

ADA, antidrug antibody; COVID-19, coronavirus disease 2019; DCO, data cut-off; IM, intramuscular; IV, intravenous; mAbs, monoclonal antibodies; N, number of participants in treatment group; n, number of participants in cohort; nAb, neutralizing antibody; NLF, nasal lining fluid; PD, pharmacodynamic; PK, pharmacokinetic; SARS-CoV-2, severe acute respiratory syndrome 2; UK, United Kingdom; US, United States.

D8850C00001 (Phase I)

This was a Phase I, FTIH, randomized, 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 randomized 10:2 to receive either EVUSHELD or placebo administered IV or IM, across 5 fixed dose cohorts as follows: Cohort 1a (EVUSHELD 300 mg or placebo IM), Cohort 1b (EVUSHELD 300 mg or placebo IV), Cohort 2 (EVUSHELD 1000 mg or placebo IV), Cohort 3 (EVUSHELD 3000 mg or placebo IV), and Cohort 4 (EVUSHELD 3000 mg with the 2 mAbs co-administered, or placebo IV). In Cohorts 1a, 1b, 2, and 3, the 2 constituent mAbs of EVUSHELD were administered as separate injections or infusions; in Cohort 4, the 2 mAbs were co-administered within the same IV infusion. Blood samples for serum PK analysis were collected at predose (baseline), mid-infusion (IV), end of dosing (IV), 8 hours post-dose, Day 2, and Post-dose Follow-up Days 4, 6, 8, 15, 31 61, 91, 151, 211, 271, and 361. Nasosorption samples for NLF PK analysis were collected at baseline (predose), Days 8, 31, 91, and 151.

Figure 1: Arithmetic Mean (± SD) Serum Concentrations of AZD8895, AZD1061, and AZD7442 (AZD8895 + AZD1061) Following Single Dose IM or IV administration to Healthy Participants, Through Day 361 (Pharmacokinetic Analysis Set) - D8850C00001 (Phase I)



AZD7442 concentration = the sum of the AZD8895 and AZD1061 concentrations.
Days on the horizontal axis are days post-dose (ie, study Day -1).
IM, intramuscular; IV, intravenous; n, number of participants included in analysis; SD, standard deviation.
Source: Replot of Figure 14.2.1.1.2 and Figure 14.2.1.2.2 with error bars (± SD).

After a single 300 mg IM dose, the geometric mean Cmax was similar for tixagevimab and cilgavimab at 16.52 and 15.27 µg/mL, respectively, which was reached at a median tmax of approximately 14 days for both antibodies. Between-participant variability (%CV) in tixagevimab AUCinf and Cmax after 300 mg IM administration was 29.75% and 35.56%, respectively, and 31.25% and 38.53%, respectively, for cilgavimab. The PK of tixagevimab and cilgavimab up to Day 361 were similar. Overall, the Cmax 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 nearly identical serum drug concentration-time curves for the two 3000 mg IV dosing regimens.
In addition, key exposure PK parameters such as AUC and Cmax for tixagevimab and cilgavimab were similar between those dosing regimens (see table below).

Table 2: Summary of PK Parameters for AZD8895 and AZD1061 Following Single Dose IM or IV Administration of AZD7442 – Day 361 (Pharmacokinetic Analysis Set)

Analyte	Parameter (Units)	300 mg AZD7442 IM [a] (N = 10)	300 mg AZD7442 IV [a] (N = 10)	1000 mg AZD7442 IV [b] (N = 10)	3000 mg AZD7442 IV [c] (N = 10)	3000 mg AZD7442 IV co-administration [c] (N = 10)
AZD8895	AUC_{last} (day·µg/mL)	2367 (28.92)	3467 (13.20) [e]	9237 (11.75) [e]	29800 (9.799)	29380 (10.81)
	AUC_{inf} (day·µg/mL)	2526 (29.75)	3677 (13.75) [e]	9893 (12.58) [e]	31850 (10.85)	31850 (11.89)
	C_{max} (µg/mL)	16.52 (35.56)	53.71 (10.24) [e]	162.2 (11.31)	505.8 (10.54)	447.8 (8.980)
	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)
	$t_{1/2kz}$ (day)	87.76 (14.56)	86.97 (5.195) [e]	92.38 (17.23) [e]	91.27 (7.827)	95.33 (11.06)
	t_{last} (day)	363.48 (356.15 – 369.98)	363.92 (356.83 – 363.94) [e]	363.95 (353.95 – 365.97) [e]	361.45 (354.93 – 366.00)	352.53 (350.10 – 357.04)
	CL(/F) (L/day)	0.06174 (0.01857)	0.04113 (0.005411) [e]	0.05090 (0.006510) [e]	0.04736 (0.005317)	0.04740 (0.005661)
	V_z(/F) (L)	7.771 (2.152)	5.150 (0.5804) [e]	6.814 (1.065) [e]	6.227 (0.5926)	6.514 (0.7232)
	V_{ss} (L)	NA	5.074 (0.4766) [e]	6.520 (0.9739) [e]	6.118 (0.5983)	6.373 (0.6854)
	F (%) [d]	68.69	NA	NA	NA	NA
AZD1061	AUC_{last} (day·µg/mL)	2018 (30.98)	3085 (13.01) [e]	9245 (11.22) [e]	28160 (10.85)	28210 (11.21)
	AUC_{inf} (day·µg/mL)	2130 (31.25)	3276 (14.17) [e]	9712 (11.69) [e]	29860 (11.71)	30030 (11.82)
	C_{max} (µg/mL)	15.27 (38.53)	51.69 (12.31) [e]	154.3 (14.66)	465.5 (11.09)	419.3 (11.62)
	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)
	$t_{1/2kz}$ (day)	79.78 (9.649)	91.08 (9.152) [e]	83.05 (16.22) [e]	88.52 (9.086)	87.17 (10.78)
	t_{last} (day)	363.48 (356.15 – 369.98)	363.92 (356.83 – 363.94) [e]	363.95 (353.95 – 365.97) [e]	361.45 (354.93 – 366.00)	352.53 (350.10 – 357.04)
	CL(/F) (L/day)	0.07383 (0.02733)	0.04618 (0.006162) [e]	0.05180 (0.006260) [e]	0.05055 (0.006086)	0.05026 (0.006036)
	V_z(/F) (L)	8.471 (2.832)	6.042 (0.5914) [e]	6.241 (0.9723) [e]	6.449 (0.6920)	6.324 (0.7784)
	V_{ss} (L)	NA	5.687 (0.4691) [e]	6.020 (0.8755) [e]	6.311 (0.6722)	6.286 (0.7465)
	F (%) [d]	65.02	NA	NA	NA	NA

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

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

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

[d] Calculated as the single ratio of geometric mean AUC_{inf} after IM to IV, thus no %CV.

[e] n = 9.

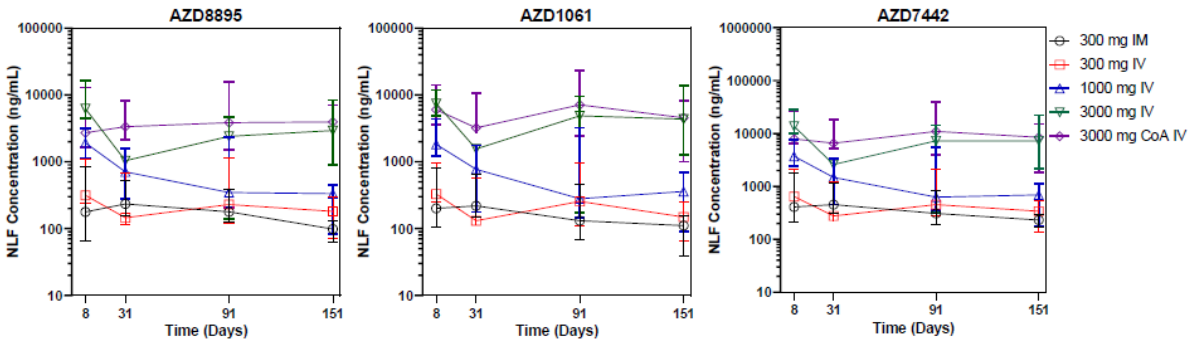
Data are presented as geometric mean (geometric CV), except for t_{max} and t_{last} as median (min – max), and CL(/F), V_z(/F), and V_{ss} as arithmetic mean (SD).

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; 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; F, bioavailability at the end of study (Day 361); IM, intramuscular; IV, intravenous; N, number of participants in each group; NA, not applicable; $t_{1/2kz}$, 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).

Source: Table 14.2.4.1 and Table 14.2.4.2.

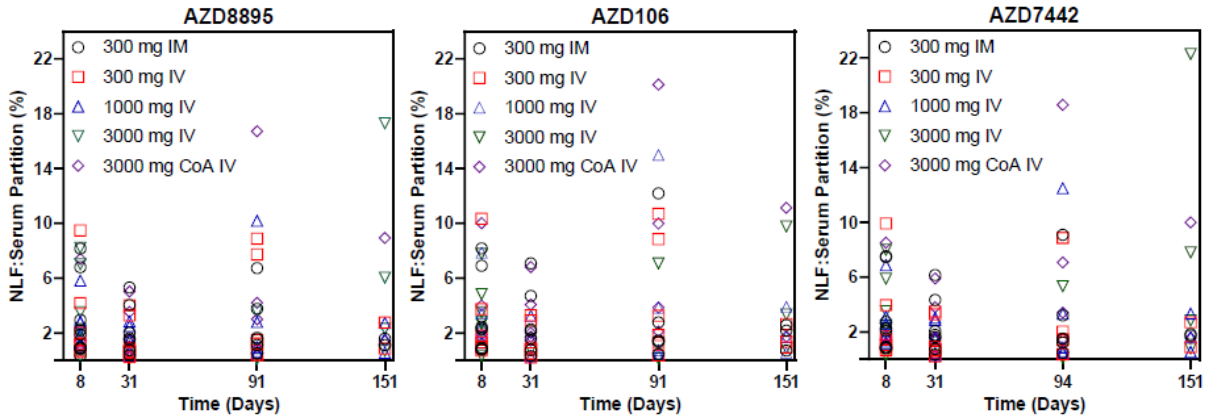
Plots of NLF concentrations to Day 151 for tixagevimab, cilgavimab, and EVUSHELD are shown in the figures below. In the 300 mg IM dose cohort, the median tixagevimab, cilgavimab, and EVUSHELD (tixagevimab and cilgavimab) NLF concentrations were 178, 201, and 409 ng/mL, respectively, at Day 8 and 98.8, 111, and 232 ng/mL, respectively, on Day 151. In the 300 mg IV dose cohort, the median tixagevimab, cilgavimab, and EVUSHELD NLF concentrations were 315, 331, and 647 ng/mL at Day 8, and 182, 150, and 341 ng/mL at Day 151.

Figure 2: Median Concentrations of AZD8895, AZD1061, and AZD7442 in Nasal Lining Fluid After a Single AZD7442 Dose (Pharmacokinetic Analysis Set)



Error bars correspond to Q1 and Q3 of results.
CoA, co-administered; IM, intramuscular; IV, intravenous; NLF, nasal lining fluid; Q1, first quartile; Q3, third quartile.
Source: Appendix 16.1.13.

Figure 3: NLF: Serum partition ratio of AZD8895, AZD1061, and AZD7442 After a Single AZD7442 Dose (Pharmacokinetic Analysis Set)



CoA, co-administered; IM, intramuscular; IV, intravenous; NLF, nasal lining fluid.
Source: Appendix 16.1.13.

Study D8851C00001 (TACKLE)

TACKLE is an ongoing Phase III, randomized, double-blind, placebo-controlled multi-country, multi-center study assessing the safety and efficacy of EVUSHELD for the treatment of COVID-19. The study enrolled individuals ≥ 18 years of age who were not hospitalized for COVID-19 treatment and had at least one or more COVID-19 symptoms that were at least mild in severity. Treatment was initiated within 3 days of obtaining the sample for a positive SARS-CoV-2 viral infection and within ≤ 7 days of COVID-19 symptom onset.

Participants were enrolled into one of 2 independent cohorts:

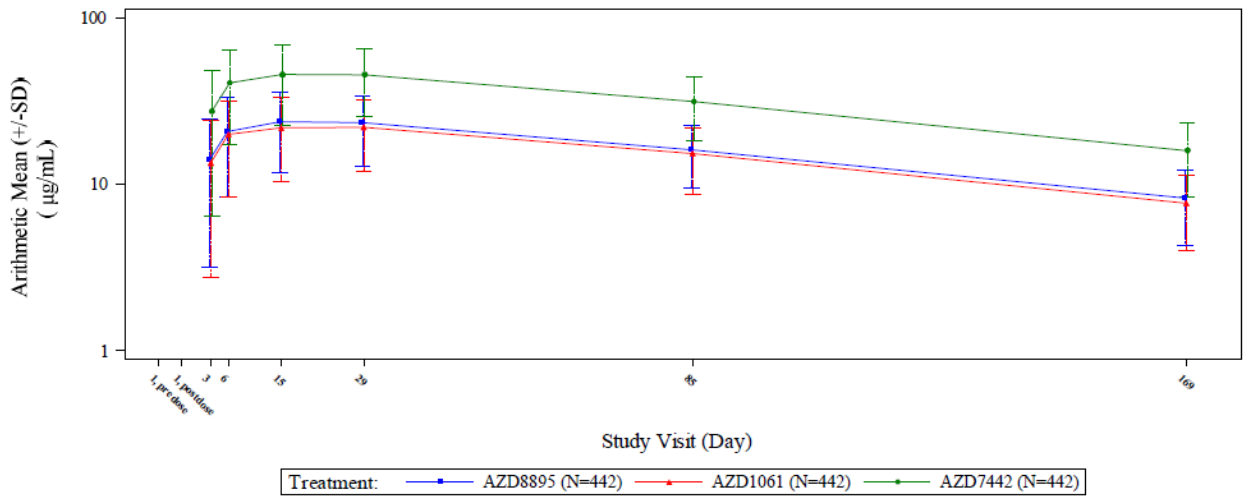
- Cohort 1 (n = approximately 300) underwent more intensive testing to characterize their virological and immunological status, and to correlate that status with clinical outcomes.
- Cohort 2 (n = up to approximately 1400) is being followed for clinical outcomes.

Blood samples for serum PK analysis were scheduled for collection at pre-dose (baseline), and at Study Days 3, 6, 15, 29, 85, 169, and 366 (and option Day 457) in Cohort 1 and at predose (baseline) and at Study Days 6, 29, 85, 169, and 366 (and option Day 457) in Cohort 2.

At the DCO of 14 January 2022, serum AZD8895 and AZD1061 concentration data are available for 442 participants up to 168 days post-dose, after a single IM dose of AZD7442 600 mg (300 mg AZD8895 + 300 mg AZD1061) in the ventrogluteal muscle. The study population included subjects with mild-moderate COVID-19 with median 5 days since symptom onset. 12.8 % of the total study population were 65 years or older; 43% of subjects were obese. Approximately 2% of subjects had chronic liver or kidney disease, respectively.

Mean (SD) serum concentration-time profiles for tixagevimab and cilgavimab following single dose of EVUSHELD 600 mg IM (300 mg tixagevimab + 300 mg cilgavimab, Cohort 1) are shown below.

Figure 4: Arithmetic Mean (± SD) of Serum Drug Concentration Versus Time by Analyte (Semi-logarithmic scale), Across Cohorts 1 and 2, TACKLE, DCO 14 January 2022



AZD7442 concentration = the sum of the AZD8895 and AZD1061 concentrations
PK, pharmacokinetic; SD, standard deviation.
Source: Figure 14.2.6.1.2A

Table 3: Summary of PK Parameters for Tixagevimab and Cilgavimab Following Single Dose IM Administration of 600 mg EVUSHELD – Over Day 28 Period Post-Dose, Cohort 1 – PK Analysis Set, TACKLE (Primary Analysis DCO)

Parameter (Units)	300 mg Tixagevimab (N = 144)	300 mg Cilgavimab (N = 142)
C_{max} (µg/mL)	21.9 (61.7)	20.3 (63.6)
t_{max} [a] (day)	14.9 (1.10 – 86.0)	15.0 (1.10 – 85.1)
AUC_{last} (day·µg/mL)	877 (102)	821 (98.8)
t_{last} [a] (day)	80.9 (5.78 – 111)	80.9 (12.9 – 111)
AUC_{0-28d} (day·µg/mL)	472 (70.0) [c]	434 (72.1) [d]
$C_{avg}28d$ [b] (µg/mL)	16.8 (70.0) [c]	15.5 (72.1) [d]

[a] Median (min-max) presented for t_{max} and t_{last}

[b] Average concentration over 28 days post-dose, calculated as $AUC_{0-28d\ /\ 28\ days}$

[c] n = 133

[d] n = 132

Data are presented as geometric mean (geometric %CV), except for t_{max} and t_{last} as median (min – max).

AUC_{0-28d}, area under the serum concentration-time curve from time zero to Day 28 post-dose; AUC_{last}, area under the serum concentration-time curve from time zero to the last measurable time point; $C_{avg}28d$, average serum concentration over 28 days post-dose; C_{max}, maximum serum concentration; %CV, percent coefficient of variation; DCO, data cut-off; IM, intramuscular; Max, maximum; Min, minimum; N, number of participants in group; n, number of participants with measurements up to Day 28; PK, pharmacokinetic; t_{last}, time to last serum concentration measurement; t_{max}, time to maximum serum concentration.

Source: Interim Pharmacokinetic Report, Version 1 (Appendix 16.5, TACKLE CSR, Module 5.3.5.1).

After a single 600 mg IM dose of EVUSHELD, the mean serum concentrations of tixagevimab and cilgavimab over time were similar, and as expected based on PK observations in previous studies. The observed PK over 84 days post-dose is consistent with the long half-life of EVUSHELD.

Absorption

After a 300 mg tixagevimab and 300 mg cilgavimab intramuscular dose in participants with mild to moderate COVID-19 in TACKLE, the mean (%CV) maximum concentration (Cmax) was 21.9 (61.7%) and 20.3 (63.6%) µg/mL for tixagevimab and cilgavimab respectively, which were reached at a median Tmax of 15 days.

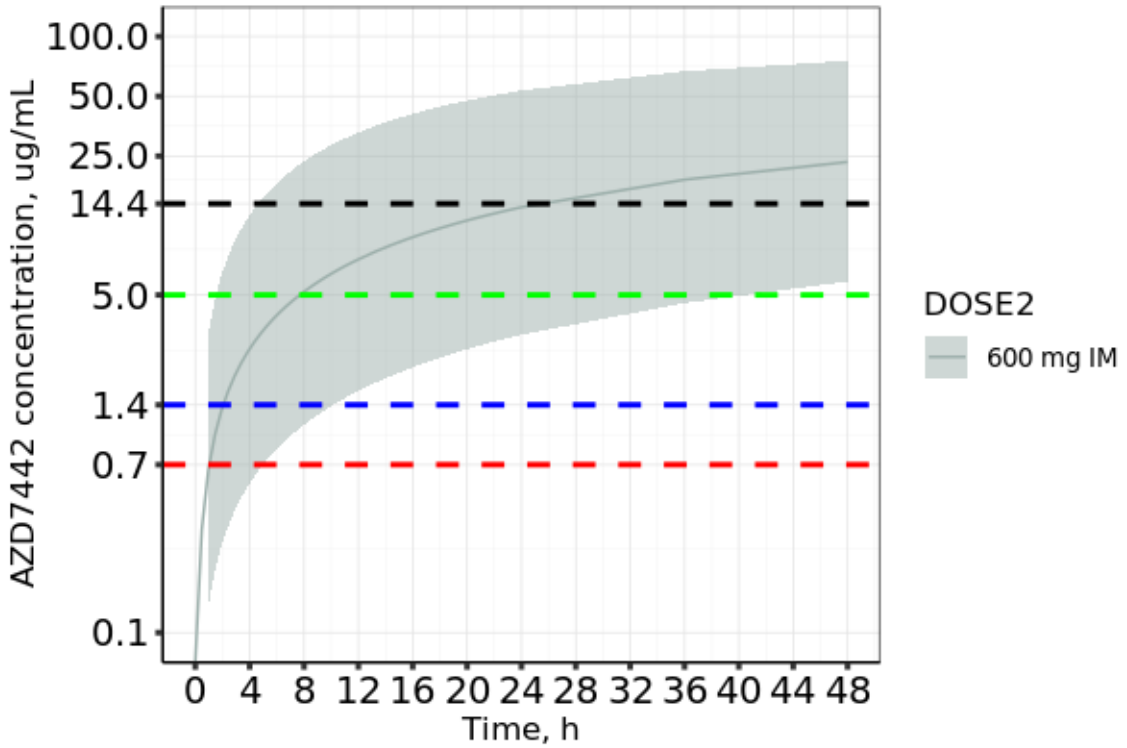
Upon request, the applicant presented the time to reach minimum protective concentration (MPC) against BA.2 (IC50=35 ng/mL) or BA.4/BA.5 (IC50=65ng/ml) in 50% of subjects (median values for a typical patient), based on popPK model using 6.5% and 12% partition ratios and IC90. Furthermore, the model predicted time to reach target serum concentration was presented for omicron-subvariants with varying estimates: nasal penetration ratio of 1.8% and BA.4/5 IC80 of 260 ng/mL; nasal lining fluid penetration ratio of 1.81% and BA.2 IC80 of 89.6 ng/mL; lung penetration ratio of 6.5% and mean BA.2 IC80 of 89.6 ng/mL; lung penetration ratio of 12% and BA.2 IC80 of 89.6 ng/mL. Time to reach minimum protective concentration (MPC) in the TACKLE population is unknown.

Table 4: Time to Reach Minimum Protective Concentration Against BA.2 or BA.4/BA.5 After Dosing with EVUSHELD 600 mg IM Using 6.5% and 12% Partition Ratios and Highest Inhibition Constants (IC90) in a Typical Participant

	BA.2[a]	BA.4/BA.5[b]
6.5% Lung Penetration ratio	7.7 h	15.6 h
12% Lung Penetration ratio	4.3 h	7.7 h

highest IC50 used is 35 ng/mL
highest IC50 used is 65 ng/mL
h, hours; IC50, 50% inhibitory concentration; IC90, 90% inhibitory concentration; IM, intramuscular.
Source:
\\samba.scp.astrazeneca.net\qcp\QCP_MODELING\OTHER\azd7442\poppk_2021_03_12_CMA_submission\Results

Figure 5: Model-Predicted Time to Reach Target Serum Concentration of EVUSHELD following the 600 mg IM Dose for the Treatment of COVID-19



Black dashed line of 14.4 µg/ml corresponds to the modeled MPC for BA.4/BA.5 using nasal penetration ratio of 1.8% and IC80 of 260 ng/mL. Green dashed line of 5 µg/ml corresponds to the modeled MPC for BA.2 using measured nasal lining fluid penetration ratio of 1.81% and IC80 of 89.6 ng/mL (mean of authentic and pseudo-virus assay of BA.2). Blue dashed line of 1.4 µg/ml corresponds to the modeled MPC for BA.2 using lung penetration ratio of 6.5% and mean IC80 of 89.6 ng/mL. Red dashed line of 0.7 µg/ml corresponds to the modeled MPC for BA.2 using lung penetration ratio of 12% and IC80 of 89.6 ng/mL.AZD7442, EVUSHELD; COVID-19, coronavirus disease 2019; IC80, 80% inhibitory concentration; IM, intramuscular; MPC, minimum protective concentration.
Source:\\samba.scp.astrazeneca.net\qcp\QCP_MODELING\OTHER\azd7442\poppk_2021_03_12_CMA_submission\Results

Distribution

Based on PK modelling, the central volume of distribution was 2.72 L for tixagevimab and 2.48 L for cilgavimab. The peripheral volume of distribution was 2.64 L for tixagevimab and 2.57 L for cilgavimab.

Metabolism/ Elimination

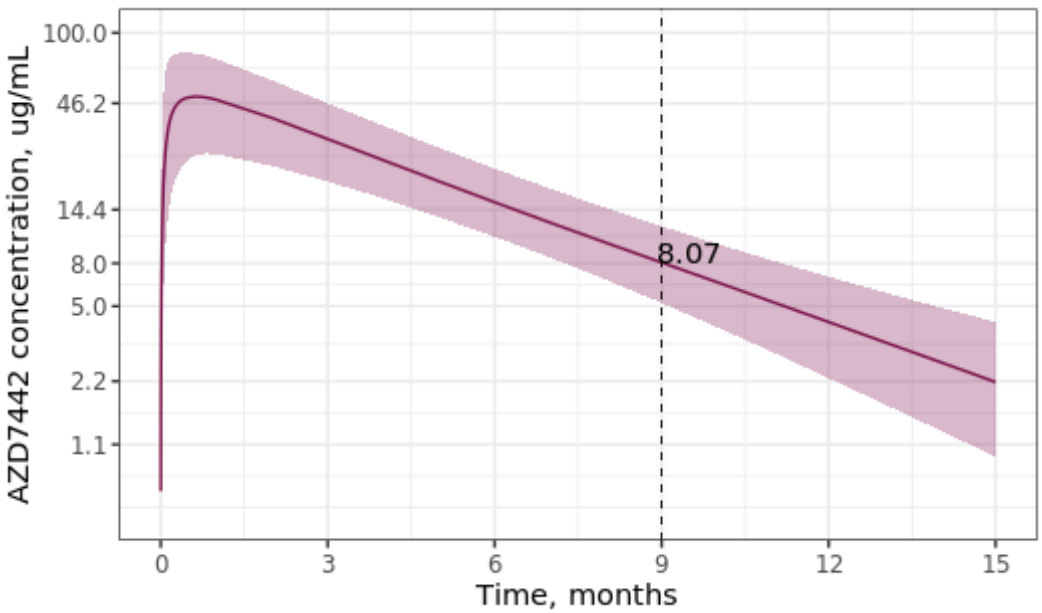
Tixagevimab and cilgavimab are expected to be degraded into small peptides and component amino acids via catabolic pathways in the same manner as endogenous IgG antibodies.

The clearance (CL) was 0.041 L/day for tixagevimab and 0.041 L/day for cilgavimab with interindividual variability of 21% and 29% respectively. The estimated population median terminal elimination half-life was 89 days for tixagevimab and 84 days for cilgavimab.

In TACKLE, following a single intramuscular dose of 300 mg tixagevimab and 300 mg cilgavimab, the geometric mean serum concentration was 42.2 µg/mL on Day 29. Based on population PK modelling serum trough concentrations 9 months after a single intramuscular dose of 300 mg tixagevimab and 300 mg cilgavimab, are expected to be equal to serum concentrations at Day 183 following single intramuscular dose of 150 mg tixagevimab and 150 mg cilgavimab. COVID-19 infection did not affect the clearance of tixagevimab and cilgavimab.

Based on population PK modeling, median serum concentrations at 9 months (8.07 ug/mL) after a single IM dose of 300 mg tixagevimab and 300 mg cilgavimab are anticipated to be equal to serum concentrations at Day 183 (7.78 ug/mL) following a single IM dose of 150 mg tixagevimab and 150 mg cilgavimab.

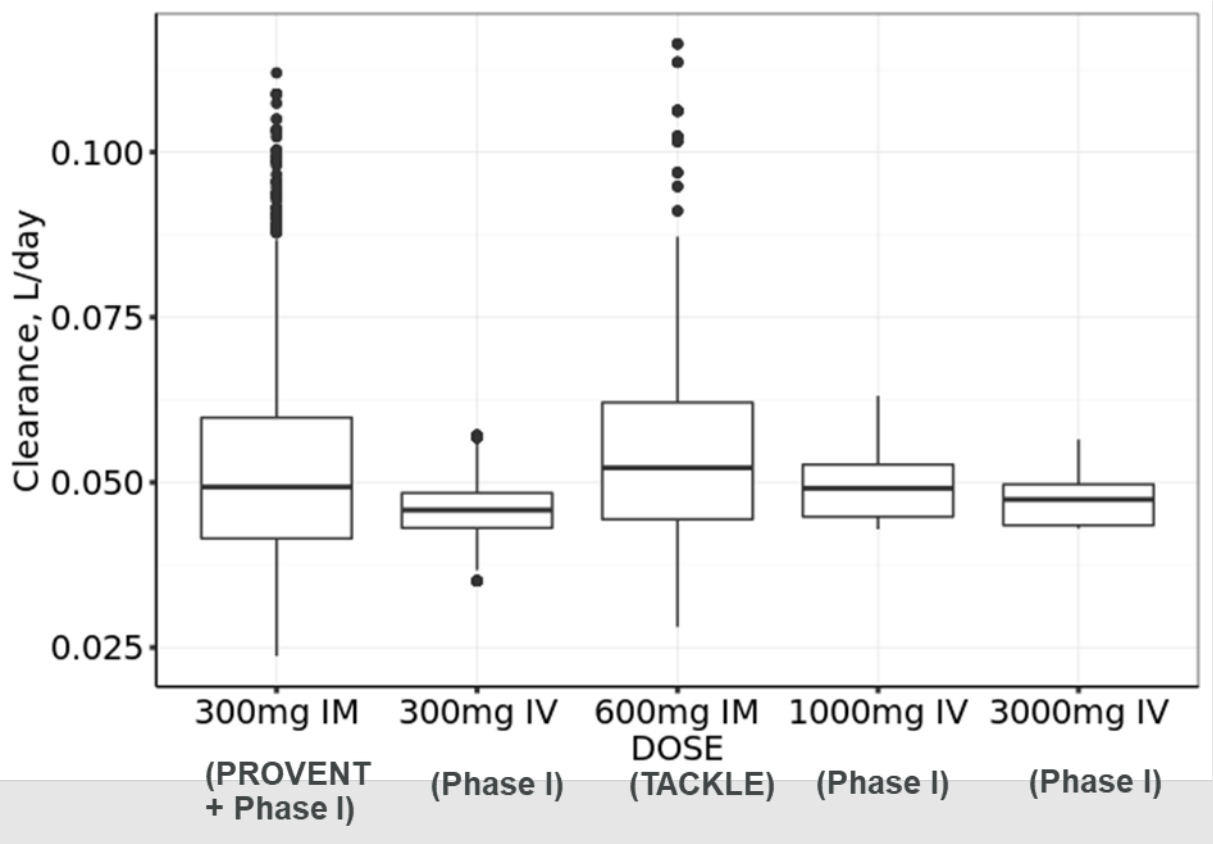
Figure 6: Simulated AZD7442 Serum Concentrations Following 600 mg IM Dose of EVUSHELD



Vertical line shows the serum concentration at 9 months (8.07 µg/mL) AZD7442, EVUSHELD, combination of tixagevimab and cilgavimab; IM, intramuscular
Source: \\samba.scp.astrazeneca.net\qcp\QCP_MODELING\OTHER\azd7442\poppk_2021_03_12_CMA_submission\Results

The post-hoc estimate of clearance based on TACKLE data (600 mg IM) was 0.0522 L/day, which was similar to 0.0488 L/day based on PROVENT data (300 mg IM). This 7% higher clearance is not considered to be a clinically meaningful effect.

Figure 7: Post-hoc Estimates of Clearance Across Studies Suggest No Impact in Participants Infected with SARS-CoV-2



IM, intramuscular; IV, intravenous; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.
Source:\\samba.scp.astrazeneca.net\qcp\QCP_MODELING\OTHER\azd7442\poppk_2021_03_12_CMA_submission\Results

Dose proportionality and time dependencies

EVUSHELD exhibited linear PK (Cmax and AUC) across the dose range from 300 mg to 3000 mg IV applied in the phase 1 study.

The PK for the 600 mg IM dose in TACKLE was as expected based on the population PK model informed dose-proportional PK of EVUSHELD resulting in exposures approximately 2-fold higher than that observed for a 300 mg IM dose.

Geom. mean Cmax increased less than dose proportional in the between-study comparison considering COVID-19 patients in study TACKLE (21.9 µg/mL for AZD8895 and 20.3 µg/ml for AZD1061, respectively) compared to healthy subjects with half dose in the phase 1 study (150 mg AZD8895 and 150 mg AZD1061 at 16.52 and 15.232 µg/mL, respectively).

Special populations

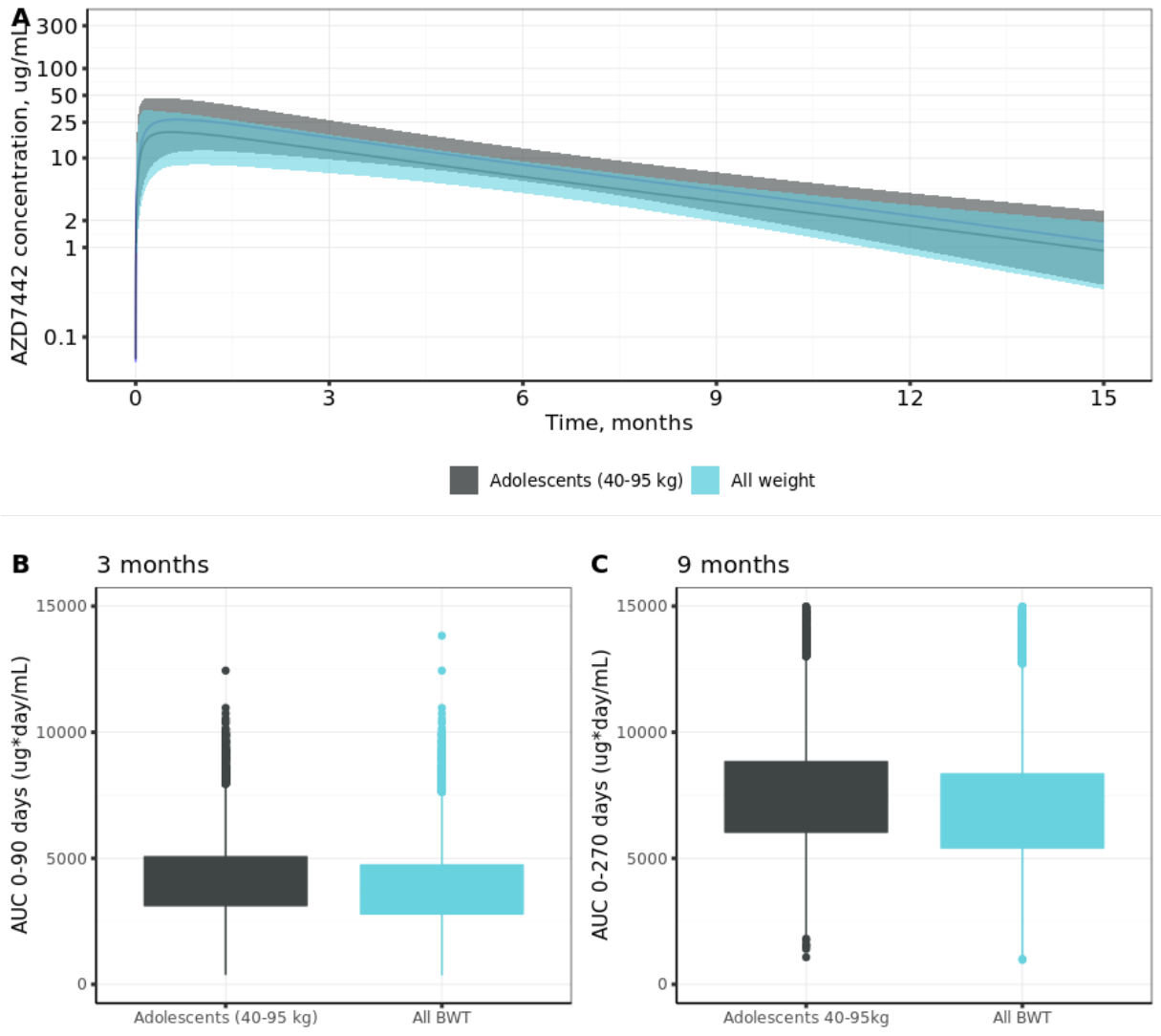
The effect of intrinsic and extrinsic factors on the PK of Evusheld in participants in the TACKLE study has not changed from what has been reported in the population PK report that was submitted as part of the prophylaxis application.

Adolescents

There is no new information on adolescents available with this application. There were no adolescents recruited to TACKLE.

The difference between simulated PK profiles (10 trials of 2555 participants) and AUC (0 to 91 days or 3 months and 0 to 270 days or 9 months) for two groups "All weight" and "Adolescents 40 to 95 kg" are presented. Overall, derived AUCs are comparable between these 2 groups at 3 and 9 months; hence, a 600 mg IM dose does not warrant adjustment for the paediatric patients with a bodyweight > 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 ~ 22-fold and ~ 65-fold for AUC(0-28) and Cmax, respectively for the 600 mg IM dose, based on PK data from TACKLE.

Figure 8: Comparison of Simulated EVUSHELD Median Concentration Over Time for Adolescents with Weight Range of 40 to 95 kg and Adults – A) PK profiles, B) AUC at 3 months, and C) AUC 9 months



AUC, area under the serum concentration-time curve; AZD7442, EVUSHELD; BWT, body weight; PK, pharmacokinetic.
Source:\\samba.scp.astrazeneca.net\qcp\QCP_MODELING\OTHER\azd7442\poppk_2021_03_12_CMA_submission\Results

Pharmacokinetic interaction studies

There is no need to conduct DDI studies with Evusheld as perpetrator based on the elimination mechanism and mechanism of action (external target).

2.3.3. Pharmacodynamics

PD (SARS-CoV-2 nAbs), PK-nAbs correlation, and immunogenicity data of EVUSHELD based on 2 clinical studies (one Phase I study and one Phase III study) that evaluated EVUSHELD for the treatment of mild to moderate COVID-19 in adults (18 years of age and older) were provided.

Genotypic and phenotypic testing are ongoing to monitor for SARS-CoV-2 spike variants containing potential tixagevimab, cilgavimab, and EVUSHELD resistance-associated substitutions in clinical trials. These data are available for TACKLE.

Mechanism of action

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

Primary and secondary pharmacology

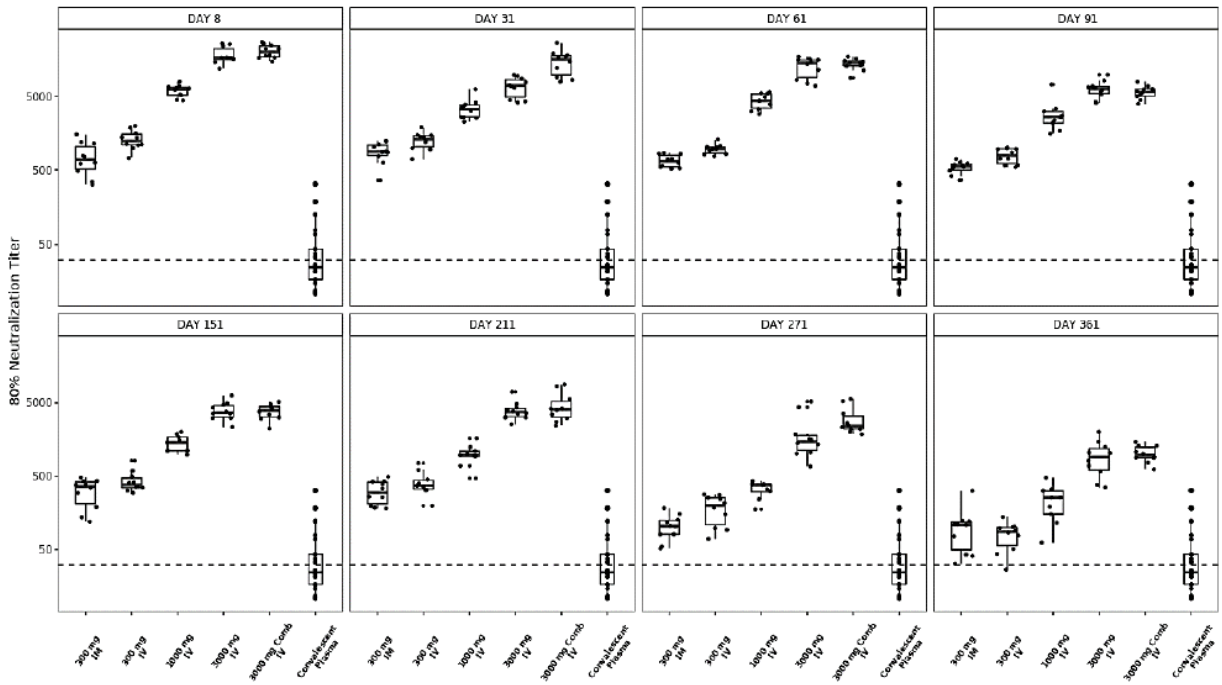
Analysis of neutralizing antibodies against SARS-CoV-2

D8850C00001 (Phase I)

Neutralizing antibody titers 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), and 360 days (Day 361) after administration of AZD7442 in a validated live neutralization assay (PRNT80) at Viroclinics.

All participants receiving AZD7442 exhibited > 4-fold increases in nAb titer compared to baseline at Day 8 and maintained this increase out to Day 271, with 95% of participants maintaining this increase out to Day 361 (2 participants receiving 300 mg IV or IM did not meet this threshold). These results are consistent with the expected pharmacodynamic activity of AZD7442 and demonstrate a dose-dependent relationship, with the 3000 mg dose cohorts showing approximately 3.3, 15.1, and 27.9 greater fold changes than the 1000 mg, 300 mg IV, and 300 mg IM, respectively, on Day 8; 2.7, 9.0, and 13.0 greater fold changes on Day 151; and 4.3, 10.4, and 13.7 greater fold changes on Day 211, and 4.4, 12.4, and 10.5 greater fold changes on Day 361. Across all doses and time points evaluated, the levels of nAbs exceeded the GMT measured in the same assay in 28 individual convalescent plasma samples.

Figure 9 Blox Plot neutralizing antibody titers against SARS-CoV-2 on Days 8, 31,91,151,211,271 and 361 in comparison with convalescent plasma (safety analysis set)



IM, intramuscular; IV, intravenous, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
Source: Table 14.3.7.3 (AZD7442 data), Loo et al 2022 submitted (convalescent plasma data).

TACKLE

Neutralizing antibody titers against SARS-CoV-2 were measured at baseline and after administration of AZD7442 or placebo using a validated pseudovirus 50% neutralization assay (Monogram Biosciences). Serum samples for evaluation of neutralizing antibody titers against SARS-CoV-2 were collected at baseline, and study Day 6, 15, 29, 85, 169, and 366 in Cohort 1, as well as at baseline, and study Day 6, 29, 85, 169, and 366 in Cohort 2.

AZD7442-treated participants exhibited > 4-fold increases in nAb titer compared to baseline starting at Day 6 and persisting through Day 169. At Day 6, nAb titer increased nearly 60-fold over baseline in the AZD7442-treated group compared to a 3.8-fold rise in the placebo group that reflects the natural immune response in these participants. Furthermore, increased titer in the AZD7442 group versus the placebo group was observed through Day 169: 16-fold; 14-fold, 22-fold, 18-fold, and 5-fold over placebo at Day 6, 15, 29, 85, and 169, respectively.

Table 5: Observed and Change from Baseline in SARS-CoV-2 nAb Titers (nAb Evaluable Analysis Set) – TACKLE DCO 14 January 2022

Visit	Statistic	AZD7442 (N = 417)	Placebo (N = 372)
Baseline			
Geometric mean titer	n	80	64
	Geometric Mean (GSD)	530.2 (6.55)	609.4 (4.40)
	95% CI	(349.0, 805.5)	(420.8, 882.4)
	Min, Max	44, 88117	46, 30001
Day 6			
Geometric mean titer	n	381	236
	Geometric Mean (GSD)	27275.3 (2.55)	891.3 (5.56)
	95% CI	(24816.8, 29977.3)	(715.2, 1110.6)
	Min, Max	841, 280570	40, 195819
Geometric mean fold rise	n	77	56
	Geometric Mean (GSD)	59.4 (6.22)	3.8 (5.29)
	95% CI	(39.2, 90.0)	(2.4, 5.9)
	Min, Max	1, 1322	0, 431
Day 15			
Geometric mean titer	n	148	132
	Geometric Mean (GSD)	31367.5 (2.35)	1361.1 (5.41)
	95% CI	(27299.5, 36041.6)	(1017.8, 1820.2)
	Min, Max	142, 146206	73, 64400
Geometric mean fold rise	n	26	24
	Geometric Mean (GSD)	36.3 (8.29)	2.6 (4.86)
	95% CI	(15.4, 85.3)	(1.3, 5.0)
	Min, Max	1, 1409	0, 72

Visit	Statistic	AZD7442 (N = 417)	Placebo (N = 372)
Day 29			
Geometric mean titer	n	292	256
	Geometric Mean (GSD)	29463.7 (2.59)	1279.8 (5.35)
	95% CI	(26407.6, 32873.4)	(1041.1, 1573.2)
	Min, Max	148, 141162	43, 129173
Geometric mean fold rise	n	56	45
	Geometric Mean (GSD)	52.2 (6.38)	2.4 (6.03)
	95% CI	(31.8, 85.7)	(1.4, 4.1)
	Min, Max	1, 1133	0, 445
Day 85			
Geometric mean titer	n	266	194
	Geometric Mean (GSD)	12623.9 (2.11)	801.7 (4.81)
	95% CI	(11534.3, 13816.3)	(642.0, 1001.3)
	Min, Max	151, 62502	46, 50548
Geometric mean fold rise	n	52	34
	Geometric Mean (GSD)	28.0 (6.19)	1.6 (9.82)
	95% CI	(16.8, 46.4)	(0.7, 3.6)
	Min, Max	0, 733	0, 190
Day 169			
Geometric mean titer	n	244	188
	Geometric Mean (GSD)	4783.0 (2.24)	1391.9 (4.56)
	95% CI	(4320.6, 5294.9)	(1119.0, 1731.2)
	Min, Max	62, 32741	44, 62280

Visit	Statistic	AZD7442 (N = 417)	Placebo (N = 372)
Geometric mean fold rise	n	40	32
	Geometric Mean (GSD)	11.1 (5.29)	2.1 (7.82)
	95% CI	(6.5, 19.0)	(1.0, 4.3)
	Min, Max	0, 229	0, 215
Day 366			
Geometric mean titer	n	1	0
	Geometric Mean (GSD)	1703.0 (NA)	NA
	95% CI	NA	NA
	Min, Max	1703, 1703	NA
Geometric mean fold rise	n	0	0
	Geometric Mean (GSD)	NA	NA
	95% CI	NA	NA
	Min, Max	NA	NA

Baseline is defined as the last non-missing measurement taken prior to the first dose of study drug.
The fold rise was calculated as the ratio of the Day x titer level to the pre-dose (screening) titer level.
The 95% CI was calculated as the anti-logarithm transformation of the upper and lower limits for a two-sided CI for the mean of the log-transformed titers.
CI, confidence interval; GSD, geometric standard deviation; Max, maximum; Min, minimum; N, number of participants in group; n, number of participants with measurements; nAb, neutralizing antibody; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
Source: Table 14.2.16.2.1A

Immunogenicity (anti-drug antibodies)

Detection of ADAs against tixagevimab and cilgavimab was conducted utilizing the same tiered approach (screen, confirm, titer) using validated MSD-based ECL assays as with previous prophylaxis application (PPD Laboratories, Richmond, Virginia). For confirmed positive samples, endpoint titers were determined. Data on anti-tixagevimab and anti-cilgavimab nAbs are currently not available but will be provided as soon as ready **(REC).**

D8850C00001 (Phase I)

In the Phase I study, blood samples for serum ADA analysis were collected at baseline, and at Post-dose Follow-up Days 8, 15, 31, 91, 151, 211, and 361. At the time of final analysis, all 60 participants in the study (50 of whom received EVUSHELD and 10 placebo) had a non-missing baseline and at least one non-missing post-baseline ADA result. One of 50 participants in the active cohorts tested positive for ADA to tixagevimab. The participant was in Cohort 1a (300 mg IM) and had a positive ADA result at Day 361 only and negative results at all other assessments. The ADA titer was low, at the limit of detection of 80. Seven of 50 participants in the active cohorts tested positive for ADA to cilgavimab, 4 in Cohort 1a (300 mg IM) and 3 in Cohort 1b (300 mg IV), including the participant who was ADA positive to cilgavimab. Using the same definition of TE-ADA positive from TACKLE (either ADA negative at baseline and ADA positive at ≥ 1 post-baseline assessments with ADA titer ≥ 2 times higher than the minimum required dilution of 80 and 40, for tixagevimab and cilgavimab, respectively, or baseline ADA titer that was boosted to ≥ 4-fold during the study period), 1 of 50 participants (2.0%) in the active cohort would be classified as TE-ADA positive. All 7 participants had a positive ADA result at Day 361 only and negative results at all other assessments. All ADA titers were low, either reported as borderline positive (≤ 40) or close to the limit of detection of 40. No participants who received placebo were ADA positive.

TACKLE

Blood samples for serum ADA analysis were collected at pre-dose on Day 1, and at Days 28, 84, 168, 365, and 456 days post-dose in Cohort 1. The bioanalytical analysis for assessing the presence of ADA against either AZD8895 or AZD1061 is currently ongoing. At the DCO date of 14 January 2022, ADA data up to 168 days post-dose are available for a subset of subjects.

Table 6: Summary of ADA Responses to Tixagevimab and Cilgavimab Following Administration of 600 mg IM EVUSHELD Over 168 Days Post-dose – ADA Evaluable Analysis Set, TACKLE DCO 14 January 2022

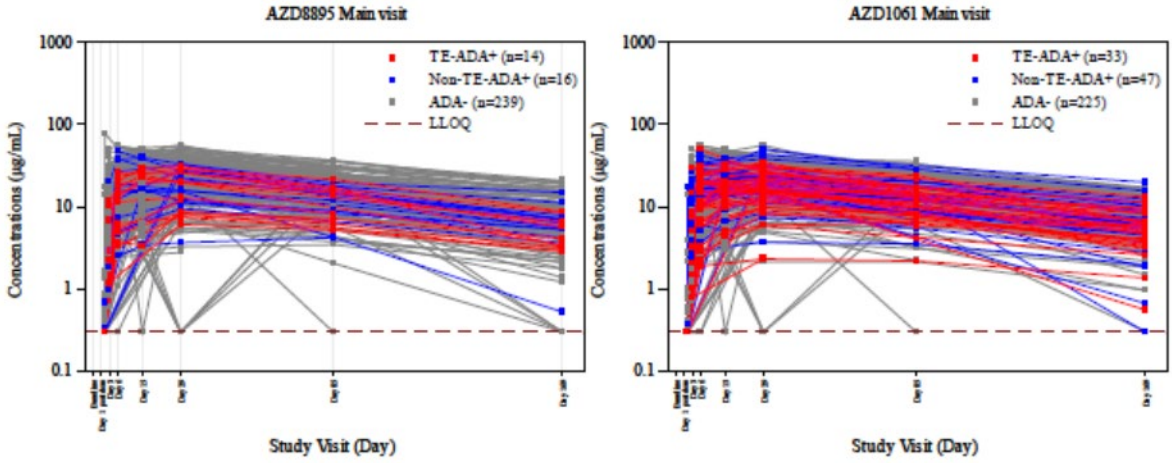
ADA Category	Statistics	AZD8895 [a]		AZD1061 [b]		AZD7442 [c]	
		AZD7442 (N = 271)	Placebo (N = 286)	AZD7442 (N = 307)	Placebo (N = 287)	AZD7442 (N = 346)	Placebo (N = 341)
ADA positive at any visit (ADA prevalence)	n (%)	30 (11.1)	12 (4.2)	81 (26.4)	19 (6.6)	89 (25.7)	26 (7.6)
	Median of maximum titer	120.0	80.0	40.0	80.0	80.0 [e]	80.0 [e]
	(min, max)	(80, 1280)	(80, 640)	(40, 2560)	(40, 1280)	(40, 2560)	(40, 1280)
TE-ADA positive [d] (ADA incidence)	n (%)	14 (5.2)	4 (1.4)	33 (10.7)	7 (2.4)	37 (10.7)	9 (2.6)
	Median of maximum titer	320.0	320.0	160.0	320.0	160.0 [e]	320.0 [e]
	(min, max)	(160, 1280)	(160, 640)	(80, 2560)	(80, 640)	(80, 2560)	(80, 640)

[a] Limit of detection = 80
[b] Limit of detection = 40
[c] ADA positive to AZD7442 is defined as ADA positive to AZD8895 and/or AZD1061; TE-ADA positive to AZD7442 is defined as TE-ADA positive to AZD8895 and/or AZD1061.
[d] Either ADA negative at baseline and ADA positive at ≥ 1 post-baseline assessments with ADA titer ≥ 160 for AZD8895 or ≥ 80 for AZD1061 or baseline positive ADA titer that was boosted to ≥ 4-fold during the study period.
[e] AZD7442 titer is defined as the higher of the 2 titers to the individual mAbs.

ADA, anti-drug antibody; IM, intramuscular; mAb, monoclonal antibody; min, minimum; max, maximum; N, number of participants in treatment group; n, number of participants included in analysis; TE-ADA, treatment-emergent ADA.
Derived from: Table 14.2.16.3.1A, Table 14.2.16.3.2A, and Table 14.2.16.3.3A.

At baseline 4.3% (15/346) of AZD7442 ADA-evaluable participants were positive. The percentage increased through Day 169: 10.7% (34/317), 14.5% (36/249), and 22.4% (35/156) at Day 29, Day 85, and Day 169, respectively. However, median ADA titer to AZD7442 (defined as the higher of the 2 titers of the individual mAbs) did not increase over the same time period: 40.0, 80.0, 40.0 and 80.0 at baseline, Day 29, Day 85, and Day 169, respectively.

Figure 10: Individual Serum Concentrations versus Time, by ADA Status and mAb Components - PK Analysis Set, TACKLE; DCO 14 January 2022



Note: TE-ADA positive is defined as either treatment-induced ADA positive (ADA negative at baseline and post-baseline ADA positive) or treatment-boosted
Note: ADA positive (ADA positive at baseline and the baseline titre is boosted 4 fold or higher post-baseline during the study period).
Note: Non TE-ADA positive is defined as subjects who are ADA positive but not fulfilling the conditions for TE-ADA (+).
Note: ADA negative is defined as subjects who are ADA negative at all assessments, including baseline and post-baseline.
Note: ADA = Anti-drug antibodies. n = Number of subjects in the ADA category. PK = Pharmacokinetic(s). LLOQ = Lower limit of quantification.

Based on available ADA data at the 14 January 2022 DCO, of the 18 participants in the AZD7442 group who had reported a primary event of either severe COVID-19 or death, 12 participants were evaluable for ADA: 7 were ADA-negative, 2 were non-TE-ADA positive and 3 were TE-ADA+. The remaining 6 participants with events were not evaluable for ADA due to insufficient data. Two TE-ADA+ participants first tested ADA-positive at either Day 29 or Day 169, after the date of event. The other TE-ADA+ participant was ADA-positive at baseline and at Day 29, which bracketed the date of primary event. Thus, available data show no clear evidence of an association of ADA with impact on efficacy. This observation is consistent with the fact that ADA had no clear clinically relevant effect on AZD7442 PK. As such, the presence of ADA is not expected to result in loss of efficacy.

Based on available ADA data at the Secondary DCO, all 4 participants in the AZD7442 group who had reported cardiac disorders SOC SAEs and thromboembolic SAEs were ADA-negative, indicating that the observed SAEs were not related to the presence of ADA to AZD7442.

Viral resistance

Genotypic and phenotypic testing are ongoing to monitor for SARS-CoV-2 spike variants containing potential tixagevimab, cilgavimab, and EVUSHELD (tixagevimab and cilgavimab) resistance-associated substitutions in TACKLE. The full-length SARS-CoV-2 spike gene is amplified and sequenced using a validated assay. The phenotypic impact of SARS-CoV-2 spike protein sequences changes, including EVUSHELD binding site substitutions, are evaluated in validated pseudovirus neutralization susceptibility assays. Key variants of concern/interest circulating at the time of the studies are further evaluated in research-grade authentic live virus neutralization susceptibility assays.

With the DCO 21 August 2021, sequencing data were available for 834 of 903 participants (413/452 EVUSHELD and 421/451 placebo) at the baseline visit.

Table 7: SARS-CoV-2 Spike Variants of Concern and Variants of Interest at Baseline and Relative Risk Reduction for Severe COVID-19 or Death through Study Day 29, TACKLE, DCO 14 January 2022

SARS-CoV-2 Spike-Based Pango Lineages[a]		Variant Prevalence (primary events/n (%))			
Variant classification[b]	WHO nomenclature[b]	EVUSHELD (N = 413)	Placebo (N = 421)	Total (N = 834)	RRR (%) and 95% CI[c]
Variants of concern					
B.1.1.7	Alpha	7/139 (5.0%)	7/119 (5.9%)	14/258 (5.4%)	16.00 (-134.74, 69.94)
B.1.351	Beta	0/0 (0%)	0/1 (0%)	0/1 (0%)	NE
P.1	Gamma	0/1 (0%)	0/0 (0%)	0/1 (0%)	NE
P.1_1	Gamma	3/37 (8.1%)	8/46 (17.4%)	11/83 (13.3%)	50.08 (-76.85, 85.91)
B.1.617.2	Delta	1/33 (3.0%)	4/33 (12.1%)	5/66 (7.6%)	70.64 (-107.42, 95.84)
Variants of interest					
C.37	Lambda	0/11 (0%)	1/9 (11.1%)	1/20 (5%)	100 (NE, NE)
B.1.621	Mu	0/0 (0%)	0/1 (0%)	0/1 (0%)	NE
B.1.621.1	Mu	0/0 (0%)	0/1 (0%)	0/1 (0%)	NE

[a] Surrogate Pango lineages based on spike sequences

[b] From: https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/ (Accessed 04 February 2022).

[c] RRR for severe COVID19 or Death from Any Cause through Study Day 29 by SARSCoV2 Spike-Based Lineages at Baseline/Day 1 (>=25% Sensitivity) for the Modified Full Analysis Set. RRR is calculated only if N >= 20 for corresponding lineage (total). Results are from a Cochran-Mantel-Haenszel stratified by time from symptom onset (<= 5 vs > 5 days) and risk of progression to severe COVID19 (high vs low).

CI, confidence interval; COVID-19, coronavirus disease 2019; N, number of participants; n, number or participants with variant; NE, not evaluable; RRR, relative risk reduction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

Source: Table 14.2.18, TACKLE CSR, Module 5.3.5.1.

At baseline, AZD7442 binding site substitutions at an allele fraction ≥ 25% were observed in in 0.1 to 29.2% of the participants and were balanced between the AZD7442 and placebo groups. For 14/19 substitutions, sensitivity to AZD8895 and AZD1061 individually, as well as in combination (AZD7442) was tested in vitro using recombinant spike research-grade pseudotyped virus microneutralization assays, and in all cases the reduction of susceptibility to AZD7442 was < 10-fold.

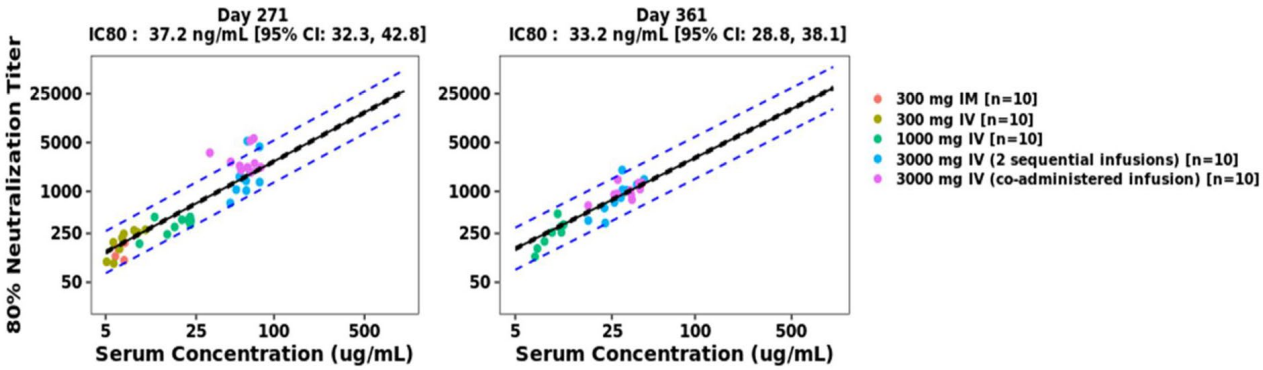
With DCO 14 January 2022, baseline and follow-up SARS-CoV-2 spike sequences were available for 380 TACKLE participants treated with AZD7442. Treatment-emergent substitutions at an allele fraction ≥ 25% (n = 137) were observed in 59/380 participants. The majority of these substitutions were first observed at Day 6 following treatment initiation. None of these treatment-emergent substitutions was observed in more than 5 participants. The individual impact of 33/137 treatment-emergent substitutions on sensitivity to AZD7442 was tested in vitro using pseudovirus neutralization assays, and in all cases the change in susceptibility was < 5-fold.

Treatment-emergent substitutions at an allele fraction 3% to 25% (n = 582) were observed in 121/380 participants. The majority of these substitutions were first observed at Day 6 following treatment initiation. None of these treatment-emergent substitutions was observed in more than 4 participants. The individual impact of 112/580 treatment-emergent substitutions on sensitivity to AZD7442 was tested in vitro using pseudovirus neutralization assays, and in all cases the change in susceptibility < 5-fold.

2.3.4. PK/PD modelling

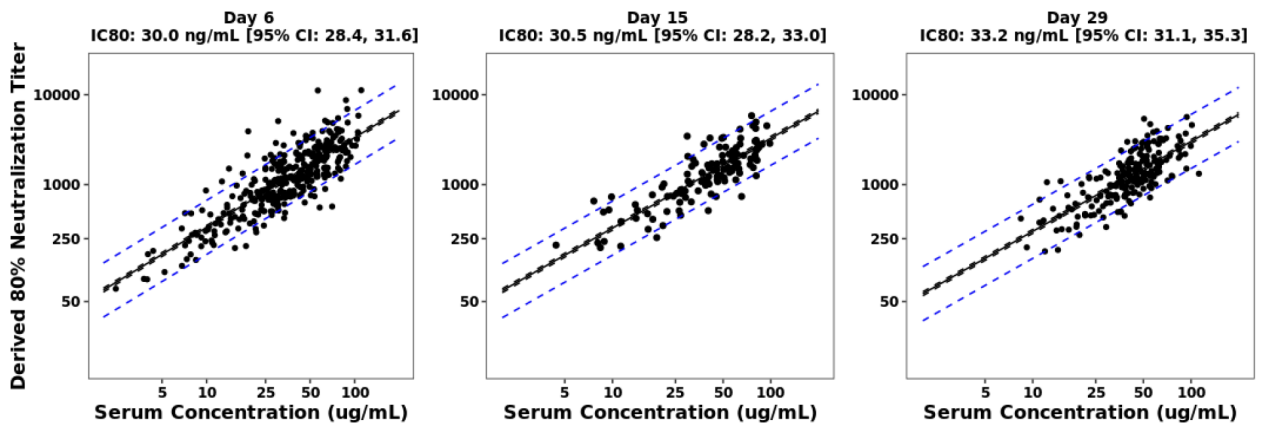
Longer follow-up data (including day 271 and 361) for correlation between the serum Evusheld concentrations and the 80% Neutralizing Antibody Titers from study D8850C00001 (Phase I) were presented with this data package.

Figure 11: PK-nAb Correlation Analysis for D8850C00001 Phase I Study in Healthy Participants



An exposure-response analysis was conducted for TACKLE.

Figure 12: Correlation Between the Serum EVUSHELD Concentrations and the 80% Neutralizing Antibody Titers on Day 6, Day 15, and Day 29 for Single 600 mg IM Dose in TACKLE (Phase III)



Horizontal line represents GMT measured in convalescent plasma samples from COVID-19 participants (n = 28). CI, confidence interval; COVID-19, coronavirus disease 2019; GMT, geometric mean titer; IC_{80}, 80% maximal inhibitory concentration; IM, intramuscular. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. Source:\\samba.scp.astrazeneca.net\qcp\QCP_MODELING\OTHER\azd7442\other_20210209_QC_Activity_EUA\Results\Tackle_submission_12112021\02_PK-nAB

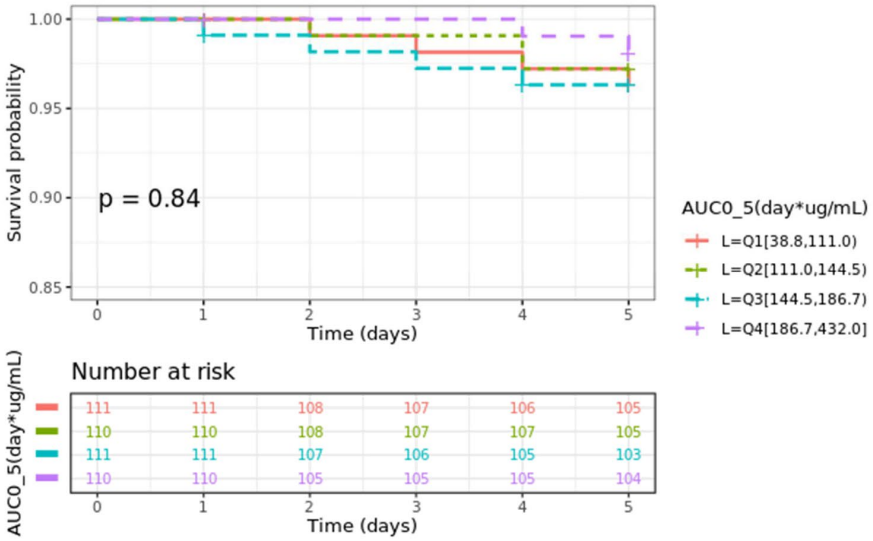
The derived median ex vivo IC80 from TACKLE was 28 to 35 ng/mL and close to the in vitro IC80 value of 40 ng/mL measured in the SARS-CoV-2 original strain microneutralization assay.

For the exposure-response analysis in TACKLE, exposure (area under the concentration-time curve [AUC] from 0 to 5 days post dose (AUC(0-5 days)) or from 0 to 28 days post dose (AUC(0-28 days)) was derived through Bayesian post-hoc estimates using a 2-compartment population PK model after a single 600 mg IM dose of EVUSHELD. The population PK model individual predicted AUC (AUC(0-5 days) and AUC(0-28 days)) divided in 4 quartiles was correlated to the incidence of severe COVID-19 illness or death that occurred by Day 5 and Day 28, respectively.

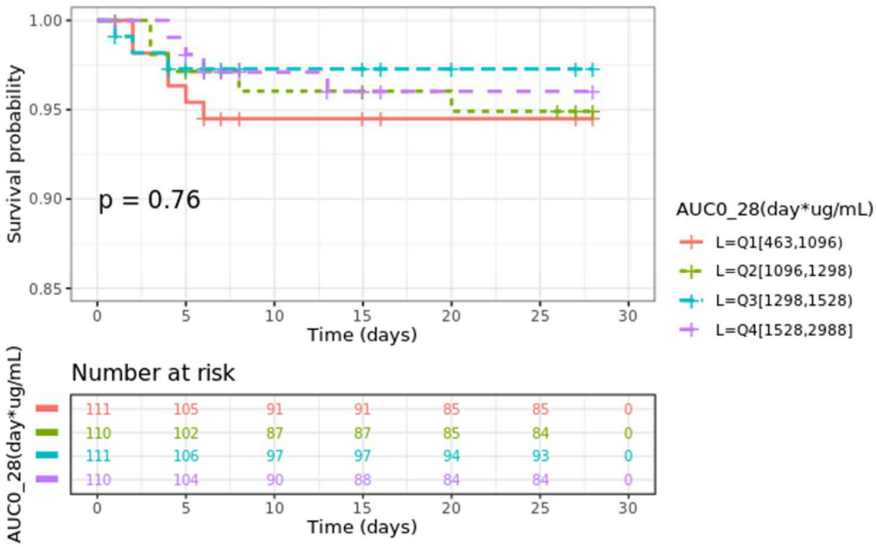
In the 5-day exposure-response data set, 13 participants progressed from mild to moderate COVID-19 to severe COVID-19. In the 28-day exposure-response data set, 16 participants progressed from mild to moderate COVID-19 to severe COVID-19 and 2 participants progressed to death, compared to 37 participants who progressed to severe COVID-19 in the placebo group.

Table 8: Exposure-Response Relationship of EVUSHELD for Treatment of Symptomatic COVID-19

A) Exposure parameter $AUC_{(0\text{-}5\ days)}$



B) Exposure parameter $AUC_{(0\text{-}28\ days)}$



Time is displayed in days. The area under the curve of EVUSHELD was split into 4 quartiles. Q1: quartile 1; Q2: quartile 2; Q3: quartile 3; Q4: quartile 4. Q, quartile.
$AUC_{(0\text{-}5\ days)}$, area under the serum concentration-time curve from time zero to 5 days post dose; $AUC_{(0\text{-}28\ days)}$, area under the serum concentration-time curve from time zero to 28 days post dose; COVID-19, coronavirus disease 2019; L, legend; Q, quartile
Source: \\samba.scp.astrazeneca.net\qcp\QCP_MODELING\OTHER\azd7442\Exposure_Response

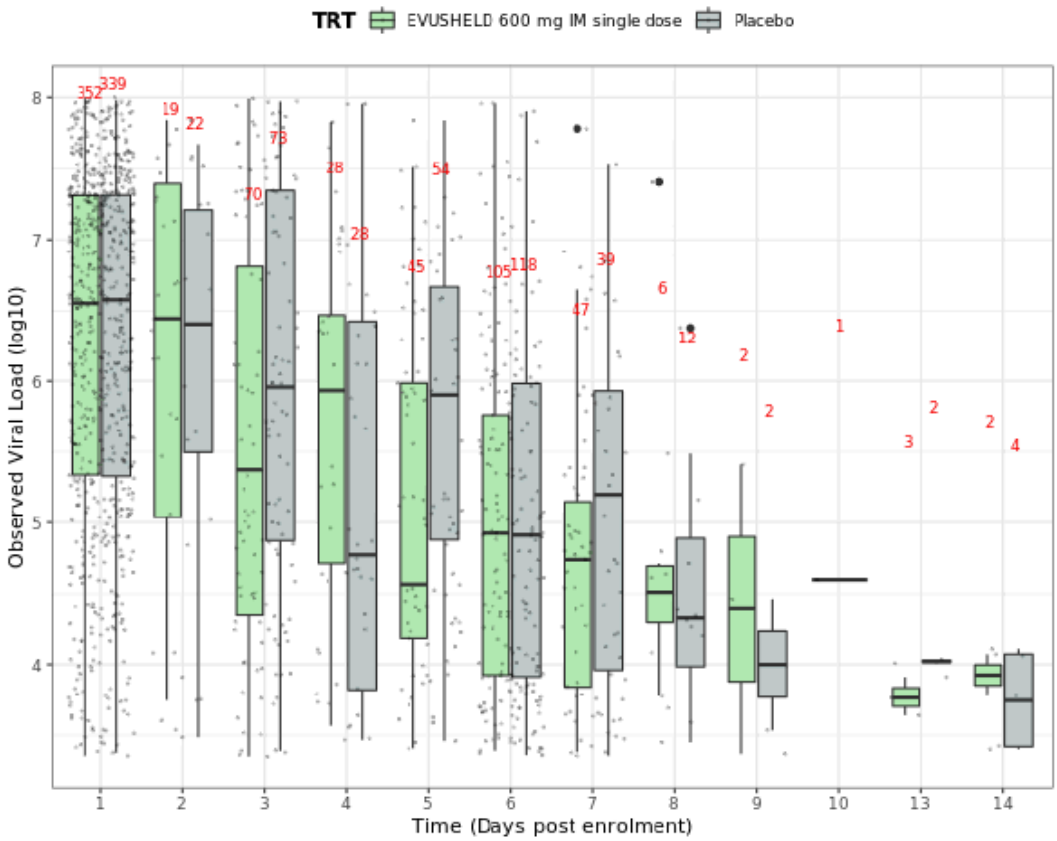
Dose Justification for Treatment of Mild to Moderate COVID-19

For the treatment indication, a dose of 600 mg was selected to ensure that high viral cell entry inhibition is reached within hours and is maintained for a duration of at least 28 days post dose. This was based on the measured in vitro potency of the variants and the understanding of the pharmacokinetics of EVUSHELD to maintain drug exposure. These PK and PD properties were used in a viral dynamic model to confirm the adequacy of the 600 mg dose selected.

The developed viral dynamics model was used to describe the TACKLE viral load data and used to support the dose selection for treatment of mild to moderate COVID-19. In total, viral load time-course profiles from 750 participants (378 EVUSHELD, 372 placebo) were used for the analysis. The dataset used for the analysis consists of a total of 750 participants with their respective EVUSHELD concentration derived from previous population PK analysis. However, finally, due to the scarcity in the measurable individual viral load data and high variability in the data, the previously described model as part of prophylaxis application was used, rather than the parameter estimates based on the TACKLE data.

A pooled analysis of the spread of observed viral load data (in log10) is depicted below.

Figure 13: Distribution of Observed Viral Load after Placebo and EVUSHELD 600 mg IM Administration in the TACKLE Study



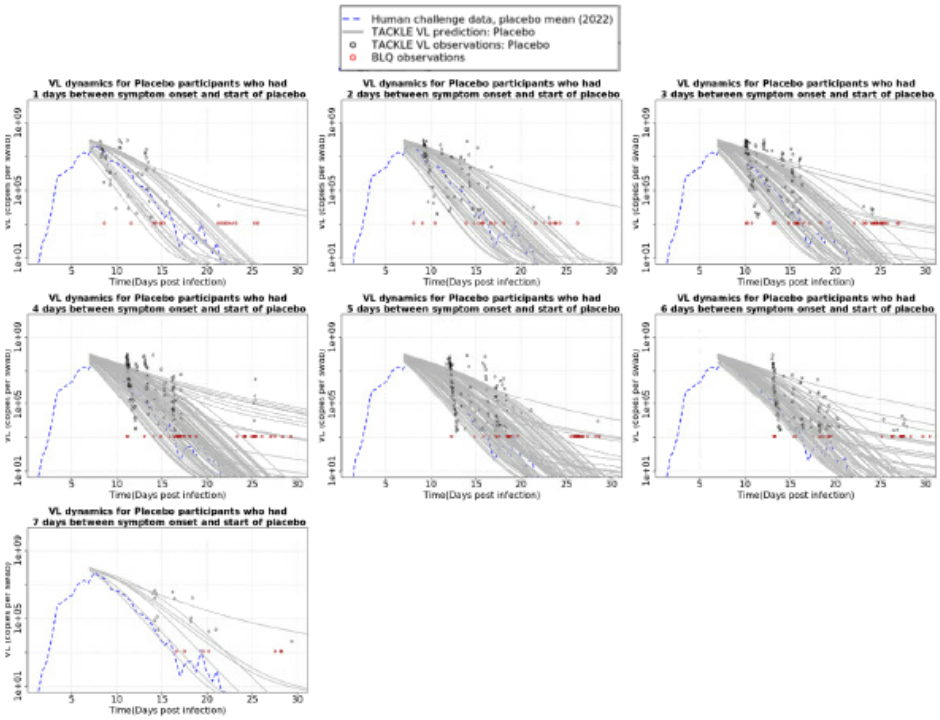
The boxplot lines represent the first quartile, median and third quartile of the observed viral load copies (in log10). The whiskers are 1.5 times of inter-quartile range. The value above the boxplot (red label) represents the number of viral load observations for each treatment group per day post enrollment. The gray closed circles represent the viral load observations. The 3 larger closed circles are outliers above the end of the whiskers.
IM, intramuscular; TRT, treatment.
Source: /ProjectDir/Scripts/TACKLE_Technicalreport_codes.R

The boxplot represents the observed viral load for participants with or without administration of EVUSHELD 600 mg IM single dose. A decrease in viral load in the EVUSHELD and placebo group is

observed. There was high variability in the observed viral load observations for each group. The number of participants for whom data were available at each study day shows the sparse data collection at time points after 7 days post-dose.

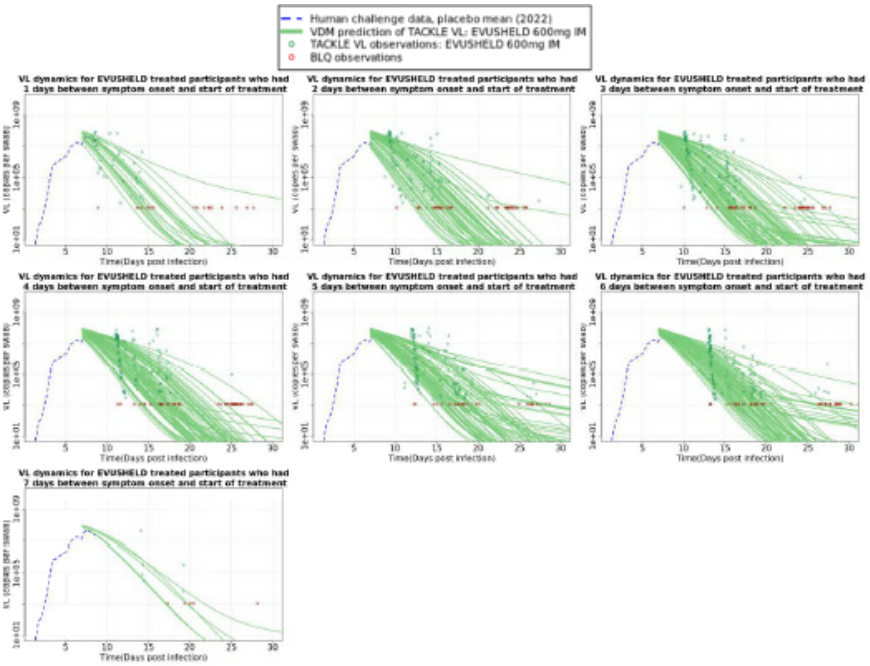
The predicted individual viral load dynamics (gray solid lines) from all the placebo participants overlaid with the observed viral load data from placebo group in TACKLE study and with the human challenge study mean placebo data (blue dashed lines) is shown below. Analogously, the predicted individual viral load response (green solid lines) and then observed viral load data from the EVUSHELD-treated participants in the TACKLE study. As the human challenge study was not conducted with EVUSHELD and the ascending viral load phase could not be observed due to the study criteria of enrolling participants (post-symptom), the human challenge study mean data for the pre-peak was overlaid as a reference to help graphical visualization of overall viral dynamics.

Figure 14: Viral Load Dynamics for All Placebo Participants, Stratified by Number of Days Between Symptom Onset and Start of Placebo



The gray lines represent the model-predicted SARS-CoV-2 viral load dynamics of the individual placebo participants. The blue dashed line represents the mean human challenge placebo data from Killingley et al 2022. The open black circles represent the viral load observation for the placebo participants. The red open circles represent the BLQ values.
BLQ, below the limit of quantification; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VL, viral load.
Source: /ProjectDir/Scripts/TACKLE_Technicalreport_codes.R

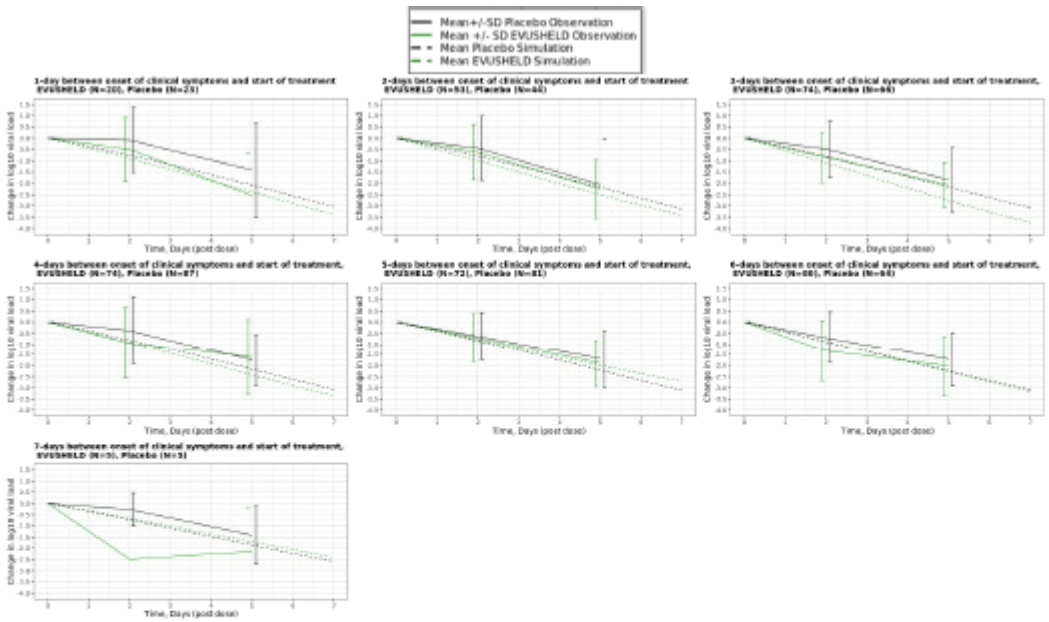
Figure 15: Viral Load Dynamics for All EVUSHELD 600 mg IM Single Dose Treated Participants, Stratified by Number of Days Between Symptom Onset and Start of Treatment



The green lines represent the SARS-CoV-2 viral load dynamics of the individual EVUSHELD 600 mg IM single dose treated participants. The blue dashed line represents the mean human challenge placebo data from Killingley et al 2022 during the ascending phase only. The open green circles represent the viral load observation for the treated participants. The red open circles represent the BLQ viral load values.
BLQ, below the limit of quantification; IM, intramuscular; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VDM, viral dynamic model; VL, viral load.
Source: /ProjectDir/Scripts/TACKLE_Technicalreport_codes.R

The parameters obtained from fitting the viral dynamic model to TACKLE study viral load data were used to compare the predicted and observed mean of change in viral load from the baseline. The viral dynamic model predictions for with- and without-dosing of EVUSHELD, stratified by the days between onset of clinical symptoms and start of treatment is shown below. Due to the spread in viral load sampling times, the protocol-defined nominal sampling times were used to group adjacent sampling times. The mean and standard deviation of viral load was calculated at the nominal days of Day 1, Day 3, and Day 6 (for plotting purposes these are moved a day earlier to 0, 2, and 5, respectively, for comparison with predictions). The model predictions are at continuous time between Day 0 and Day 7.

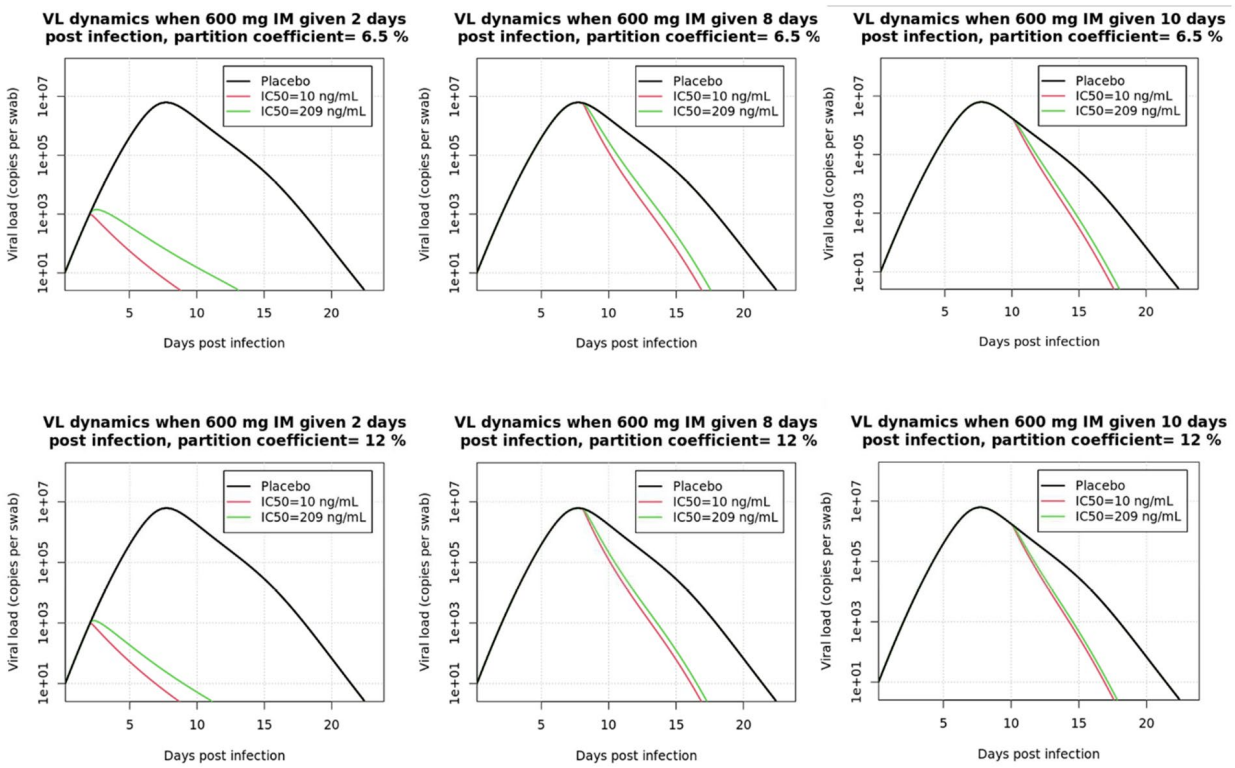
Figure 16: Predicted and Observed Change in Mean Viral Load (log10) from Baseline over the First 7 days post Placebo or EVUSHELD Administration



The viral dynamic model predictions in TACKLE stratified by number of days between onset of clinical symptoms and dosing EVUSHELD, overlayed with the observed mean (± SD) viral load. The black solid line represents the observed change in placebo viral load mean from baseline. The green solid line represents the observed change in EVUSHELD 600 mg IM single dose viral load mean data from baseline. The black dashed line represents the VDM predicted change in mean viral load from baseline based on the VDM fit to the placebo viral load data. The green dashed line represents the predicted change in mean viral load from baseline when VDM is fit to EVUSHELD 600 mg IM single dose viral load data.

Due to the mentioned limitation, the viral dynamic model parameter estimates as described in the viral dynamic modelling report previously submitted as part of the prophylaxis application were used to compare the anti-viral effect of different EVUSHELD doses when infected by either the original SARS-CoV-2 strain or the Omicron BA.1 variant. Based on the similarity in the viral load dynamics in nasal swab versus epithelial lining fluid, the viral dynamic simulations were conducted to predict the response in the lower respiratory tract (Patrucco et al 2020, Goyal et al 2020b). The simulations were conducted using the IC50 of 10 ng/mL for the original SARS-CoV-2 strain and 209 ng/mL for the Omicron BA.1 subvariant (geometric mean of the first IC50 reported by 4 independent labs), assuming a lower respiratory tract penetration of either 6.5% (Chigutsa et al 2022) or 12% (Magyarics et al 2019) and dose of either 300 mg or 600 mg IM.

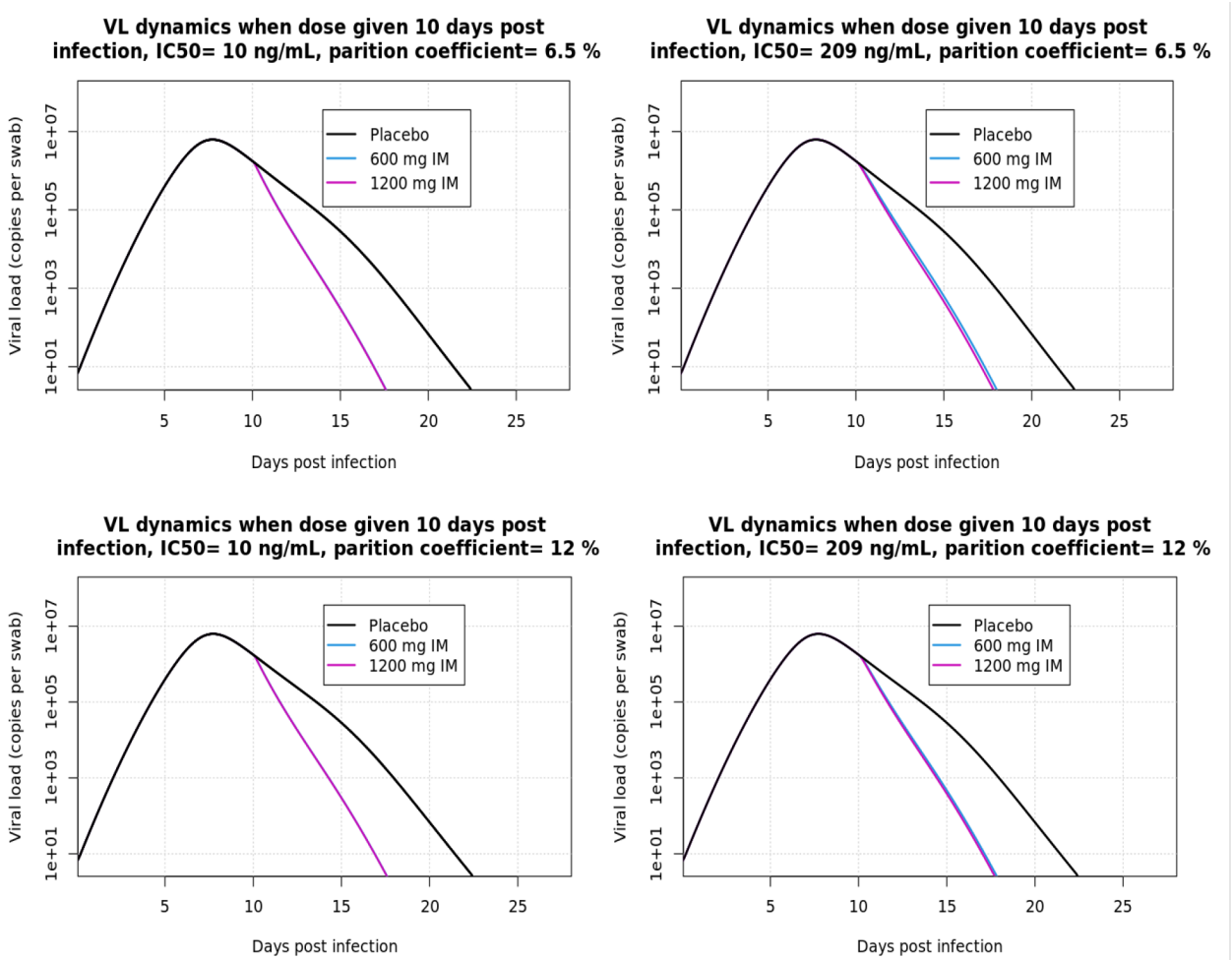
Figure 17: Viral Dynamics for EVUSHELD 600 mg IM with Dosing at Different Days Post-Infection (IC50 = 209 ng/mL), Partition Coefficient 6.5% or 12%



IC_{50}, Half-maximal inhibitory concentration; IM, intramuscular; VL, viral load
Source: /ProjectDir/Scripts/TACKLE_Technicalreport_codes.R

The viral dynamics model predicts that the viral load clearance in the symptomatic patient population is faster when administering EVUSHELD earlier within the 1 to 7 days post-symptom period. This has been confirmed in TACKLE with fewer primary events (severe COVID-19 and death) observed when EVUSHELD was dosed within fewer days post symptom onset.

Figure 18: Viral Dynamics with EVUSHELD 600 mg and 1200 mg IM Dosed 10 Days Post-Infection (IC50 = 10 versus 209 ng/mL), Partition Coefficient 6.5% or 12%



IC_{50}, Half-maximal inhibitory concentration; IM, intramuscular; VL, viral load
Source: /ProjectDir/Scripts/TACKLE_Technicalreport_codes.R

The viral dynamic time-course is similar for 600 mg IM and 1200 mg IM for 6.5% and 12%, respectively

2.3.5. Discussion on clinical pharmacology

Pharmacokinetics

PK, PD (SARS-CoV-2 nAbs), PK-nAbs correlation, immunogenicity, and antiviral resistance data based on 2 clinical studies (one Phase I study and one Phase III study) that evaluated Evusheld for the treatment of mild to moderate COVID-19 in adults (18 years of age and older) were provided with this data package. Bioanalytical reports for the determination of AZD8895 and AZD1061 human serum concentrations in TACKLE are currently outstanding and should be provided as soon as available (Q4, 2022) (**REC**). No updated population PK model has been provided. The pooled population PK analysis provided with the initial application included data of 442 Participants with 1473 observations (up to study day 85) in the interim PK dataset. An update of pop PK was requested in form of a REC in the context of the MAA for prophylaxis indication.

The applicant presented the final CSR of the phase 1 study D8850C00001 including PK data until day 361; previously calculated PK parameters only marginally changed with final analysis. The NLF concentration data show that both, AZD8895 and AZD1061, distribute significantly into the upper

respiratory tract up to day 151. The mAb concentrations in NLF increase dose-proportionally in the range of 300 mg IV to 3000 mg IV. Individual values varied widely (more than factor 10).

NLF concentration data were used to determine the partition ratio. It was shown that partition ratio is dose-independent, mAb-independent, and time-independent up to day 151. For the prophylactic dose of 300 mg IM, the median partition from serum to NLF was calculated as 1.81% for AZD7442. Based on the results presented, it is reasonable to estimate a similar ratio for the intended higher dose of 600 mg used in study TACKLE.

A higher dose of 600 mg Evusheld (300 mg AZD8895 and 300 mg AZD1061) as compared to the prophylaxis indication (150 mg AZD8895 and 150 mg AZD1061) was applied in study TACKLE in the treatment of mild-moderate COVID-19. PK data are preliminary and available for 291 participants at day 169. The sampling scheme in the target population was sparse.

Based on data from 21 August 2021 DCO (PK data available for up to day 84 from approximately half of the subjects), the mean (%CV) maximum concentration (Cmax) was 21.9 (61.7%) and 20.3 (63.6%) µg/mL for AZD8895 and AZD1061, respectively, after a 300 mg AZD8895 and 300 mg AZD1061 intramuscular dose in participants with mild to moderate COVID-19 in TACKLE. As Evusheld 600 mg dose IM was not tested in healthy subjects, a direct between-study comparison of PK parameters is not possible. In relative terms, geom. mean Cmax was lower in COVID-19 patients in study TACKLE (21.9 µg/mL for AZD8895 and 20.3 µg/ml for AZD1061, respectively) as would have been expected from data in healthy subjects with half dose (150 mg AZD8895 and 150 mg AZD1061 at 16.52 and 15.232 µg/mL, respectively). An impact of COVID-19 disease on exposure is not expected and PK was described as dose-proportional by the popPK model. Thus, this difference might be a result of differences in numbers of subjects (N=10 in study 1 receiving 300 mg IM and N=144 in TACKLE receiving 600 mg IM), different sampling scheme (more dense in study 1), or due to body weight effect (subjects heavier in TACKLE). Median Tmax was reached with approximately Day 15 and was comparable with what has been observed in study 1 and phase 3 studies for prophylaxis indication. The average concentration was approximately 16 µg/ml up to day 28 for each of the 2 mAbs. Between-subject variability (geometric CV%) was high for the PK parameters investigated (approximately 62% to 72%). The time to reach minimal protective concentration (MPC) based on the TACKLE data and predominant strains (alpha, gamma, delta) at the time of the study have not been provided explicitly. Based on the IC50 level, however, time to reach MPC is not expected to exceed that calculated for BA.2 (~ 8 h, expected value to be reached by 50% of the patients). Unfortunately, no range has been calculated for the time to reach MPC, or, in other words, time to reach MPC has only been stated for the median (50% of subjects to reach) and not for a higher % of subjects to reach MPC.

The distribution, metabolism, and elimination attributes of Evusheld, have not changed from what has been reported in the Population PK Report that was submitted as part of the prophylaxis application.

Pharmacokinetics in special populations

The effect of intrinsic and extrinsic factors on the PK of Evusheld in participants in the TACKLE study has not changed from what has been reported in the population PK Report that was submitted as part of the prophylaxis application.

No adolescent PK data are available from Evusheld clinical trial program so far, however, adolescents aged 12 years and older and weighing at least 40 kg are included in the proposed indication for COVID-19 treatment. Due to the lower body weight, and the fix dose regimen, slightly higher exposure is expected for the adolescent subpopulation. However, considering the broad safety margins of the 600 mg dose based on preclinical and phase 1 human studies, it is agreed that a slightly higher exposure will presumably not result in safety problems. A weight range of 40-95 kg was assumed for adolescents. In study TACKLE, the median (min-max) body weight was 78.4 (45.0-160.0) kg in the Evusheld group. In the lower weight groups, 600 mg Evusheld were administered without known safety problems. The weight range of subjects that provided data for pop PK modelling was from 40.8 kg.

As discussed in the prophylaxis application, paediatric dosing of adolescent patients aged 12 years or older and weighing at least 40 kg based on exposure matching with adult exposure is endorsed.

Acceptable simulations for adolescents based on the previously developed popPK model have been presented.

Pharmacodynamics

Primary pharmacology

In the FITH study D8850C00001, > 4-fold increases in neutralizing antibody titers against SARS-CoV-2 compared to baseline were obtained at Day 8 and maintained out to Day 271, with 95% of participants maintaining this increase out to Day 361 (2 participants receiving 300 mg IV or IM did not meet this threshold). For the TACKLE trial, preliminary results on neutralizing antibody titers against SARS-CoV-2 were presented up to Day 366 after administration of Evusheld. Results until day 29 are considered to be the most relevant time frame for the treatment indication (long-term effect rather relevant for prophylaxis). On days 6, 15, and 29, median neutralizing titers in AZD7442 treated subjects were clearly above placebo level, however, titers in placebo treated subjects varied widely (difference in endogenous response to infection). For treatment of an active infection, a fast onset of PD effect is considered important. According to data on neutralising antibody titers against SARS-CoV-2 presented starting from day 6 after treatment, this condition cannot be really assessed. Overall, it is accepted that the studies have shown a satisfactory PD response.

Immunogenicity (anti-drug antibodies)

Current results on development of ADA against either AZD8895 or AZD1061 confirm that there is a rather low risk for immunogenicity.

ADA measurements from patient study TACKLE are ongoing; ADA data to Evusheld are available for a subset of 307 AZD7442 subjects up to day 168. The number of subjects ADA positive at baseline was 15/346 (4.3%) and thus, rather low. ADA prevalence (positive at any visit) was N=26 (7.6 %) in the placebo group and thus above the targeted 1% false-positive rate of the confirmatory assays. ADA prevalence and ADA incidence of Evusheld in the Evusheld group were 25.7 % (89/346) and 10.7% (37/346), respectively. The percentage of ADA-evaluable participants increased over time through day 169, while median ADA titers remained to be low and comparable to titers seen with placebo. For the treatment of an acute infection with a single application, the impact of ADAs at later time points is deemed to be of minor relevance for PK and efficacy. For TE-ADA positive subjects, serum AZD8895 and AZD1061 concentrations were within the range of those in participants negative for ADA. The limited information on efficacy and safety in ADA positive subjects does not raise a certain concern. Thus, overall, no clinically relevant impact of ADAs on PK, efficacy and safety in COVID-19 patients with mild-moderate disease is expected based on preliminary data available so far.

Viral resistance

Genotypic and phenotypic testing are ongoing to monitor for SARS-CoV-2 spike variants containing potential AZD8895, AZD1061, and Evusheld (AZD8895 and AZD1061) resistance-associated substitutions in TACKLE. With the data package provided, the majority (834 of 903) of subjects were virally sequenced at baseline, with alpha (n=258) being the predominant form at the time of study conduct. Prevalence of variants of concern and variants of interest was balanced between both treatment groups. No clinical data on variant omicron are available from AZD clinical trial program so far.

Numbers of primary endpoint events were presented by variant of concern/ variant of interest together with relative risk reduction. For delta variant, relative risk reduction (RRR% (95% CI): 70.64 (-107.42, 95.84)) was higher compared to overall population (see section 5.4 on clinical efficacy). In contrast, there was no relevant effect of Evusheld on clinical outcome in subjects infected with alpha variant (RRR% (95% CI): 16.00 (-134.74, 69.94)). However, alpha variant was not associated with reduced susceptibility in non-clinical assays. The clinical data set is too small to draw conclusion on potential loss of efficacy; further data are not expected as alpha is superseded by other strains. Thus, the issue is not

further pursued in the present procedure. The discussion on significance of in vitro susceptibility assays and how their results might translate in clinical effects is currently ongoing and of relevance for recent and upcoming variants. Overall, the study was not designed to detect treatment differences with high statistical power within subgroups infected with certain viral variants.

With DCO 14 January 2022, results on SARS-CoV-2 spike sequences after AZD7442 treatment were available for 380 TACKLE participants. Treatment-emergent substitutions at an allele fraction ≥ 25% were observed in 59/380 participants, with change in susceptibility < 5-fold in all cases. Most of the substitutions were observed as early as day 6 and none of them was observed in more than 5 participants. Although treatment-emergent substitutions were detected in a relevant number of subjects, the modest change in susceptibility seen in vitro and the diversity of detected substitutions does not point towards a strong selection of mutations in the AZD7442 binding site. Thus, data available so far do not raise a strong concern regarding development of Evusheld-resistant escape mutants.

Overall, information on potential viral resistance from clinical trials is limited. The risk of viral resistance will be adequately addressed post approval by "other forms of routine pharmacovigilance activities for lack of efficacy".

PK/PD modelling

A good correlation between plasma concentration and 80% SARS-CoV-2 neutralizing antibody titers was expected (as kind of concept proof) and is seen with data from TACKLE as well as final data from study D8850C00001 (Phase I) with 1-year follow up.

An exposure-response analysis for efficacy has been conducted with 600 mg data from study TACKLE: PK model individual predicted AUCs divided in 4 quartiles were correlated to the incidence of severe COVID-19 or death that occurred by Day 5 and Day 28 (primary endpoint). There was no statistically significant effect of exposure on the outcome of severe symptoms or death within 5 or 28 days post start of treatment. Thus, it might be concluded that the differences seen in exposure within the proposed dose of 600 mg did not have an effect on efficacy. However, it needs to be emphasised that numbers in this analysis were overall low.

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

Dose Justification for Treatment of Mild to Moderate COVID-19

The 600 mg IM dose was the only dose applied in COVID-19 patients with mild-moderate disease within the clinical trial program. A viral dynamics model (VDM) was developed and utilised to confirm the adequacy of the 600 mg dose selected.

The previously developed final VDM structure (submitted as part of the prophylaxis application) was used as the structural model to describe the viral load data collected in the TACKLE study (with and without administration of Evusheld). The VDM has been validated by comparing the predicted mean viral load through the VDM to the observed viral dynamics in a human challenge study (Killingly et al 2022). There was a reasonably good concordance between the shape and magnitude of the predicted and observed viral load in the rising and declining phase of the curve. The dataset of TACKLE study used for the analysis consists of a total of 750 participants with their respective Evusheld concentration derived from population PK analysis and their viral load time-course profiles. However, due to frequent BLQ data, most of the participants had only 1 or 2 detectable viral load data and high variability in data was observed. Therefore, the applicant decided not to use the obtained parameter estimates for simulations (e.g., for

virus variants) but to use parameter estimates obtained for the VDM as previously described in the VDM Report submitted as part of the prophylaxis application.

Viral dynamic simulations were conducted to predict the response to Evusheld treatment in the lower respiratory tract. It is agreed that the lower respiratory tract is the relevant site of action for prevention of severe COVID-19 or death (treatment objective in patients with mild-moderate disease). Data from literature was consulted, assuming a lower respiratory tract penetration of anti-infective mAbs of either 6.5% (Chigutsa et al 2022) or 12% (Magyarics et al 2019). Furthermore, an IC50 of 10 ng/mL for the original SARS-CoV-2 strain and of 209 ng/mL for the Omicron BA.1 subvariant (geometric mean of the first IC50 reported by 4 independent labs) was used. As discussed extensively within the Evusheld prophylaxis application, there is some degree of uncertainty in these estimates (lower respiratory tract penetration rate not based on own data; high variability in in vitro experiments for determination of IC50; appropriateness of IC80 instead of IC90). Thus, all model-based simulations in particular based on viral load data (PD marker) should be interpreted with caution and serve as supportive information only. Worst-case simulation scenarios have been requested to explore the impact of these variabilities on the minimum effective concentration to be reached. As long as the VDM model was not deemed qualified, the IC90 in vivo values was regarded appropriate to be considered. There are outstanding RECs from the prophylaxis setting of relevance for this variation (see updated REC letter in the appendix).

The applicant presented predictions on viral load time-course after treatment with a 600 or 1200 mg IM dose 10 days post infection: Simulations indicate that Evusheld's effect on viral course is regardless of the dose applied. The applicant further states that in the treatment setting, Evusheld is expected to be dosed after peak viral load and the viral production rate will progressively reduce over time due to endogenous immune response and thus, the maximal achievable effect by AZD7442 can be achieved at progressively lower doses with ongoing infection. Thus, theoretical considerations as well as model predictions on viral load do not fully support selection of a higher dose (600mg) compared to the prophylaxis setting (300mg), where administration is performed before peak viral load is achieved. However, as no additional safety signals were detected by the use of the 600 mg IM dose in the pivotal study, the chosen dose may be acceptable, also under consideration of the potentially reduced susceptibility of (future) viral variants.

Nevertheless, the long-lasting high serum concentrations resulting from 600 mg IM dose are not required for the acute treatment of mild-moderate COVID-19 and data on its impact on active SARS-CoV-2 immunisation are outstanding. A potentially resulting delay in COVID-19 vaccination is seen critical, especially in patients at high risk for progression to severe disease. As a data-based decision for the best timing of vaccination following Evusheld treatment is currently not feasible, this will be a matter of national/local recommendations.

Based on simulation provided within the prophylaxis application using the same estimates as presented here, it is acknowledged that the 600 mg IM dose will likely result in efficacious Evusheld level in the high majority of omicron BA.1-infected subjects within the first month after treatment. With his responses, the applicant presented the model predicted time to reach target serum concentration for omicron-subvariants (BA.2, BA.4/BA.5) with varying estimates for IC50 values and lung penetration rate. Based on the presented data for BA.4/BA.5, 50% of the subject are predicted to reach efficacious target level in less than 24h with the 600 mg dose (assuming 6.5% lung partition ratio and IC90 based on IC50=65 ng/mL). This may be acceptable for treatment of an acute infectious disease.

The applicant's plan to conduct continuous reviews post-authorisation of genomic databases such as GISAID for emerging Variants of Interest and Variants of Concern and subsequent phenotypic evaluation by use of in vitro assays is supported.

2.3.6. Conclusions on clinical pharmacology

Pharmacokinetics

The data package on pharmacokinetics is overall deemed sufficient to characterize the PK of AZD8895, AZD1061, and Evusheld (combination of both mAbs) in COVID-19 patients with mild-moderate disease.

PK data and pop PK data analysis indicate linear and approximately dose proportional PK over the dose ranges studied with regard to both monoclonal antibodies AZD8895 and AZD1061, respectively (300 mg to 3000 mg IV, 300 mg and 600 mg IM). Obtained PK parameters are in line with what would have been expected for mAbs with exogenous target and half-life extension.

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

Pharmacodynamics

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

Presented data on immunogenicity (anti-drug antibodies) do not raise concern.

Viral sequencing data from the TACKLE study are too limited to allow conclusion on clinical efficacy in treatment against certain VOC/VOI. No clinical data on latest VOC (including omicron sub-variants) are available. The risk of viral resistance will be addressed post approval by "other forms of routine pharmacovigilance activities for lack of efficacy".

The chosen dose of 600 mg Evusheld IM for the treatment of mild-moderate COVID-19 is not fully supported by theoretical considerations as well as model predictions on viral load. The expected long-lasting high serum concentrations resulting from 600 mg IM dose are not required for the acute treatment of mild-moderate COVID-19. However, as no additional safety signals were detected by the use of the 600 mg IM dose in the pivotal study, the chosen dose may be acceptable, also under consideration of the potentially reduced susceptibility of (future) viral variants.

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

The following measures are considered necessary to address issues related to pharmacology:

- Bioanalytical reports for the determination of AZD8895 and AZD1061 human serum concentrations in TACKLE are currently outstanding and should be provided as soon as available (Q4, 2022) **(REC).**

- The final CSR for the TACKLE study should be provided as soon as available **(REC).**

2.4. Clinical efficacy

2.4.1. Dose response studies

N/A

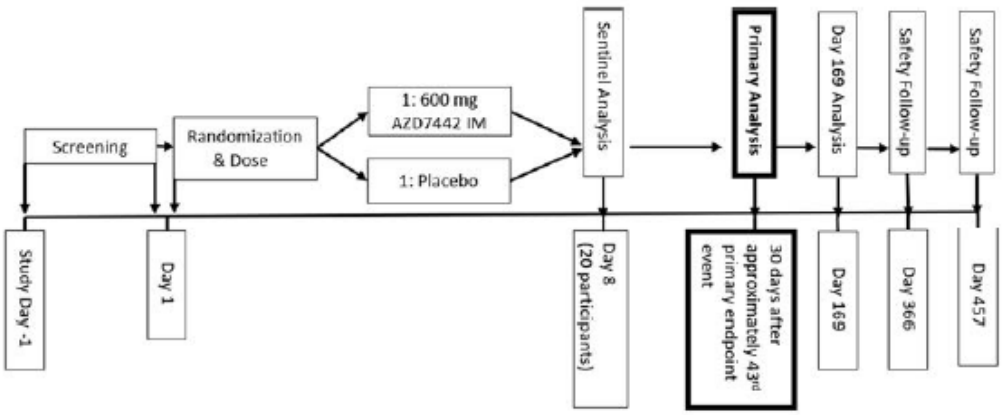
2.4.2. Main study

A Phase III Randomized, Double-blind, Placebo-controlled, Multicenter Study to Determine the Safety and Efficacy of AZD7442 for the Treatment of COVID-19 in Non-hospitalized Adults (TACKLE; D8851C00001)

Methods

TACKLE is an ongoing Phase III, randomized, double-blind, placebo-controlled study assessing the safety and efficacy of a single dose of EVUSHELD (× 2 sequential IM injections) compared to placebo for the treatment of COVID-19 in non-hospitalized adults. Participants were randomized 1:1 to receive a single dose (× 2 IM injections) of EVUSHELD 600 mg IM or placebo on Day 1, and thereafter undergo follow-up for 15 months (until Day 457).

Figure 19. TACKLE, study schematic



An independent DSMB monitors safety throughout, including the safety data through Day 8 from the participants in the sentinel group.

Primary analysis was conducted 30 days after the 43rd event was confirmed.

DSMB, Data Safety Monitoring Board; IM, Intramuscular.

The study is ongoing and is being conducted at 95 sites across 14 countries (Argentina, Brazil, Czech Republic, Germany, Hungary, Italy, Japan, Mexico, Poland, Russian Federation, Spain, UK, Ukraine, and USA).

Study participants

Participants were outpatient adults (≥ 18 years) with a documented positive SARS-CoV-2 molecular test (antigen or nucleic acid) from a sample collected ≤ 3 days prior to study entry and with ≤ 7 days of symptoms of COVID-19 at study entry ('Day 1' symptom count starts from the first day of symptoms), plus the presence of select symptoms within 24 hours prior to Day 1. At least 60% of participants were to meet the protocol definition of being at high risk of progression to severe COVID-19 as defined by any of the following:

- Persons aged 65 years and older at randomization

- Persons aged < 65 years and having at least one of the following conditions:
    - Cancer
    - Chronic lung disease or moderate to severe asthma
    - Obesity (body mass index ≥ 30; may be based on self-report of recent height and weight measurement)
    - Hypertension
    - Cardiovascular disease (including history of stroke)
    - Diabetes
    - Chronic kidney disease
    - Chronic liver disease
    - Immunocompromised state from solid organ transplant, blood or bone marrow transplant, immune deficiencies, human immunodeficiency virus, use of corticosteroids, or use of other immunosuppressive medicines
    - Sickle cell disease
    - Smoking (current or former)

It was planned that the first 20 participants dosed (approximately 10 planned in the AZD7442 group and 10 planned to placebo) formed a sentinel group. After the entire sentinel group was dosed, further enrolment was paused until the sentinel group's safety data through Day 8 was reviewed by the DSMB in order to provide a recommendation to continue or to halt dosing of additional participants.

Participants were enrolled into one of 2 independent cohorts:

- Cohort 1 (n = approximately 300), which included the sentinel group, underwent more intensive testing to characterize their virological and immunological status, and to correlate that status with clinical outcomes.
- Cohort 2 (n = up to approximately 1400) is being followed for clinical outcomes.

Inclusion criteria (D885100001 CSP V7):

1. Participant must be ≥ 18 years of age inclusive at the time of signing the informed consent.
2. Participant who has a documented laboratory-confirmed SARS-CoV-2 infection, as determined by a molecular test (antigen or nucleic acid) from any respiratory tract specimen (eg, oropharyngeal, NP, or nasal swab, or saliva) collected ≤ 3 days prior to Day 1.
3. WHO Clinical Progression Scale score > 1 and < 4.
4. Participant must be dosed with IMP no more than 7 days from self-reported onset of COVID-19-related symptoms (mild to moderate COVID) or measured fever, defined as the self-reported date of first reported sign/symptom from the following list:
    - Subjective fever or feeling feverish
    - Cough
    - Shortness of breath or difficulty breathing at rest or with activity
    - Sore throat
    - Body pain or muscle pain/aches
    - Fatigue
    - Headache
    - Chills
    - Nasal obstruction or congestion
    - Nasal discharge
    - New loss of taste or smell
    - Nausea or vomiting
    - Diarrhea
    - Documented temperature > 37.8°C/100°F

- New onset confusion (only for participants ≥ 60 years old)
- Appetite loss or decreased food intake (only for participants ≥ 60 years old)
- Increased supplemental oxygen requirement (only for participants on baseline supplemental oxygen)

5. One or more of the following signs/symptoms must be present within 24 hours prior to Day 1:
    - Cough
    - Sore throat
    - Shortness of breath or difficulty breathing at rest or with activity
    - Body pain or muscle pain/aches
    - Fatigue
    - Headache
    - Chills
    - Nasal obstruction or congestion
    - Nasal discharge
    - Nausea or vomiting
    - Diarrhea
    - New loss of taste or smell
6. Oxygenation saturation of ≥ 92% obtained at rest by study staff within 24 hours prior to Day 1, unless the potential participant regularly receives chronic supplementary oxygen for an underlying lung condition.
7. Agrees not to participate in another clinical trial for the treatment of COVID-19 or SARS-CoV-2 during the study period until reaching hospitalization or 28 days post-entry, whichever is earliest.
8. Contraceptive use by men or women. (for details see D885100001 CSP V7)
9. Able to understand and comply with study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative) based on the assessment of the investigator.
10. If able, signed informed consent. Ensure that participants who are considered by the investigator clinically unable to consent at screening and who are entered into the study by the consent of a legally acceptable representative show evidence of assent, as applicable in accordance with local regulations.

Exclusion criteria (D885100001 CSP V7)**:**

1. History or current hospitalization for COVID-19

    ("Hospitalization" is defined as ≥ 24 hours of acute care, in a hospital or similar acute care facility, including emergency rooms or temporary facilities instituted to address medical needs of those with severe COVID-19 during the COVID-19 pandemic.)
2. Current need for hospitalization or immediate medical attention in a clinic or emergency room service in the clinical opinion of the site investigator
3. Previous hypersensitivity, infusion-related reaction, or severe adverse reaction following administration of a mAb.
4. 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 administration immediately after enrolment
5. Current requirement for mechanical ventilation or anticipated impending need for mechanical ventilation.
6. Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture.

7. Any other significant disease, disorder, or finding that 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.
8. Known allergy/sensitivity or any hypersensitivity to components of the IMP or placebo.
9. Any co-morbidity requiring surgery within 7 days prior to study entry, or that is considered life-threatening in the opinion of the site investigator within 30 days prior to study entry.
10. Use of any prohibited medication listed in the protocol within 30 days or 5 half-lives, whichever is longer, prior to study entry.
11. Receipt of convalescent COVID-19 plasma treatment at any time prior to study entry.
12. Receipt of systemic steroids (eg, prednisone, dexamethasone) or inhaled steroids within 30 days prior to study entry unless a stable dose used for a chronic condition.
13. Receipt of any IMP in the preceding 90 days or 5 half-lives, whichever is longer, or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.
14. Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.
15. Previous randomization in the present study.
16. For women only, currently pregnant (confirmed with positive pregnancy test) or breast feeding.
17. Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to randomization.
18. Employees of the Sponsor involved in planning executing, supervising, or reviewing the AZD7442 program, clinical study site staff, or any other individuals involved with the conduct of the study, or immediate family members of such individuals.
19. 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 subjects are excluded.

Table 9: Summary of Permitted, Prohibited, or Restricted Medications

Use Category	Type of Medication/treatment	Timeline/instructions
Permitted	Routine vaccines[a]	Licensed influenza vaccines are permitted at any time. All other routine vaccines are permitted beginning > 30 days after IMP dose
	Allergen immunotherapy	Allowed if participant has been receiving stable desensitization therapy for allergies for at least 30 days prior to Day 1 and there is no anticipated change during the treatment period. Allergen immunotherapy should not be administered on the same day as IMP. Non-prescription treatments for allergies such as antihistamines, decongestants, and nasal steroids are permitted.
	Commercial biologics, prednisone, immunosuppressive medications (eg, azathioprine, tacrolimus, cyclosporine, methotrexate, hydroxychloroquine, or cytotoxic chemotherapy)	Allowed, provided the participant is stable on maintenance dose (at steady state) prior to Day 1 and up to Day 29, OR Allowed if participant is hospitalized for treatment of COVID-19
	Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance. Primary care providers, or where appropriate investigators, should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study.	
Prohibited	• Investigational products indicated for the treatment or prevention of SARS-CoV-2 or COVID-19 • Hydroxychloroquine • Chloroquine • Ivermectin • HIV protease inhibitors	• Note: For participants who become hospitalized with COVID-19, receipt of approved/licensed treatment options are permitted and they should be treated according to local standard of care, including investigational agents under emergency use authorization or equivalent regulations. • Use of hydroxychloroquine is acceptable if used chronically for autoimmune disease, and the dose is stable prior to Day 1 and up to Day 29. • Use of chloroquine if used to treat a parasitic infection • Use of ivermectin is acceptable if used to treat a parasitic infection • HIV protease inhibitors are acceptable if used chronically for HIV infection, and the dose is stable prior to Day 1 and up to Day 29.

Use Category	Type of Medication/treatment	Timeline/instructions
	• COVID-19 vaccine[a]	• It is expected that most participants in this trial would have a protective infection-induced immune response. At this time, we have no reason to believe that the protection afforded by natural infection is less frequent or less robust than the protection provided by any vaccine and hence may not be required during acute illness. • If participants request vaccination, the procedures described below apply.
Restricted	Contraceptive methods	See Section 5.1
	Blood/plasma donation	Participants must abstain from donating blood or plasma from the time of informed consent for one year after dose of study drug.
	Ova/Sperm donation	See Sections 8.3.10.1 and 8.3.10.2

[a] The potential impact of AZD7442 on COVID-19 vaccines is not known and has not been studied. See Section 6.5.1 for instructions on COVID vaccinations.

COVID-19 Coronavirus disease 2019; HIV Human immunodeficiency virus; IMP Investigational medicinal product; SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2.

Treatments

Table 10: TACKLE Investigational Medicinal Products

Intervention name	AZD7442 (AZD8895 + AZD1061)	Placebo (not to be matched to AZD7442)
Dose formulation	**Liquid Product** AZD7442 will be supplied as separate vials of AZD8895 and AZD1061 as 150 mg colorless to slightly yellow, clear to opalescent solutions for injection. The solutions contain 100 mg/mL of active ingredient (AZD8895 or AZD1061) in 20 mM L-histidine/L-histidine hydrochloride, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0. The label-claim volume is 1.5 mL.	0.9% (w/v) saline
Unit dose strength(s)	600 mg AZD7442 consisting of 300 mg AZD8895 and 300 mg AZD1061 each at 100 mg/mL	0.9% (w/v) saline solution
Dosage level(s)	600 mg single dose of AZD7442 (combined doses of AZD8895 and AZD1061 each represents half of the total dose)	Single dose
Route of administration	IM injection	IM injection
Use	Experimental	Placebo-comparator
Sourcing	AZD7442 (AZD8895 + AZD1061): AstraZeneca	0.9% (w/v) saline solution supplied by study site
Packaging and labeling	IMP will be provided in glass vials. Each glass vial will be labeled as required per country requirement.	Not applicable

IMP Investigational medicinal product; IM Intramuscular; w/v Weight/volume.

AZD7442 (AZD8895 and AZD1061) or placebo should be administered intramuscularly with one 3.0 mL injection in each gluteal region. The 2 drug products, AZD8895 and AZD1061 (comprising AZD7442), must both be administered separately to the participant in sequential order, with no participant receiving doses of AZD8895 without also receiving the matching dose of AZD1061.

Objectives

Primary:

To estimate the efficacy of EVUSHELD in the prevention of the composite endpoint of either severe COVID-19 or death from any cause through study Day 29.

Key secondary:

To estimate the efficacy of EVUSHELD in the prevention of the composite endpoint of either death or hospitalization for COVID-19 complications or sequelae through Day 169.

Other secondary:

- To determine if EVUSHELD will prevent respiratory failure through study Day 29.
- To determine whether EVUSHELD reduces participants' severity of participant-reported COVID-19 symptoms through Day 29.
- To determine if EVUSHELD reduces the progression of participant-reported COVID-19-associated symptoms through Day 29.
- To determine if EVUSHELD reduces SARS-CoV-2 detection or levels of RNA in nasal swabs through Day 29.
- To evaluate differences in symptom duration between the EVUSHELD and placebo treatment groups through Day 29.

Outcomes/endpoints

Table 11: Efficacy Objectives and Endpoints - TACKLE

Objective	Estimand Description/Endpoint
Primary	
To estimate the efficacy of EVUSHELD in the prevention of the composite endpoint of either severe COVID-19 or death from any cause through study Day 29	**Population:** Modified full analysis set
	Endpoint: A composite of either severe COVID-19 or death from any cause through Day 29. Severe COVID-19 is characterized by a minimum of either pneumonia (fever, cough, tachypnea, or dyspnea, AND lung infiltrates) or hypoxemia (SpO_2 < 90% in room air and/or severe respiratory distress) and a WHO Clinical Progression Scale score of 5 or higher.
	Intercurrent events: The set of intercurrent events for this estimand consists of receipt of COVID-19 treatment product prior to Day 29 without already having met the primary efficacy endpoint. The set of intercurrent events will be handled following the treatment policy strategy.
	Summary measure: Relative risk reduction of severe COVID-19 or death from any cause in participants taking EVUSHELD compared to those taking placebo during the 28-day post-dose period (Day 1 to Day 29).
Key Secondary	
To estimate the efficacy of EVUSHELD in the prevention of the composite endpoint of either death or hospitalization[a] for COVID-19 complications or sequelae through Day 169 **(Data not currently available)**	**Population:** Modified full analysis set
	Endpoint: A composite of either death from any cause or hospitalization[a] for COVID-19 complications or sequelae during the 168-day post-dose period (Day 1 to Day 169).
	Intercurrent events: The set of intercurrent events for this estimand consists of receipt of COVID-19 treatment product or becoming unblinded to properly consider vaccination for COVID-19, prior to Day 169 without already having met the key secondary efficacy endpoint. The set of intercurrent events will be handled following the treatment policy strategy.
Other Secondary	
To determine if EVUSHELD will prevent respiratory failure through study Day 29	The incidence of participants with respiratory failure, defined as requirement for mechanical ventilation, ECMO, non-invasive ventilation, or high flow nasal cannula oxygen delivery (an oxygen supply system capable of delivering up to 100% humidified and heated oxygen at a flow rate of up to 60 liters per minute).
To determine whether EVUSHELD reduces participants' severity of participant-reported COVID-19 symptoms through Day 29	COVID-19 symptom severity assessments based on symptom severity scores over time during the 28-day period from and including the day of the dose of EVUSHELD or placebo. Each symptom is scored from 0 to 4.

Objective	Estimand Description/Endpoint
To determine if EVUSHELD reduces the progression of participant-reported COVID-19-associated symptoms through Day 29	Progression through Day 29 of one or more COVID-19-associated symptoms to a worse status than recorded in the participant-reported symptom diary at study entry, prior to start of EVUSHELD or placebo.
To determine if EVUSHELD reduces SARS-CoV-2 detection or levels of RNA in nasal swabs through Day 29.	Detection (detectable versus undetectable), level, and change from baseline of SARS-CoV-2 RNA from nasal swabs through Day 29.
To evaluate differences in symptom duration between the EVUSHELD and placebo treatment groups through Day 29	Time to return to usual (pre-COVID-19) health through Day 29. Duration of fever through Day 29 defined as the last day in the participant-reported symptom diary on which a temperature greater than 37.8 °C was recorded or a potentially antipyretic drug, such as acetaminophen or ibuprofen, was taken.

[a] Hospitalization was defined as ≥ 24 hours of acute care, in a hospital or similar acute care facility, including Emergency Rooms or temporary facilities instituted to address medical needs of those with severe COVID 19 during the COVID-19 pandemic.

COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SpO_2, oxygen saturation; RNA, ribonucleic acid; WHO, World Health Organization.

Source: Table 1, TACKLE CSR in Module 5.3.5.1

Sample size

Up to approximately 1700 participants, allowing for variability of the placebo group's primary endpoint event rate, were planned to be randomized in a 1:1 ratio to receive a single IM 600 mg dose of AZD7442 (n = up to approximately 850) or placebo (n = up to approximately 850) on Day 1. At least 60% of participants were required to meet the protocol definition of being at high-risk of progression to severe COVID-19.

Published study results (Lilly BLAZE-1 2021 and Regeneron Pharmaceuticals, Inc. REGENCOV Outpatient Trial 2021) from Phase III trials testing monoclonal antibody drug products in non-hospitalized COVID-19 participants have shown efficacy > 70% in a high-risk population. In these studies, attack rates in the placebo arms have been observed to range from 4.6% to 5.8%. As this study is conducted in a population of participants of both high- and low-risk for progression to severe disease or death, an expected efficacy of 65%, and an attack rate in the placebo group of 4.6% were assumed.

This is an event-driven study with a primary analysis initiated 30 days after 43 primary endpoint events had occurred. The study was planned to have 90% power to detect a relative reduction of 65% in the incidence of severe COVID-19/death between the study groups (AZD7442 versus placebo), assuming the incidence of severe COVID-19/death in the placebo group was 4.6%. This was considered plausible based on evolving surveillance information from various sources.

Randomisation

All participants were centrally assigned to randomized IMP using an IRT. Before the study was initiated, user guides, the log in information, and directions for the IRT were provided to each study site. Randomization was stratified (using centralized blocked randomization) by:

1. Time from symptom onset (≤ 5 days versus > 5 days).

2. High risk versus low risk of progression to severe COVID-19.

Blinding (masking)

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

The primary analysis was carried out by an unblinded analysis team, and the procedure to maintain the integrity of the study blinding is detailed in the Study Integrity Plan.

During the study, when participants become eligible for access to a SARS-CoV-2 vaccine, it is appropriate that they can discuss with the investigator and others after Day 30 so as to make an informed choice. Participants may wish to be vaccinated. If so, they may be unblinded as to their randomized investigational treatment in this study. The Investigator was to document and report the action to the Sponsor, without revealing the treatment given to the participant to the Sponsor staff.

In case of an emergency, in which the knowledge of the specific blinded IMP could affect the immediate management of the participant's condition (eg, antidote available), the Investigator has the sole responsibility for determining if unblinding of a participants' IMP assignment is to be warranted. Participant safety has always been the first consideration in making such a determination. If a participant's IMP assignment was unblinded, the Sponsor had to be notified within 24 hours after breaking the blind.

Statistical methods

The primary efficacy endpoint is a composite of either severe COVID-19 or death from any cause through Day 29. Severe COVID-19 is characterized by a minimum of either pneumonia (fever, cough, tachypnea, or dyspnea, AND lung infiltrates) or hypoxemia (SpO2 < 90% in room air and/or severe respiratory distress) and a WHO Clinical Progression Scale score of 5 or higher.

The primary estimand was planned to be based on participants in the modified full analysis set defined in the below table. The set of intercurrent events for this estimand was planned to consist of receipt of an experimental or approved COVID-19 treatment product prior to Day 29 without already having met the primary efficacy endpoint. The set of intercurrent events was planned to be handled following the treatment policy strategy, meaning data collected after an intercurrent event was planned to be analyzed as observed. Absence of data following participants' withdrawal/lost to follow-up prior to having met the primary efficacy endpoint was planned to be treated as missing. Participants were planned to be considered as not having the event through the time of last observation.

Population/Analysis Set	Description
All participants analysis set	All participants screened for the study, to be used for reporting disposition and screening failures.
Full analysis set	All randomized participants who received IMP, irrespective of their protocol adherence and continued participation in the study. Participants will be analyzed according to their randomized treatment, irrespective of whether or not they have prematurely discontinued, according to the intent-to-treat principle. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination.
Modified full analysis set	All participants in the full analysis set who received IMP ≤ 7 days from symptom onset and were not hospitalized at baseline (≤ Day 1) for isolation purposes.
Early intervention analysis set	All participants in the modified full analysis set who received IMP ≤ 5 days from symptom onset.
Seronegative analysis set	All participants in the modified full analysis set who were seronegative at baseline.
Safety analysis set	The safety analysis set consists of all participants who have received IMP. Erroneously-treated participants (eg, those randomized to treatment A, but were actually given treatment B) are accounted for in this analysis set by assigning them to the treatment they actually received. A participant who has received active IMP is classified as active.
PK analysis set	Dosed participants for whom an adequate (measurable drug concentration) PK profile has been obtained. All participants who received AZD7442 and from whom PK blood samples are assumed not to be affected by factors such as protocol violations, and who had at least one quantifiable serum PK observation post-dose, will be included in the PK analysis dataset.
Virology analysis set	The Virology analysis set consists of all participants in Cohort 1, who undergo more intensive virologic and immunologic assessments. Participants will be analyzed according to their received treatment, irrespective of whether or not they have prematurely discontinued, according to the intent-to-treat principle. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination.

IMP Investigational medicinal product; PK Pharmacokinetic.

For the primary efficacy analysis, the stratified CMH method (by the stratification factors) was planned to be used. The RR was planned to be estimated by the CMH method, and the efficacy was planned to be calculated as the RRR = 100 × (1−RR), which represents the percent reduction in incidence of severe COVID-19 or death from any cause in the AZD7442 group relative to the placebo group. The 95% 2-sided CI was planned to be presented. Participants who do not have an event and do not remain in the study until the Day 29 assessment, were planned to be treated as having a missing primary endpoint.

The following alternative estimands for the primary efficacy population were planned to be conducted and included in the hierarchical testing methodology:

1. First supportive estimand

Analysis to be conducted in the early intervention analysis set, with all other components of the primary estimand remaining the same.

2. Second supportive estimand

Analysis to be conducted in the modified full analysis set and only considering events occurring from Day 4 through Day 29, with all other components of the primary estimand remaining the same. Participants with events occurring prior to Day 4 to be considered not experiencing an event.

3. Third supportive estimand

Analysis to be conducted in the full analysis set, with all other components of the primary estimand remaining the same.

4. Fourth supportive estimand

Analysis to be conducted in the seronegative analysis set, with all other components of the primary estimand remaining the same.

A hierarchical approach was planned to be used to control multiplicity for the primary estimand, supportive estimands, and key secondary efficacy endpoint. That is, the null hypotheses for the efficacy endpoints was planned to be tested in a hierarchical order, and the subsequent null hypothesis was planned to be tested only if the prior null hypothesis is rejected. The supportive estimands were planned to be tested only if the primary estimand null hypothesis is rejected and was planned to be tested in the order presented above (primary estimand, first to fourth supportive estimand). The key secondary efficacy endpoint was planned to be only be tested once, when all enrolled participants have been followed through Day 169, and if all higher ordered null hypotheses have been rejected. For any null hypothesis that fails to be rejected, all subsequent p-values were planned to be considered nominal.

The key secondary endpoint is a composite of either death from any cause or hospitalization for COVID-19 complications or sequelae during the 168-day post-dose period (Day 1 to Day 169) and was planned to be analyzed in participants in the modified full analysis set.

For the analysis of the key secondary endpoint, the set of intercurrent events for the estimand was planned to consist of receipt of an experimental or approved COVID-19 treatment product, or becoming unblinded to properly consider vaccination for COVID-19, prior to Day 169 without already having met the key secondary efficacy endpoint. The set of intercurrent events was planned to be handled following the treatment policy strategy, meaning data collected after an intercurrent event were planned to be analyzed as observed. Absence of data following participants' withdrawal/lost to follow-up prior to having met the key secondary efficacy endpoint was planned to be treated as missing.

Participants were planned to be considered as not having the event through the time of last observation.

The key secondary efficacy endpoint was planned to be analyzed as described for the primary efficacy analysis. The analysis was to be conducted once, when all participants complete their Day 169 visit. The point estimate of the RRR of the key secondary endpoint by AZD7442 compared to placebo, as well as the 95% CI, were planned to be calculated and reported following the same methodology as described for the primary efficacy analysis.

To support the primary analysis, Kaplan-Meier curves for time to severe COVID-19 or death from any cause during the first 28 days of follow-up were planned to be generated for each randomized group. A stratified Log-Rank test was planned to be conducted. A Cox-Proportional Hazards model was planned to be conducted to obtain hazard ratios and their respective 95% CIs. The stratification factors were planned to be included as covariates in the Cox model. Absence of data following participants' withdrawal/lost to follow-up was planned to be treated as missing and censored at the date of last known status. Additionally, the absolute risk reduction of AZD7442 with respect to placebo in preventing severe COVID-19 or death from any cause at Day 29, was planned to be presented, along with the 2-sided 95% CI using the stratified Miettinen and Nurminen's score method.

Results

Participant flow

Table 12: Participant Disposition (All Participants Analysis Set)

Category	Number (%) of Participants		
	AZD7442	Placebo	Total
Participants enrolled [a]	NA	NA	1014
Participants randomized	456 (100)	454 (100)	910 (100)
Participants who were not randomized	NA	NA	104
Screen failure	NA	NA	82
Withdrawal by participant	NA	NA	15
Other	NA	NA	7
Participants who received treatment	452 (99.1)	451 (99.3)	903 (99.2)
Participants who did not receive treatment [b]	4 (0.9)	3 (0.7)	7 (0.8)
Physician decision	1 [c] (0.2)	0	1 (0.1)
Withdrawal by participant	3 (0.7)	1 (0.2)	4 (0.4)
Other	0	2 (0.4)	2 (0.2)
Participants who completed study	0	0	0
Total number of participants withdrawn from study at primary DCO	16 (3.5)	19 (4.2)	35 (3.8)
Death [d]	6 (1.3)	5 (1.1)	11 (1.2)
Adverse event	0	2 (0.4)	2 (0.2)
Lost to follow-up	2 (0.4)	2 (0.4)	4 (0.4)
Physician decision	1 (0.2)	0	1 (0.1)
Withdrawal by participant	7 (1.5)	7 (1.5)	14 (1.5)
Other	0	3 (0.7)	3 (0.3)

[a] Informed consent received.
[b] Participants who discontinued after randomization but prior to dosing.
[c] Physician discontinued participant post-randomization but prior to dosing due to progression of disease.
[d] A single participant experienced an AE prior to DCO which led to death after DCO. This is not included as a death in disposition tables but is presented as an AE leading to death in safety summary tables.

'Other' included 'participants was not eligible to begin study', 'participant moved permanently to another city', and 'randomized in error'.
All percentages are based on the number of participants randomized in each treatment group.
AE, adverse event; DCO, data cut-off; NA, not applicable
Source: Table 14.1.1 and Appendix 16.2.1.1

Recruitment

The first participant was randomized on 29 January 2021.

Last participant last visit: ongoing

The analyses are based on the following Data Cut-Off (Database Lock):

Primary analysis DCO (21 August 2021)

The median on-study follow-up time was 84.0 days.

Conduct of the study

Table 13: Protocol Amendments Related to Changes in Study Conduct (TACKLE)

Amendment Number/Date	Key details of amendment	Main reason(s) for amendment
Amendments made *before* the start of participant recruitment		
Version 2.0, 22 December 2020	Guidance was added regarding the procedure to be followed in the event that a participant became eligible for a COVID-19 vaccine.	To add the option for study participants to receive an approved vaccine for protection against SARS-CoV-2.
Amendments made *after* the start of participant recruitment		
Version 3.0, 26 February 2021	• The exclusion of pregnant or breast feeding women has been removed from the CSP. • The study has been extended to 15 months allowing a safety assessment and an optional serum sample for PK, ADA, and nAb to be added at Day 457. Study endpoints have been adjusted accordingly. • Change in statistical approach to alpha spending for the proposed efficacy analyses • Instructions have been added to confirm that participants may receive investigational agents for COVID-19, if required, and per local health authority guidance.	• COVID places pregnant women at increased risk of poor outcomes and poor pregnancy outcomes (CDC, 2021). A fetal TCR study showed no binding of AZD7442 mAbs to any fetal tissues tested. Prior experience with antibody therapy against infectious diseases and with other mAbs suggests low risk in pregnancy. Therefore, the exclusion of pregnant or breastfeeding women has been removed from the CSP. • To provide data on AZD7442 for 5 half-lives the study has been extended to 15 months allowing a safety assessment and an optional serum sample for PK, ADA, and nAb to be added at Day 457. • In response to a health authority request to use a different statistical approach to alpha spending for the proposed efficacy analyses, the boundaries for the interim analysis and primary analysis have been changed.
Version 4.0, 10 March 2021	Pregnant women and breastfeeding mothers are excluded from the trial (Criterion 16).	Since there was insufficient data on the drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes or effects of the drug on the breastfed infant, or on milk production. All women of childbearing potential had to have a negative pregnancy test result at Visit 1 (Criterion 8b). It was decided to establish the risk/benefit profile in adults before including pregnant women in the clinical trial.

Amendment Number/Date	Key details of amendment	Main reason(s) for amendment
Version 5.0, 31 March 2021	The interim analysis was removed and the primary analysis adjusted to be completed 30 days after the 52nd event occurred.	Highly efficacious vaccines against SARS-CoV-2 were being deployed on a mass scale in the participating countries, leading to substantially decreasing attack rates for COVID-19 and reduced potential for study enrollment. Therefore, the interim analysis was removed and the primary analysis adjusted to be completed 30 days after the 52nd event occurred. This period of 30 days allowed sufficient time for the 52nd event to be monitored, and any other events occurring during this time interval to also be evaluated. Enrollment was to stop after the 52nd event occurred. Given recent efficacy results reported in treatment studies using other anti-SARS-CoV-2 mAbs the standard of efficacy needed appears to be higher than those based on assumptions in place at the beginning of the pandemic, therefore, the sample size, the RRR and assumed incidence of severe COVID-19/death have been reassessed.
Version 6.0, 21 April 2021	Further guidance was provided regarding what constitutes these temporary facility or alternate care sites used for managing participants with severe COVID-19.	Amid a rising number of coronavirus disease 2019 (COVID-19) hospitalizations across the world, leading to a shortage of hospital beds, temporary facilities are being utilized increasingly to manage severe COVID-19 patients who would have usually been treated in a traditional hospital setting. As hospitalizations are an integral component of both the primary and key secondary endpoints in the study, further guidance was needed.

Amendment Number/Date	Key details of amendment	Main reason(s) for amendment
Version 7.0, 05 July 2021	• The primary analysis population has been clarified to ensure that the efficacy of AZD7442 for the treatment of COVID-19 was assessed only in non-hospitalized adults. • The statistical power has been reduced from 95% to 90%, as a result, the number of events required for the primary analysis has been reduced. • The primary analysis method has been amended to the CMH approach, consistent with methods used in other studies. • Alternative estimands for the primary efficacy population have been added to assess efficacy in clinically important subpopulations identified in recently published data. These supportive estimands were included in the multiple testing hierarchy.	The study was initially powered at 95%, however, to ensure a timely assessment of efficacy during the pandemic, statistical power has been reduced to 90%. As a result, the number of events required for the primary analysis has been reduced. Published data from non-hospitalized COVID-19 patients showed that most COVID-19-related hospitalizations or deaths occur disproportionately within the first 2 weeks of drug administration. Consequently, the primary analysis method has been amended to the CMH approach, consistent with methods used in other studies. Alternative estimands for the primary efficacy population have been added to assess efficacy in clinically important subpopulations identified in recently published data. These supportive estimands were included in the multiple testing hierarchy. The 3 new analysis sets (subpopulations) are: mFAS, early intervention analysis set and seronegative analysis set.

ADA, anti-drug antibody; CMH, Cochran-Mantel-Haenszel; COVID-19, coronavirus disease 2019; FAS, full analysis set; mAb, monoclonal antibody; mFAS, modified FAS; nAb, neutralizing antibody; PK, pharmacokinetics; RRR, relative risk reduction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TCR, tissue cross-reactivity.

In addition, there were 5 local amendments: Japan and Russia to allow participants hospitalized at baseline for observation per local guidelines to be enrolled; Brazil and Hungary to allow specific medications prohibited in global CSP; and USA to allow enrolment of adolescents; however, it was subsequently retracted, and the USA returned to the global CSP.

Important Protocol Deviations

Table 14: Important Protocol Deviations (FAS) - TACKLE

Important Protocol Deviation Category [a]	Number (%) of Participants		
	AZD7442 (N = 452)	Placebo (N = 451)	Total (N = 903)
Participants with at least 1 important protocol deviation	200 (44.2)	186 (41.2)	386 (42.7)
Eligibility criteria not met (incorrectly randomized)	15 (3.3)	13 (2.9)	28 (3.1)
Deviations from key inclusion criteria	8 (1.8)	13 (2.9)	21 (2.3)
Deviations from key exclusion criteria	7 (1.5)	0	7 (0.8)
Issue worthy of study withdrawal, but participant not withdrawn	0	0	0
IMP deviation	1 (0.2) [b]	0	1 (0.1)
Prohibited medication taken	7 (1.5)	11 (2.4)	18 (2.0)
Deviations Related to Study Procedure	8 (1.8)	7 (1.6)	15 (1.7)
Other Important Deviations	180 (39.8)	173 (38.4)	353 (39.1)

[a] Important protocol deviations before the start of treatment and during treatment.
[b] Due to an Investigator miscounting the number of symptom days, one participant received IMP within 8 days of self-reported symptoms rather than 7 days.

Details regarding important protocol deviation criteria and the process for reviewing them are provided in the Non-Compliance Handling Plan.
The same participant may have had more than one important protocol deviation.
All percentages were based on the total number of participants in each treatment group.
FAS, full analysis set; IMP, investigational medicinal product; N, number of participants in treatment group.
Source: Table 14.1.2

The most frequent category of important protocol deviation was Other Important Deviations 353 (39.1%), and the majority of important protocol deviations within this category were related to eDiary non-compliance. Participant non-compliance to daily symptom self-assessment and symptom diary completion was defined as either an overall compliance of < 70% after Day 29, or missing ≥ 3 entries within a 7-day period.

Baseline data

Table 15: Demographic and Baseline Characteristics – Full Analysis Set, TACKLE

Characteristic	AZD7442 (N = 452)	Placebo (N = 451)	Total (N = 903)
Age (years), n	452	451	903
Mean	46.3	45.9	46.1
Median	46.0	46.0	46.0
SD	15.42	14.99	15.20
Age group (years), n (%)			
≥ 18 - < 65	393 (86.9)	394 (87.4)	787 (87.2)
≥ 65 - < 75	38 (8.4)	46 (10.2)	84 (9.3)
≥ 75 - < 80	12 (2.7)	6 (1.3)	18 (2.0)
≥ 80	9 (2.0)	5 (1.1)	14 (1.6)
< 65	393 (86.9)	394 (87.4)	787 (87.2)
≥ 65	59 (13.1)	57 (12.6)	116 (12.8)
Sex, n (%)			
Male	213 (47.1)	235 (52.1)	448 (49.6)
Female	239 (52.9)	216 (47.9)	455 (50.4)
Race, n (%)			
White	285 (63.1)	274 (60.8)	559 (61.9)
Black or African American	16 (3.5)	20 (4.4)	36 (4.0)
Asian	30 (6.6)	21 (4.7)	51 (5.6)
American Indian or Alaska Native [a]	100 (22.1)	115 (25.5)	215 (23.8)
Not Reported	21 (4.6)	21 (4.7)	42 (4.7)
Ethnic group, n (%)			
Hispanic or Latino	230 (50.9)	238 (52.8)	468 (51.8)
Not Hispanic or Latino	222 (49.1)	213 (47.2)	435 (48.2)

Characteristic	AZD7442 (N = 452)	Placebo (N = 451)	Total (N = 903)
Region, n (%)			
United States	64 (14.2)	40 (8.9)	104 (11.5)
Europe	187 (41.4)	191 (42.4)	378 (41.9)
Latin America	175 (38.7)	206 (45.7)	381 (42.2)
Asia	26 (5.8)	14 (3.1)	40 (4.4)
Body Mass Index (kg/m2), n	450	447	897
Mean	28.86	29.23	29.04
SD	5.464	6.559	6.034
Min	14.2	16.7	14.2
Q1	24.99	24.38	24.68
Median	28.43	28.29	28.37
Q3	32.46	32.87	32.54
Max	49.6	66.1	66.1
Body Mass Index (kg/m2) Category, n(%)			
< 25	113 (25.0)	126 (27.9)	239 (26.5)
25 - < 30	142 (31.4)	130 (28.8)	272 (30.1)
30 - < 35	146 (32.3)	114 (25.3)	260 (28.8)
≥ 35	49 (10.8)	77 (17.1)	126 (14.0)
Missing	2 (0.4)	4 (0.9)	6 (0.7)
Time from Symptom Onset (day), n	452	451	903
Mean	4.9	5.0	5.0
SD	1.61	1.59	1.60
Min	1	1	1
Q1	4.0	4.0	4.0
Median	5.0	5.0	5.0
Q3	6.0	6.0	6.0
Max	8	9	9
Time from Symptom Onset n (%)			
≤ 5 days	268 (59.3)	265 (58.8)	533 (59.0)
> 5 days	184 (40.7)	186 (41.2)	370 (41.0)
Risk Group n (%)			
High	404 (89.4)	405 (89.8)	809 (89.6)
Low	48 (10.6)	46 (10.2)	94 (10.4)
Smoking History n(%)			
Current smoker	100 (22.1)	94 (20.8)	194 (21.5)
Former smoker	80 (17.7)	90 (20.0)	170 (18.8)
Never smoker	272 (60.2)	267 (59.2)	539 (59.7)

[a] This category includes participants recruited in Mexico who identify as Native American.
All percentages are based on the number of participants with data.
For Risk of Progression, 'high' was derived based on the selection of any risk factors on the SCOV2RP eCRF page, and 'low' was derived based on the absence of any selection of risk factors. For any participant for which missing records exist on SCOV2RP eCRF page, and no 'Yes' response is provided for any available record, the Risk of Progression variable was set to the IRT captured response.
To derive the Time from Symptom Onset strata (≤ 5 day/> 5 days), time from symptom onset was calculated as Date of IMP Administration - Date of Earliest Symptom Onset + 1, where Date of Earliest Symptom onset is captured on the SCOV2SS eCRF page.
eCRF, electronic case report form; FAS, full analysis set; IMP, investigational medicinal product; IRT, interactive response technology; Max, maximum; Min, minimum; N, number of participants in treatment group; n, number of participants included in analysis; SCOV2RP, SARS-CoV-2 risk for progression.
Source: Table 14.1.4.1.

Table 16: Participant Disease Characteristics at Baseline - Full Analysis Set, TACKLE

Characteristic	EVUSHELD (N = 452)	Placebo (N = 451)	Total (N = 903)
COVID-19 co-morbidities [a] n (%)			
no co-morbidity	52 (11.5)	52 (11.5)	104 (11.5)
> = 1 co-morbidity	400 (88.5)	399 (88.5)	799 (88.5)
Serum for SARS-CoV-2 Serology n (%)			
Positive	60 (13.3)	67 (14.9)	127 (14.1)
Negative	384 (85.0)	374 (82.9)	758 (83.9)
Missing	8 (1.8)	10 (2.2)	18 (2.0)
WHO Clinical Progression Scale score n (%)			
2	396 (87.6)	398 (88.2)	794 (87.9)
3	56 (12.4)	53 (11.8)	109 (12.1)

[a] Co-morbidity = Risk factors in CRF for both adults and adolescents: SARS-CoV-2 Progression risk to COVID-19, excluding the risk factor "Person aged >=65 year" for adult participants.

All percentages are based on the number of participants with data.

COVID-19, coronavirus disease 2019; CRF, case report form; N, number of participants in treatment group; n, number of participants included in analysis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

Source: Table 14.1.4.2, TACKLE CSR in Module 5.3.5.1

Table 17: High Risk Co-morbidities for Progression to Severe COVID-19 or Death - TACKLE

Co-morbidity	EVUSHELD (N = 452)	Placebo (N = 451)	Total (N = 903)
n (%)	400 (88.5)	399 (88.5)	799 (88.5)
Cancer	18 (4.0)	15 (3.3)	33 (3.7)
Chronic Lung Disease/Asthma	58 (12.8)	50 (11.1)	108 (12.0)
Obesity	195 (43.1)	193 (42.8)	388 (43.0)
Hypertension	135 (29.9)	121 (26.8)	256 (28.3)
Cardiovascular Disease	42 (9.3)	38 (8.4)	80 (8.9)
Diabetes	53 (11.7)	55 (12.2)	108 (12.0)
Chronic Kidney Disease	10 (2.2)	9 (2.0)	19 (2.1)
Immunocompromised State	22 (4.9)	23 (5.1)	45 (5.0)
Chronic Liver Disease	7 (1.5)	13 (2.9)	20 (2.2)
Sickle Cell Disease	0	0	0
Smoking	180 (39.8)	184 (40.8)	364 (40.3)

Co-morbidity = Risk factors in CRF: SARS-CoV-2 Progression risk to COVID-19, excluding the risk factor "Person aged >=65 year".

Obesity: BMI > 30; may be based on self-report of recent height and weight measurement.

BMI, body mass index; COVID-19, coronavirus disease 2019; CRF, case report form; N, number of participants in treatment group; n, number of participants included in analysis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Source: Table 14.1.4.3, TACKLE CSR in Module 5.3.5.1

Numbers analysed

Table 18: Analysis Sets (All Randomized Participants) - TACKLE

Category	Number of Participants	
	EVUSHELD	Placebo
Participants randomized	456	454
Participants included in full analysis set (FAS)	452	451
Participants included in modified full analysis set (mFAS)	413	421
Participants included in early intervention analysis set (EIAS)	255	253
Participants included in seronegative analysis set (SNAS)	353	351

Source: Table 13, TACKLE CSR in Module 5.3.5.1

Outcomes and estimation

Primary Endpoint: Severe COVID-19 or Death from Any Cause Through Day 29

Treatment with AZD7442 compared with placebo led to a 50.49% (95% CI: 14.56 to 71.31) RRR for developing severe COVID-19 or death from any cause in non-hospitalized adults who had been symptomatic for 7 days or less. Rejection of the null hypothesis for the primary objective initiated sequential testing of the supporting estimands. The study achieved statistically significant results in all supportive estimands.

Table 19: Overview of Analysis Hierarchy – Primary Endpoint TACKLE

Statistical Category	Endpoint	Population	AZD7442 e/n (%)	Placebo e/n (%)	RRR (%)	95% CI	p-value [a]
Primary	Severe COVID-19 or death from any cause through Day 29	Non-hospitalized participants dosed ≤ 7 days from symptom onset (mFAS)	18/407 (4.4)	37/415 (8.9)	50.49	14.56, 71.31	0.010
First supportive estimand	Severe COVID-19 or death from any cause through Day 29	Non-hospitalized participants dosed ≤ 5 days from symptom onset (EIAS)	9/253 (3.6)	27/251 (10.8)	66.93	31.11, 84.12	0.002
Second supportive estimand	Severe COVID-19 or death from any cause from Day 4 through Day 29	Non-hospitalized participants dosed ≤ 7 days from symptom onset (mFAS)	12/407 (2.9)	33/415 (8.0)	62.98	29.45, 80.57	0.002
Third supportive estimand	Severe COVID-19 or death from any cause through Day 29	All randomized participants (FAS)	24/446 (5.4)	41/444 (9.2)	41.59	5.01, 64.08	0.028
Fourth supportive estimand	Severe COVID-19 or death from any cause through Day 29	Non-hospitalized participants, who are seronegative at baseline, dosed ≤ 7 days from symptom onset (SNAS)	14/347 (4.0)	36/345 (10.4)	61.26	29.67, 78.66	0.001

[a] Results from a CMH test stratified by time from symptom onset (≤ 5 versus > 5 days), and risk of progression to severe COVID-19 (high versus low).
The relative risk reduction RRR represents the percent reduction in incidence of severe COVID-19 or death from any cause in the AZD7442 group relative to placebo. A RRR > 0 represents favorable efficacy in the AZD7442 group. A p-value < 0.05 indicates a statistically significant result.
Missing response data were not imputed.
The denominator 'n' excludes participants who did not have a Day 29 assessment at the Data Cut-Off resulting from either Loss-to-Follow-up, Study Withdrawal, or missed/delayed visit.
CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, coronavirus disease 2019; e, number of events; EIAS, early intervention analysis set; FAS, full analysis set; mFAS, modified FAS; n, number of participants included in analysis; RRR, relative risk reduction; SNAS, seronegative analysis set.
Source: Table 14.2.1

The results of the primary composite endpoint were driven by the incidence of severe COVID-19. Up to Day 29, 7 deaths had been reported, 3 in the EVUSHELD arm and 4 in the placebo arm. Of the 7 deaths, 2 were not COVID-19 related. Both of these were in the EVUSHELD arm and contributed to the primary composite endpoint.

Non-responder Sensitivity Analysis

Participants who discontinued or were lost to follow-up prior to their Day 29 visit, had the primary endpoint imputed as an event.

Table 20: Sensitivity Analysis of Primary Endpoint - Severe COVID-19 or Death from Any Cause Through Day 29 –Non-Responder Analysis Cochran-Mantel-Haenszel Test (Modified Full Analysis Set) - TACKLE

Stratum		AZD7442 (N=413) n	(%)	Placebo (N=421) n	(%)	RRR(%) and 95% CI	p-value
Overall	Event	24	(5.8)	43	(10.2)	43.05 (8.00, 64.75)	0.019[a]
	Severe COVID-19	16	(3.9)	37	(8.8)		0.191[b]
	Death[c]	2	(0.5)	0			
	Imputed[d]	6	(1.5)	6	(1.4)		
	No Event	389	(94.2)	378	(89.8)		

a. Results from a CMH test stratified by time from symptom onset (<= 5 vs. > 5 days) and risk of progression to severe COVID-19 (high vs. low).
b. Breslow-Day test of homogeneity of RRR across stata.
c. Participants who experience death without documented severe COVID-19.
d. Participants without Day 29 assessment are considered as having an event.
The relative risk reduction RRR represents the percent reduction in incidence of severe COVID-19 or death from any cause in the AZD7442 group relative to placebo. A RRR > 0 represents favorable efficacy in the AZD7442 group.
N Number of participants in treatment groups. n Number of participants included in analysis.

Multiple Imputation Sensitivity Analysis

The primary analysis of the primary efficacy endpoint was repeated using multiple imputation methods to account for missing primary endpoint data.

Table 21: Sensitivity Analysis of Primary Endpoint - Severe COVID-19 or Death from Any Cause Through Day 29 – Cochran-Mantel-Haenszel Test with Multiple Imputation Using Placebo Event Rate (Modified Full Analysis Set) - TACKLE

Parameter	Statistic	AZD7442	Placebo
Number of Participants in the Analysis Set	N	413	421
Participants with Observed Events	n (%)	18 (4.4)	37 (8.8)
Participants without Events	n (%)	395 (95.6)	384 (91.2)
Participants Requiring Imputation[b]	n (%)	6 (1.5)	6 (1.4)
Imputation Results (20 Imputations)			
	RRR	49.37	
	RRR 95% CI	(12.48, 70.71)	
	P-value	0.012[a]	
Participants with Events (including observed and imputed) over 20 imputations	n/N* (%)	375/8260 (4.5)	753/8420 (8.9)

a. Results from a CMH test stratified by time from symptom onset (<= 5 vs. > 5 days) and risk of progression to severe COVID-19 (high vs. low).
b. Participants who had no events and withdrew from the study prior to the time of analysis.
The relative risk reduction RRR represents the percent reduction in incidence of severe COVID-19 or death from any cause in the AZD7442 group relative to placebo. A RRR > 0 represents favorable efficacy in the AZD7442 group.
N Number of participants in treatment groups. n Number of participants included in analysis. N* = Total number of records of 20 imputations.
Missing response data were imputed using multiple imputation method with placebo event rate, for which a random seed 15498 was used. Twenty datasets with imputed data were generated and analyzed. The final RRR and p-value were based on the combined results from the 20 datasets.

Table 22: Sensitivity Analysis of Primary Endpoint - Severe COVID-19 or Death from Any Cause Through Day 29 – Cochran-Mantel-Haenszel Test with Multiple Imputation Using Observed Event Rate (Modified Full Analysis Set)

Parameter	Statistic	AZD7442	Placebo
Number of Participants in the Analysis Set	N	413	421
Participants with Observed Events	n (%)	18 (4.4)	37 (8.8)
Participants without Events	n (%)	395 (95.6)	384 (91.2)
Participants Requiring Imputation[b]	n (%)	6 (1.5)	6 (1.4)
Imputation Results (20 Imputations)			
	RRR	50.36	
	RRR 95% CI	(14.21, 71.28)	
	P-value	0.010[a]	
Participants with Events (including observed and imputed) over 20 imputations	n/N* (%)	367/8260 (4.4)	752/8420 (8.9)

a. Results from a CMH test stratified by time from symptom onset (<= 5 vs. > 5 days) and risk of progression to severe COVID-19 (high vs. low).
b. Participants who had no events and withdrew from the study prior to the time of analysis.
The relative risk reduction RRR represents the percent reduction in incidence of severe COVID-19 or death from any cause in the AZD7442 group relative to placebo. A RRR > 0 represents favourable efficacy in the AZD7442 group.
N Number of participants in treatment groups. n Number of participants included in analysis. N* = Total number of records of 20 imputations.
Missing response data were imputed using multiple imputation method with observed event rate, for which a random seed 25478 was used. Twenty datasets with imputed data were generated and analysed. The final RRR and p-value were based on the combined results from the 20 datasets.

Additional Sensitivity Analysis

The primary efficacy analysis repeated with the covariates for region and continuous time from symptom onset, separately, were consistent with the primary analysis. When further stratified by region, a RRR 46.50% (95% CI: 6.27, 69.46); p-value 0.025 was observed. Using a logistic regression including continuous time from symptom onset, an Odds Ratio of 0.47 (95% CI: 0.26, 0.85); p-value 0.0116 was observed.

The repeated analysis at the **Key Secondary DCO (14 January 2022)** was in line with the Primary DCO analysis, showing treatment with AZD7442 compared to placebo led to a 50.38% (95% CI: 14.38, 71.25) reduction in the risk of developing severe COVID-19 or death from any cause in non-hospitalized adults who had been symptomatic for 7 days or less. The small numerical changes seen were due to updates to the database after the Primary DCO eg, participants completing their Day 29 visit after the Primary DCO.

At the Primary DCO and Key Secondary DCO, supplemental analysis by Cox regression of time to first event of severe COVID-19 or death from any cause through Day 29 were similar, Hazard Ratio 0.49 (95% CI: 0.28, 0.86); p-value 0.0123 and 0.49 (95% CI: 0.28, 0.85); p-value 0.0122.

Table 23: Supplementary Analysis of the Primary Endpoint – Time to Severe COVID-19 or Death from Any Cause through Day 29 – Kaplan-Meier Analysis (mFAS), Primary and Key Secondary DCO

Category	Primary DCO		Key Secondary DCO	
	AZD7442 (N = 413)	Placebo (N = 421)	AZD7442 (N = 413)	Placebo (N = 421)
Number of participants with event, n (%)	18 (4.4)	37 (8.8)	18 (4.4)	37 (8.8)
Number of participants censored, n (%)	395 (95.6)	384 (91.2)	395 (95.6)	384 (91.2)
Reason for censoring				
No Event	389 (94.2)	378 (89.8)	**392 (94.9)**	**382 (90.7)**
No Day 29 assessment	6 (1.5)	6 (1.4)	**3 (0.7)**	**2 (0.5)**
Kaplan-Meier failure time (days) estimates				
25th percentile (95% CI)	NE	NE	NE	NE
Median (95% CI)	NE	NE	NE	NE
75th percentile (95% CI)	NE	NE	NE	NE
Min, max	1, 29	1, 29	1, 29	1, 29
Kaplan-Meier failure probability at Day 29 (95% CI)	4.4 (2.8, 6.8)	8.8 (6.5, 11.9)	4.4 (2.8, 6.8)	8.8 (6.5, 11.9)
Stratified log-rank p-value	0.0103		**0.0104**	

Text in bold indicates change from the Primary DCO to Key Secondary DCO.
Percentages are based on the number of participants in the analysis set by study group.
P-value is based on log-rank test stratified by time from symptom onset (≤ 5 versus > 5 days) and risk of progression to severe COVID-19 (high versus low).
Follow-up time is calculated as T = Date of event – Date of dosing + 1. Participants who do not have an event on or before Day 29, they are censored at Day 29. Participants who have no Day 29 assessment are censored at the date of last known status before Day 29, ie, T = Date of last known status before Day 29 – Date of dosing + 1.
CI, confidence interval; COVID-19, coronavirus disease 2019; DCO, data cut-off; Max, maximum; Min, minimum; mFAS, modified full analysis set; NE, not evaluable; N, number of participants in treatment group; n, number of participants included in analysis.
Source: Table 14.2.3.1.1 and Table 14.2.3.1.1A

Table 24: Third supportive analysis of the primary endpoint: Severe COVID-19 or death from any cause through say 29 – Cochran-Mantel-Haenszel Test (FAS) – Key Secondary DCO

Stratum		AZD7442 (N=452) n	(%)	Placebo (N=451) n	(%)	RRR(%) and 95% CI	p-value
Overall	Event	24	(5.3)	41	(9.2)	41.47 (4.82, 64.00)	0.028[a]
	Severe COVID-19	22	(4.9)	41	(9.2)		0.058[b]
	Death[c]	2	(0.4)	0			
	No Event	425	(94.7)	407	(90.8)		
	Total	449		448			
	Missing	3		3			

a. Results from a CMH test stratified by time from symptom onset (<= 5 vs. > 5 days) and risk of progression to severe COVID-19 (high vs. low).
b. Breslow-Day test of homogeneity of RRR across strata.
c. Participants who experience death without documented severe COVID-19.

The relative risk reduction RRR represents the percent reduction in incidence of severe COVID-19 or death from any cause in the AZD7442 group relative to placebo. A RRR > 0 represents favorable efficacy in the AZD7442 group. A p-value <0.05 indicates a statistically significant result. Participants who discontinued or were lost to follow up prior to Day 29 are considered missing.
N Number of participants in treatment group. n Number of participants included in analysis.
The percentages were based on total participants with non-missing response data. Missing response data were not imputed.

Key secondary endpoint

Table 25: Analysis of Key Secondary Endpoint - Death from Any Cause or Hospitalization for COVID-19 Complications or Sequelae through Day 169 – CMH Test (mFAS), Key Secondary DCO

Stratum	AZD7442 (N = 413)	Placebo (N = 421)	RRR (%) (95% CI)	P-value
Overall, n (%)				
Event	20 (5.0)	40 (9.8)	49.11 (14.47, 69.72)	0.009 [a]
Hospitalization for COVID-19 complications or sequelae	17 (4.3)	40 (9.8)	-	-
Death [b]	3 (0.8)	0	-	-
No event	379 (95.0)	367 (90.2)	-	-
Total	399	407	-	-
Missing	14	14	-	-

[a] Results from a CMH test stratified by time from symptom onset (≤ 5 versus > 5 days) and risk of progression to severe COVID-19 (high versus low).

[b] Participants who experienced death without documented hospitalization for COVID-19 complication or sequelae.

The RRR represents the percent reduction in incidence of death from any cause or hospitalization for COVID-19 complications or sequelae in the AZD7442 group relative to placebo. A RRR > 0 represents favorable efficacy in the AZD7442 group. A p-value < 0.05 indicates a statistically significant result. Participants who discontinued or were lost to follow up prior to Day 169 are considered missing.
The percentages were based on total participants with non-missing response data. Missing response data were not imputed.
CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, coronavirus disease 2019; DCO, data cut-off; mFAS, modified full analysis set; N, number of participants in group; n, number of participants included in analysis; RRR, relative risk reduction.
Source: Table 14.2.5.1A

Sensitivity analyses of the key secondary endpoint revealed similar results to the primary endpoint:

- Analysis using CMH test with multiple imputation using placebo event rate: RRR 46.90 (95% CI: 10.57, 68.47), p = 0.014
- Analysis using CMH test with multiple imputation using observed event rate: RRR 49.47 (95% CI: 14.77, 70.04), p = 0.008
- Analysis using CMH test adding region as a stratification factor: RRR 45.91 (95% CI: 7.71, 68.30), p = 0.021
- Analysis using logistic regression with continuous time from symptom onset: Odds ratio 0.48 (95% CI: 0.28, 0.84), p = 0.0106
- Analysis using CMH test considering unblinding for vaccination (ie, participants without a reported prior key secondary endpoint who were unblinded to consider vaccination prior to Day 169 were imputed as missing in the analysis): RRR 50.70 (95% CI: 17.51, 70.54), p = 0.006
- Analysis using CMH test in the FAS: RRR 40.31 (95% CI: 5.50, 62.30), p = 0.025

Other secondary endpoints

Incidence of Participants with Respiratory Failure

Table 26: Respiratory Failure Through Day 29 - Cochran-Mantel-Haenszel Test (mFAS) - TACKLE

Category	AZD7442 (N = 413)		Placebo (N = 421)		RRR(%) and 95% CI	p-value
	n	(%)	n	(%)		
Respiratory failure	3	(0.7)	11	(2.7)	71.86 (0.25, 92.06)	0.036 [a]
No respiratory failure	402	(99.3)	401	(97.3)		
Total	405	-	412	-		
Missing	8	-	9	-		

a. Results from a CMH test stratified by time from symptom onset (≤ 5 versus > 5 days) and risk of progression to severe COVID-19 (high versus low). P-value is nominal.
The relative risk reduction RRR represents the percent reduction in incidence of respiratory failure of the AZD7442 group relative to placebo. A RRR > 0 represents favourable efficacy in the AZD7442 group.
The percentages were based on total participants with non-missing response data. Missing response data were not imputed.
CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, coronavirus disease 2019; mFAS, modified full analysis set; N, number of participants in treatment group; n, number of participants included in analysis; RRR, relative risk reduction.
Derived from Table 14.2.8.1

COVID-19 Symptom Severity Assessments Based on Symptom Severity Scores over Time up to Day 29

Treatment with EVUSHELD, compared to placebo, reduced the severity of cough (LS mean difference -0.05 [95% CI -0.10, -0.01]) and muscle ache symptoms (LS mean difference -0.05 [95% CI -0.09, -0.01]). There was no difference between EVUSHELD and placebo treatment groups for other assessed symptoms. Symptom severity data were derived from self-reported E-diary data. As this was not collected for those participants who went on to be hospitalized, missing data may have affected these analyses; as such, these data should be interpreted accordingly.

Table 27: COVID-19 Symptom Severity Overall Change from Baseline Through Day 29 – Mixed Model for Repeated Measures (Modified Full Analysis Set) -TACKLE

Symptom	LS Mean Difference (95% CI)[a, b]	p-value
Shortness of breath	0.03 (-0.01, 0.06)	0.106
Difficulty breathing	0.02 (-0.01, 0.05)	0.258
Chills	-0.01 (-0.03, 0.01)	0.483
Cough	-0.05 (-0.10, -0.01)	0.024
Fatigue	-0.03 (-0.08, 0.02)	0.253
Muscle aches	-0.05 (-0.09, -0.01)	0.018
Body aches	-0.02 (-0.06, 0.02)	0.342
Headache	0.02 (-0.02, 0.05)	0.378
New loss of taste	0.04 (-0.01, 0.08)	0.127
New loss of smell	0.04 (-0.01, 0.09)	0.141
Sore throat	0.02 (-0.01, 0.05)	0.208
Congestion	0.02 (-0.01, 0.05)	0.238
Runny nose	0.01 (-0.02, 0.04)	0.510
Nausea	-0.01 (-0.04, 0.01)	0.289
Vomiting	-0.00 (-0.01, 0.01)	0.523
Diarrhea	0.00 (-0.02, 0.02)	0.881

[a] Results from a Mixed Model for Repeated Measures, including terms for baseline value, time from symptom onset (≤ 5 vs > 5 days), risk of progression to severe COVID-19 (high vs low), treatment, visit, and treatment by visit interaction. An autoregressive covariance structure of order 1 was used. P-values are nominal.

[b] Average LS mean difference in symptom severity through 29 days

Missing response data were not imputed.

CI, confidence interval; LS, least squares.

Source: Table 14.2.10.1, Table 14.2.10.2, Table 14.2.10.3, Table 14.2.10.4, Table 14.2.10.5, Table 14.2.10.6, Table 14.2.10.7, Table 14.2.10.8, Table 14.2.10.9, Table 14.2.10.10, Table 14.2.10.11, Table 14.2.10.12, Table 14.2.10.13, Table 14.2.10.14, Table 14.2.10.15, and Table 14.2.10.16, TACKLE CSR in Module 5.3.5.1

Progression Through Day 29 of One or More COVID-19-Associated Symptoms

The number of participants with COVID-19 symptom progression through study Day 29 was 167 (54.9%) for AZD7442 versus 199 (62.2%) for placebo, regardless of baseline serology status: overall RRR 12.16% (95% CI: -0.20, 22.99); nominal p-value 0.053; serostatus positive at baseline RRR 16.88% (95% CI: -40.48, 50.82); nominal p-value 0.494; serostatus negative at baseline RRR 12.34% (95% CI: -0.38, 23.46); nominal p-value 0.056.

Table 28: Progression of One or More COVID-19-associated Symptoms to Worse Status Through Day 29 - Cochran-Mantel-Haenszel Test (Modified Full Analysis Set), Primary Analysis DCO - TACKLE

Summary Statistics	EVUSHELD (N = 413) n (%)	Placebo (N = 421) n (%)	RRR (95% CI)	p-value
Overall				
Participants with at Least One Baseline Symptom Grade < 4 N*	305	322	-	-
COVID-19 Symptom Progression	167 (54.9)	199 (62.2)	12.16 (-0.20, 22.99)	0.053[a]
No Progression	137 (45.1)	121 (37.8)	-	0.325[b]
Total	304	320	-	-
Missing	1	2	-	-
Baseline Serostatus Positive				
Participants with at Least One Baseline Symptom Grade < 4 N*	42	49	-	-
COVID-19 Symptom Progression	14 (33.3)	20 (40.8)	16.88 (-40.48, 50.82)	0.494[a]
No Progression	28 (66.7)	29 (59.2)	-	0.887[b]
Total	42	49	-	-
Missing	0	0	-	-
Baseline Serostatus Negative				
Participants with at Least One Baseline Symptom Grade < 4 N*	257	268	-	-
COVID-19 Symptom Progression	148 (57.8)	175 (65.8)	12.34 (-0.38, 23.46)	0.056[a]
No Progression	108 (42.2)	91 (34.2)	-	0.395[b]
Total	256	266	-	-
Missing	1	2	-	-

[a] Results from a CMH test stratified by time from symptom onset (≤ 5 vs > 5 days) and risk of progression to severe COVID-19 (high vs low). P-values are nominal.

[b] Breslow-Day test of homogeneity of RRR across strata.

Progression of One or More COVID-19-associated Symptoms to Worse Status: Increasing in severity scale by ≥ 1 than recorded in the participant-reported symptom diary entry prior to start of EVUSHELD or placebo

The relative risk reduction RRR represents the percent reduction in incidence of COVID-19 symptom progression in the EVUSHELD group relative to placebo. A RRR > 0 represents favorable efficacy in the EVUSHELD group.

The percentages were based on total participants with non-missing response data. Missing response data were not imputed.

Participants with severity score of 4 on every scale at baseline were excluded.

Not all participants had serostatus available.

'Total' is the denominator used for the percent calculations.

Differences in Symptom Duration Between Groups

A separation of the return to usual health Kaplan-Meier curves favoring AZD7442 is apparent on visual inspection, however, there was no statistical difference (p-value 0.1499) in time to return to usual health by Day 29 in the AZD7442 group compared to the placebo group. The lack of statistical difference may reflect anchoring to Day 15 and Day 29 visits, which results in overlap of the curve at Day 29.

Table 29: Time (Days) to Return to Usual Health through Day 29 - Kaplan-Meier Analysis (Modified Full Analysis Set)- TACKLE

Category	EVUSHELD (N = 413)	Placebo (N = 421)
Number of Participants with event, n (%)	271 (65.6)	267 (63.4)
Number of Participants censored, n (%)	142 (34.4)	154 (36.6)
Reason for censoring		
No Event	135 (32.7)	144 (34.2)
No Day 29 assessment	7 (1.7)	10 (2.4)
Kaplan-Meier Return to Health Time (days) Estimates		
25th Percentile (95% CI)	14 (11, 15)	16 (14, 20)
Median (95% CI)	29 (27, 29)	29 (NE, NE)
75th Percentile (95% CI)	NE	NE
Min, Max	2, 29	2, 29
Kaplan-Meier Return to Health Probability at Day 29 (95% CI)	66.9 (62.3, 71.5)	65.4 (60.7, 70.0)
Stratified Log-Rank P-value	0.1499	

Percentages are based on the number of participants in the analysis set by study arm.

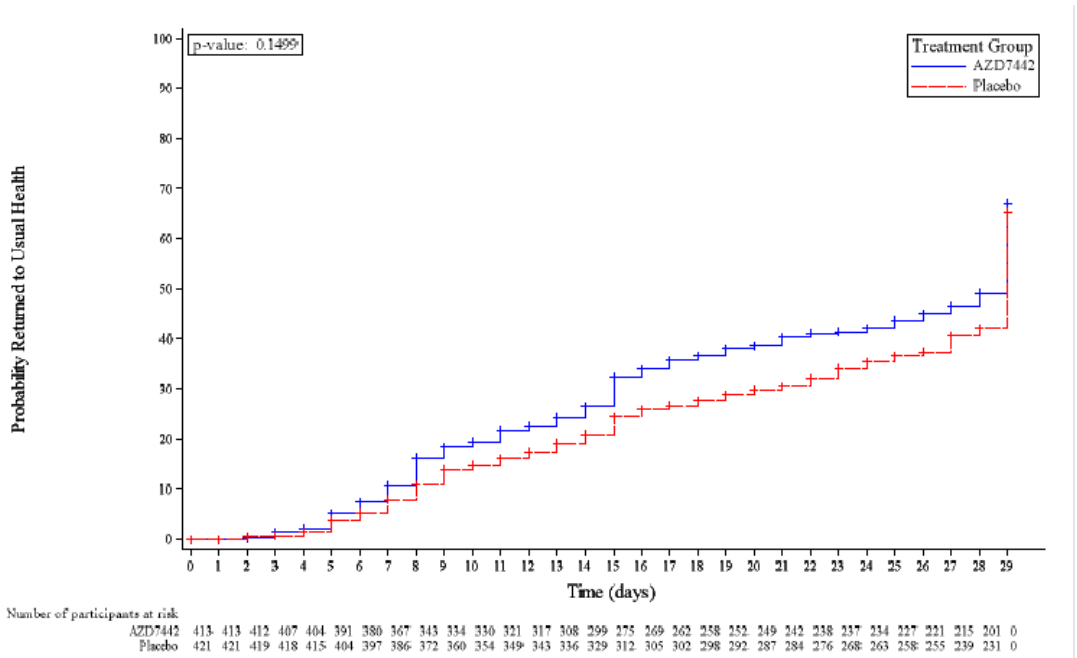
P-value is based on log-rank test stratified by time from symptom onset (≤ 5 vs > 5 days) and risk of progression to severe COVID-19 (high vs low).

Follow-up time is calculated as T = Date of event – Date of dosing + 1. Participants who do not have an event on or before Day 29 are censored at Day 29. Participants who have no Day 29 assessment are censored at the date of last known status before Day 29, ie, T = Date of last known status before Day 29 – Date of dosing + 1.

CI, confidence interval; COVID-19, coronavirus disease 2019; Max, maximum; Min, minimum; N, number of participants in treatment groups; n, number of participants included in analysis; NE, not evaluable.

Source: Table 14.2.12.1, TACKLE CSR in Module 5.3.5.1

Figure 20: Time to Return to Usual (Pre-COVID-19) Health through Day 29 - Kaplan-Meier Curve and Stratified Log-Rank Test (mFAS) - TACKLE



P-value is based on log-rank test stratified by time from symptom onset (≤ 5 versus > 5 days) and risk of progression to severe COVID-19 (high versus low).
COVID-19, coronavirus disease 2019; mFAS, modified full analysis set.
Source: Figure 14.2.2.4

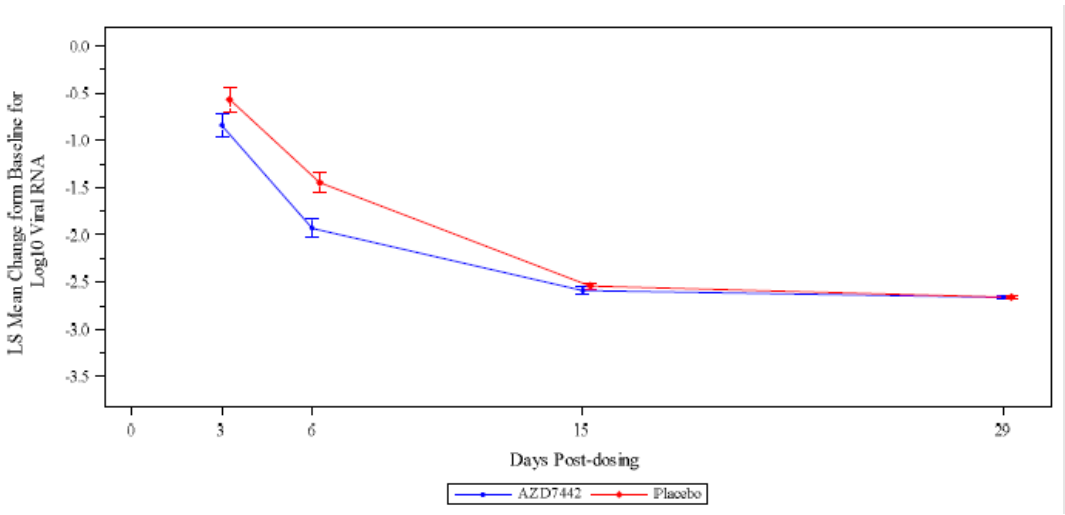
Detection, Level, and Change from Baseline of SARS-CoV-2 RNA from Nasal Swabs Through Day 29

The change from baseline of SARS-CoV-2 RNA, and RNA levels from nasal swabs at each treatment visit through Day 29 are presented for 2 cohorts with differing sampling schedules. In Cohort 1 (Virology Analysis Set), samples were taken at baseline and Day 3, 6, 15, and 29. In Cohort 2, samples were taken at baseline, Day 6, and Day 29.

In Cohort 1, treatment with AZD7442 compared with placebo resulted in numerically greater reductions in log10 SARS-CoV-2 RNA mean change from baseline at Day 3 (LS mean difference -0.28 [95% CI: -0.64, 0.09]) and Day 6 (LS mean difference -0.48 [95% CI: -0.76, -0.20]). No difference was observed at day 15 (LS Mean Difference -0.05 [95% CI -0.28, -0.18]) and day 29 (LS Mean Difference -0.03 [95% CI -0.20, -0.25]).

Overall (Cohorts 1 and 2, analyzed at Day 6 and Day 29 only), treatment with AZD7442 compared with placebo resulted in greater reductions in log10 SARS-CoV-2 RNA mean change from baseline at Day 6 (LS mean difference -0.39 [95% CI: -0.56 to -0.22]). No difference was observed at day 29 (LS Mean Difference 0.02 [95% CI -0.02, -0.07]).

Figure 21: LS Mean Change from Baseline for Log10 Viral RNA from Nasal Swab Over Time in Cohort 1 (Virology Analysis Set)



Exploratory endpoints

SARS-CoV-2 positivity through Day 29 among household contacts for participants that had at least one contact was lower for participants in the AZD7442 group (34 [8.2%]) compared to placebo group (43 [10.2%]).

There were 416/452 (92.0%) participants with a post-treatment response for **SARS-CoV-2 nucleocapsid antibodies** in the AZD7442 group compared to 404/451 (89.6%) participants in the placebo group.

Changes in the Hospital Course Once a Participant Required Hospitalization: The number of participants hospitalized for the disease under study (including COVID-19 complications) through Day 29 was numerically fewer in the AZD7442 group (17 [4.1%]) compared with the placebo group (40 [9.5%]). The lower number of hospitalizations in participants treated with AZD7442 was accounted for by fewer hospitalizations in the categories: In-patient hospital setting, ER admission > 24 hours, and Acute hospital care at home. Of these hospitalized participants, fewer were admitted to the ICU in the AZD7442 group (3 [0.7%]) compared to placebo (11 [2.6%]).

Among participants hospitalized for COVID-19 complications or sequelae the mean (SD) duration of hospital admission was 14.9 (10.83) days for the AZD7442 group and 11.6 (6.33) days for the placebo group. For participants admitted to ICU for COVID-19 complications the mean admission time was 8.3 (0.58) days for AZD7442 group and 8.8 (3.43) days for AZD7442.

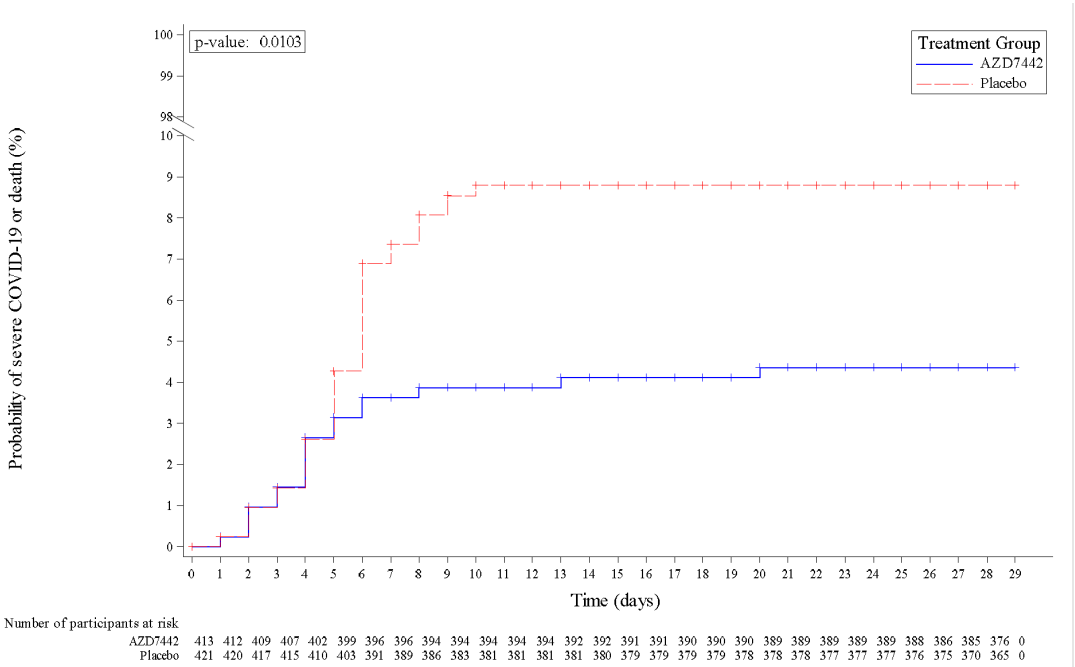
The worst clinical status (assessed using ordinal scale among participants who become hospitalized) among participants who were hospitalized for disease under study was similar between the AZD7442 group and placebo group.

Ancillary analyses

Supplemental Analyses to Primary Endpoint

Supplemental analyses of time to first event of severe COVID-19 or death from any cause through Day 29 were conducted.

Figure 22: Supplementary Analysis of the Primary Endpoint: Time to Severe COVID-19 or Death from Any Cause Through Day 29 - Kaplan-Meier Curve and Stratified Log-Rank Test (Modified Full Analysis Set) - TACKLE



P-value is based on log-rank test stratified by time from symptom onset (≤ 5 vs > 5 days) and risk of progression to severe COVID-19 (high vs low).

AZD7442, EVUSHELD; COVID-19, coronavirus disease 2019.

Source: Figure 14.2.2.1, TACKLE CSR in Module 5.3.5.1

Additional pre-specified analyses were conducted to further examine the effect of treating early after symptom onset on the reduction of risk of severe COVID-19 or death from any cause.

Table 30: Severe COVID-19 or Death through Day 29 by Time from Symptom Onset (Modified Full Analysis Set)

Time From Symptom Onset	Analysis Type	EVUSHELD e/n (%)	Placebo e/n (%)	RRR (%)	95% CI	p-value
≤ 7 Days	Primary analysis (Pre-specified [hierarchically tested])	18/407 (4.4)	37/415 (8.9)	50.49	14.56, 71.31	0.010[a]
≤ 5 Days	First supportive estimand (Pre-specified [hierarchically tested])	9/253 (3.6)	27/251 (10.8)	66.93	31.11, 84.12	0.002[b]
≤ 3 Days	Pre-specified (subgroup)	1/90 (1.1)	8/84 (9.5)	88.01	9.40, 98.41	0.013[b,c]

[a] Results from a CMH test stratified by time from symptom onset (≤ 5 vs > 5 days), and risk of progression to severe COVID-19 (high vs low).

[b] Results from a CMH test stratified by risk of progression to severe COVID-19 (high vs low).

[c] P-value is nominal.

The relative risk reduction RRR represents the percent reduction in incidence of severe COVID-19 or death from any cause in the EVUSHELD group relative to placebo. A RRR > 0 represents favorable efficacy in the EVUSHELD group. A p-value < 0.05 indicates a statistically significant result.

Missing response data were not imputed.

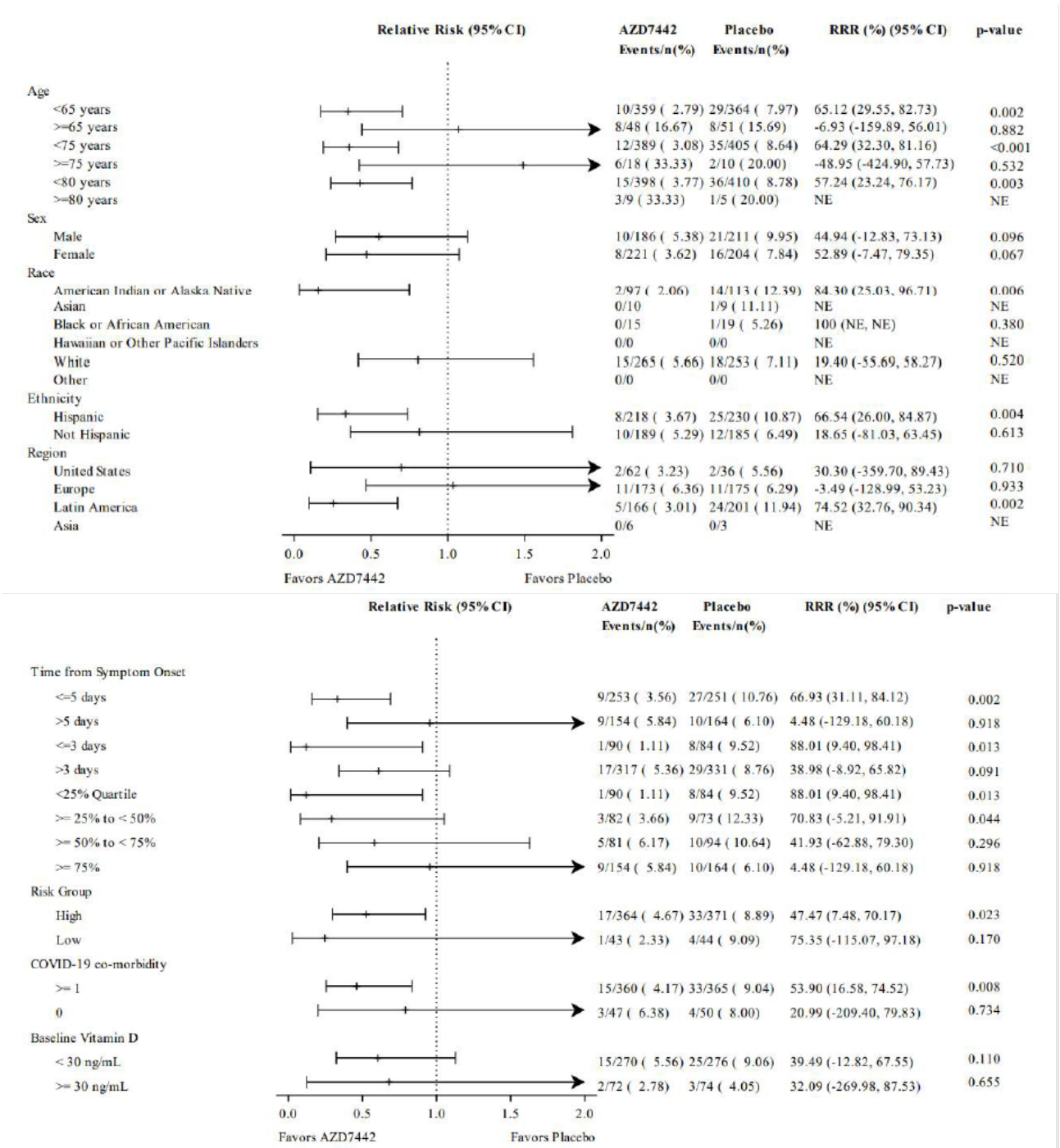
CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, coronavirus disease 2019; e, number of events; n, number of participants included in analysis; NE, not evaluable; RRR, relative risk reduction.

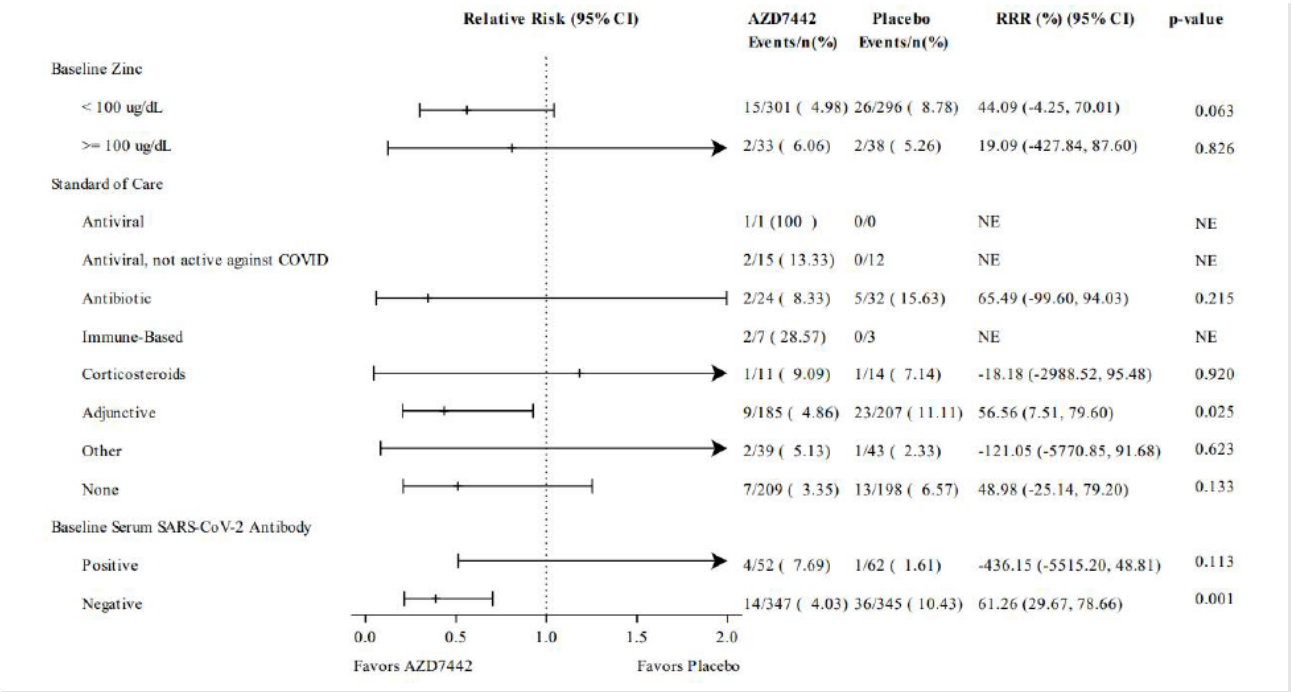
Source: Table 14.2.1 and Table 14.2.4, TACKLE CSR in Module 5.3.5.1

Subgroup Analysis of the Primary Endpoint

Subgroup analyses of demographics and other baseline medical characteristics were conducted for pre-specified subgroups. The study was not designed to detect treatment differences with high statistical power within subgroups. Nominal p-values are reported.

Figure 23: Forest Plot for the Subgroup Analysis of the Primary Endpoint - Severe COVID-19 or Death from Any Cause through Day 29 – Cochran-Mantel-Haenszel Test (mFAS) - TACKLE





Results were from a CMH test with stratification factors used in the primary analysis. For the subgroup of time from symptom onset or risk group, time from symptom onset or risk of progression was not a stratification factor. For the subgroups of age, risk of progression was not a stratification factor. If there was no stratification factor, a chi-square test was used.

CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, coronavirus disease 2019; mFAS, modified full analysis set; n, number of participants included in analysis; NE, not evaluable; RRR, relative risk reduction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Source: Figure 14.2.1.1

Summary of main study

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

Table 31 Summary of Efficacy for trial TACKLE

Title: A Phase III Randomized, Double-blind, Placebo-controlled, Multicenter Study to Determine the Safety, and Efficacy of AZD7442 for the Treatment of COVID-19 in Nonhospitalized Adults		
Study identifier	D8851C00001; TACKLE	
Design	Randomized, double-blind, placebo-controlled, multicenter	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	457 days not applicable not applicable
Hypothesis	Superiority	
Treatments groups	EVUSHELD	EVUSHELD, single dose, 600 mg intramuscular (IM), 456 participants randomized
	Placebo	Placebo, single dose, IM, up to approximately 454 participants randomized

Endpoints and definitions	Primary endpoint	Severe COVID-19 or death	Severe Coronavirus Disease 2019 (COVID-19) or death from any cause through Day 29 in non-hospitalized participants dosed ≤ 7 days from symptom onset
	First supportive estimand of the primary endpoint	Severe COVID-19 or death	Severe COVID-19 or death from any cause through Day 29 in non-hospitalized participants dosed ≤ 5 days from symptom onset
	Second supportive estimand of the primary endpoint	Severe COVID-19 or death	Severe COVID-19 or death from any cause from Day 4 through Day 29 in non-hospitalized participants dosed ≤ 7 days from symptom onset
	Third supportive estimand of the primary endpoint	Severe COVID-19 or death	Severe COVID-19 or death from any cause through Day 29 in all randomized participants
	Fourth supportive estimand of the primary endpoint	Severe COVID-19 or death	Severe COVID-19 or death from any cause through Day 29 in non-hospitalized participants, who are seronegative at baseline, dosed ≤ 7 days from symptom onset
	Secondary endpoint	Respiratory failure	The incidence of participants with respiratory failure, defined as requirement for mechanical ventilation, extracorporeal membrane oxygenation (ECMO), non-invasive ventilation, or high flow nasal cannula oxygen delivery
Database lock	21 August 2021 (primary analysis data cut-off [DCO]) The primary analysis was initiated 30 days after the 43rd primary endpoint event was confirmed.		
Results and Analysis			
Analysis description	**Primary endpoint: Severe COVID-19 or death from any cause through Day 29 in non-hospitalized participants dosed ⩽ 7 days from symptom onset**		
Analysis population and time point description	Modified full analysis set (mFAS) (all participants in the full analysis set [FAS] who received investigational medicinal product [IMP] ≤ 7 days from symptom onset and were not hospitalized at baseline [≤ Day 1] for isolation purposes)		
Descriptive statistics and estimate variability	Treatment group	EVUSHELD	Placebo
	Number of subject	407	415
	Severe COVID-19 or death n (%)	18 (4.4)	37 (8.9)
Effect estimate per comparison	Severe COVID-19 or death	Comparison groups	EVUSHELD versus placebo
		Relative risk reduction (RRR)	50.49
		95% confidence interval (CI)	14.56, 71.31
		P-value	0.010

Notes	Treatment with EVUSHELD within 7 days of symptom onset led to a statistically significant reduction in the incidence of severe COVID-19 or death from any cause compared to placebo through study Day 29.		
Analysis description	**First supportive estimand of the primary endpoint: Severe COVID-19 or death from any cause through Day 29 in non-hospitalized participants dosed ≤ 5 days from symptom onset**		
Analysis population and time point description	Early intervention analysis set (EIAS; all participants in the mFAS who received IMP ⩽ 5 days from symptom onset)		
Descriptive statistics and estimate variability	Treatment group	EVUSHELD	Placebo
	Number of subject	253	251
	Severe COVID-19 or death n (%)	9 (3.6)	27 (10.8)
Effect estimate per comparison	Severe COVID-19 or death	Comparison groups	EVUSHELD versus placebo
		Relative risk reduction (RRR)	66.93
		95% confidence interval (CI)	31.11, 84.12
		P-value	0.002
Analysis description	**Second supportive estimand of the primary endpoint: Severe COVID-19 or death from any cause from Day 4 through Day 29 in nonhospitalized participants dosed ⩽ 7 days from symptom onset**		
Analysis population and time point description	mFAS		
Descriptive statistics and estimate variability	Treatment group	EVUSHELD	Placebo
	Number of subject	407	415
	Severe COVID-19 or death n (%)	12 (2.9)	33 (8.0)
Effect estimate per comparison	Severe COVID-19 or death	Comparison groups	EVUSHELD versus placebo
		Relative risk reduction (RRR)	62.98
		95% confidence interval (CI)	29.45, 80.57
		P-value	0.002
Notes	none		
Analysis description	**Third supportive estimand of the primary endpoint: Severe COVID-19 or death from any cause from through Day 29 in all randomized participants**		
Analysis population and time point description	FAS (all randomized participants who received IMP, irrespective of their protocol adherence and continued participation in the study)		
Descriptive statistics and estimate variability	Treatment group	EVUSHELD	Placebo
	Number of subject	446	444
	Severe COVID-19 or death n (%)	24 (5.4)	41 (9.2)
		Comparison groups	EVUSHELD versus placebo

Effect estimate per comparison	Severe COVID-19 or death	Relative risk reduction (RRR)	41.59
		95% confidence interval (CI)	5.01, 64.08
		P-value	0.028
Analysis description	**Fourth supportive estimand of the primary endpoint: Severe COVID-19 or death from any cause from through Day 29 in non-hospitalized participants, who are seronegative at baseline, dosed ⩽ 7 days from symptom onset**		
Analysis population and time point description	Seronegative analysis set (SNAS; all participants in the mFAS who were seronegative at baseline)		
Descriptive statistics and estimate variability	Treatment group	EVUSHELD	Placebo
	Number of subject	347	345
	Severe COVID-19 or death n (%)	14 (4.0)	36 (10.4)
Effect estimate per comparison		Comparison groups	EVUSHELD versus placebo
		Relative risk reduction (RRR)	61.26
		95% confidence interval (CI)	29.67, 78.66
		P-value	0.001
Notes	Statistically significant results were achieved in all supportive estimands. These analyses indicate that participants treated early in their disease course derive the greatest treatment benefits.		
Analysis description	**Key secondary endpoint: A composite of either death from any cause or hospitalization for COVID-19 complications or sequelae during the 168-day post-dose period (Day 1 to Day 169).**		
Analysis population and time point description	mFAS		
Descriptive statistics and estimate variability	Treatment group	EVUSHELD	Placebo
	Number of subject	413	421
	Hospitalization for COVID-19 complications or sequelae or Death n (%)	20 (5.0)	40 (9.8)
Effect estimate per comparison	Hospitalization for COVID-19 complications or sequelae or Death	Comparison groups	EVUSHELD versus placebo
		Relative risk reduction (RRR)	49.11
		95% confidence interval (CI)	14.47, 69.72
		P-value	0.009
Notes:	Results from a CMH test stratified by time from symptom onset (⩽ 5 versus > 5 days) and risk of progression to severe COVID-19 (high versus low).		
Analysis description	**Secondary endpoint: The incidence of participants with respiratory failure, defined as requirement for mechanical ventilation, ECMO, non-invasive ventilation, or high flow nasal cannula oxygen delivery**		

Analysis population and time point description	mFAS		
Descriptive statistics and estimate variability	Treatment group	EVUSHELD	Placebo
	Number of subject	405	412
	Respiratory failure n (%)	3 (0.7)	11 (2.7)
Effect estimate per comparison	Respiratory failure	Comparison groups	EVUSHELD versus placebo
		Relative risk reduction (RRR)	71.86
		95% confidence interval (CI)	0.25, 92.06
		P-value	0.036
Notes	Treatment with EVUSHELD reduced the incidence of respiratory failure compared with placebo through study Day 29.		

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

N/A

Clinical studies in special populations

N/A

Supportive studies

N/A

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of Evusheld for the treatment of COVID-19 in adults with mild-moderate disease was investigated in TACKLE, an ongoing Phase III, randomized, double-blind, placebo-controlled study. As further discussed in the Pharmacology section of this report, double the dose (2x300 mg) as approved for the prophylaxis indication (2x150mg) was applied. The use of placebo as comparator is endorsed in the studied population as the study started the recruitment in January 2021 where no approved treatment of mild-moderate disease was available. Overall, the chosen study design is deemed appropriate.

In order to meet the entry criteria for mild-moderate COVID-19, patients had to have (1) a documented positive SARS-CoV-2 molecular test (antigen or nucleic acid) from a sample collected ≤ 3 days prior to study entry; (2) ≤7 days of symptoms of COVID-19 at study entry; (3) selected self-reported symptoms within 24 hours prior to Day 1; (4) WHO Clinical Progression Scale score 2 or 3; (5) oxygenation saturation of ≥ 92% at rest within 24 hours prior to Day 1; (6) non-hospitalized state. Overall, the applied patient characteristics are largely in line with FDA guidance (COVID-19: Developing Drugs and Biological Products for Treatment or Prevention) definition of mild or moderate COVID-19, as patients had to be symptomatic (including possible shortness of breath) but without severely impaired oxygen

saturation (≥ 92%). Adolescents, pregnant and breast-feeding women as well as previously SARS-CoV-2 vaccinated subjects were excluded. Overall, the chosen population seems adequate for investigation of a treatment effect in adult patients with mild-moderate COVID-19.

At least 60% of the subjects had to be of increased risk for progression to severe COVID-19. The chosen definition of high-risk is in line with current knowledge and deemed appropriate. Stratified recruitment (meaning at least 60% high risk patients) is in principle supported but may limit information in patients without documented risk factors.

Additional treatment for COVID-19 was only allowed in case of hospitalization due to clinical worsening and with approved or licensed (emergency use) products only. Other treatment for COVID-19 prior to day 29 was defined as intercurrent event and handled by policy strategy, which is deemed appropriate.

As primary endpoint, a composite of either severe COVID-19 or death from any cause through day 29 was applied. This is acceptable as it is a relevant measure of overall clinical status and in line with current CHMP recommendations for pivotal studies investigating treatment of mild to moderate COVID-19 in a non-hospitalised setting. Severe COVID-19 was defined as selected symptoms of pneumonia (always in combination with lung-infiltrates) or signs of hypoxia plus score ≥5 on WHO COVID-19 progression scale, which requires hospitalisation and at least oxygen support by mask. Thereby, hospitalisation was defined as ≥ 24 hours of acute care, in a hospital or similar acute care facility. The combination of these requirements for definition of "severe" is deemed largely objective, however, regional or individual site differences (e.g., in admission to hospital/use of oxygen/diagnostics) that might potentially affect primary endpoint analysis cannot entirely be excluded.

The key secondary endpoint investigates the composite of either death from any cause or hospitalization for COVID-19 complications or sequelae through day 169 and thus, captured longer-term outcomes. No precise definition of "COVID-19 complications or sequelae" could be found in the submission package. It is presumed that this was based on investigators decision. Furthermore, it can be interpreted from the protocol that stroke, myocardial infarction, and thromboembolic disease should be counted as such events of COVID-19 complications or sequelae, which is endorsed.

The other secondary endpoints supplement the efficacy analyses by day 29 by investigation of respiratory failure, symptom severity, progression, and duration as well as viral load (SARS-CoV-2 RNA) reduction. For the secondary endpoint "Incidence of respiratory failure through day 29", respiratory failure was defined as requirement for mechanical ventilation, ECMO, non-invasive ventilation, or high-flow nasal cannula oxygen delivery. Symptom assessments for secondary endpoints are based on daily use of 37 questions in a self-reported symptom diary. No information is available on validation of the PRO instrument. Additional investigation of viral load might be informative for assessment of infectivity of the patient but not for clinical outcome per se as it is no established surrogate for efficacy.

The study was planned to enrol 1700 patients, in order to have 90% power to detect a relative reduction of 65% in the incidence of severe COVID-19/death between the study groups (AZD7442 versus placebo), assuming the incidence of severe COVID-19/death in the placebo group was 4.6%. Several design aspects have been amended during the ongoing study. This includes the changes to the alpha spending for the initially planned interim analysis, removal of the interim analysis, changes to the primary analysis model, reduction of the planned number of events for the event-driven analysis (and power, accordingly). Thus, although the sample size seems is acceptable, there is uncertainty how these changes might have affected results. It is evident that the study was planned and conducted with relevant uncertainty.

Double blinding is endorsed. Unblinding for SARS-CoV-2 vaccination was only possible after day 30 was reached in the individual subject. Thus, influence on the primary endpoint and all other secondary endpoints investigating events until day 29 should be negligible. However, the key-secondary endpoint

death from any cause or hospitalization for COVID-19 complications or sequelae during the 168-day post-dose period (Day 1 to Day 169) may be affected by this unblinding, or by vaccination of subjects.

The primary analysis strategy is overall acceptable, but some uncertainties remain. The analysis plan was amended several times throughout the study, including changes to the timing of analyses, interim analyses, primary analysis model and multiplicity adjustment. This is considered to reflect uncertainty during the pandemic and is understood.

The primary analysis population is restricted to subjects not hospitalized and with time from symptom onset to treatment initiation ≤ 7 days. This is not fully in line with the intention to treat principle, and it is not entirely clear why a broader population was included, and the analysis was restricted. Accordingly, the primary estimand does not seem to be fully in line with a treatment policy estimand.

The third supportive estimand includes the entire FAS, and this is endorsed. Consistency of the primary results with results targeting the third supportive estimand provides reassurance. In fact the third supportive estimand is considered closer to a treatment policy estimand and is considered more robust and more relevant for the regulatory decision. The FAS is restricted to subjects who received IMP, and this is acceptable in a double-blinded study, provided that the extent of exclusion due to not receiving IMP is small.

The primary analysis was planned to be conducted by means of a CMH test stratified for the stratification factors of randomization, and this is considered reasonable. The RR was planned to be estimated by the CMH method, and the efficacy was planned to be calculated as the RRR = 100 × (1−RR). The fact that initially another analysis was planned (poisson-regression) and was changed in a very late amendment (amendment 7, dated 05 July 2021) shortly before the data cutoff date (21 August 2021) may reflect uncertainty in planning and conduct of the study.

It should be noted that the primary outcome is a composite outcome, including the components of severe COVID-19 and death for any cause. The study is not powered to detect effects on death and no analysis of death was pre-specified with multiplicity control. Deaths are investigated in an exploratory manner.

A two-sided significance level of 0.05 and the hierarchical testing sequence are in principle acceptable.

However, there is some uncertainty around multiplicity, as the testing approach was changed during the conduct of the study. Initially, an interim analysis was planned. The alpha spending for the interim analysis was later revised in an amendment. In another, later amendment the interim analysis was removed. The testing hierarchy was introduced in amendment 7. Taken together, there are currently no strong concerns, but some uncertainty around these changes.

Missing response data were not imputed. This is not fully in line with the intention to treat principle. However, the impact of missing values and the strategy for handling missing data is considered small, in the updated analysis (DCO 14 January 2022) there were only 3 missing outcome values in the Evusheld group and 3 in the placebo group (in the FAS, 3 vs 2 in the mFAS, respectively).

Subgroup analyses are descriptive, and this is acceptable. It seems that the expected information in subgroups was not prospectively discussed (except for "high risk" patients who are well represented). This is not necessarily problematic per se, but uncertainty in in relevant subgroups may add uncertainty to the overall results.

The Study TACKLE is still running. Based on the presented data cut-off (DCO 21 August 2021), none of the 1014 enrolled participants has already completed the study. The median on-study follow-up time was 84 days with the presented data cut-off. Considering the long half-life of the drug, exposure is assumed to be still high enough for all PD effects with this median follow-up time.

Approximately 10% of subjects were screened but not randomised, with the majority being screening failures. Less than 1% of the subjects were randomised but not dosed. The treatment arms are similar in numbers of patients who were randomized and treated. The reasons for withdrawal from study show a comparable picture for both treatment arms and do not raise a concern.

In total, 6 protocol amendments became necessary. Overall, the changes seem to be well justified, but the need to revise the study planning (including the primary analysis model, time of analysis, multiplicity adjustment) indicates that the study was planned and conducted with relevant uncertainty. An additional guidance on "hospitalisation definition" taking into account treatment of severe disease outside the traditional hospital setting in temporary facilities due to limited capacities in the ongoing pandemic was introduced with protocol version 6 in April 2021. As "hospitalisation definition" is an integral component of the primary endpoint (via WHO score definition) and the further guidance was introduced late, regional or individual site differences in hospitalisation due to limited capacities in times of high infection rates that might potentially affect primary endpoint analysis cannot entirely be excluded.

The number of important protocol deviations was quite high: 42.7% of participants had 1 or more important protocol deviations. The important protocol deviations were generally balanced between treatment groups (Evusheld: 44.2%; placebo: 41.2%). The great majority of deviations (39.1% of all subjects in FAS) was assigned to 'Other Important Deviations'. The applicant states that the majority of these cases was related to "eDiary non-compliance" without stating on numbers. High eDiary non-compliance is expected to result in a high number of missing values for symptom-related endpoints. As these were other secondary endpoints only, the impact on overall study interpretation should be minor. However, this high degree of non-compliance questions somewhat the appropriateness of the used questionnaire and/or device.

Efficacy data and additional analyses

In the TACKLE study, demographic and baseline characteristics, including age, race, BMI, time from symptom onset, risk group and smoking history were generally balanced between treatment groups. Furthermore, all participant disease characteristics, including COVID-19 co-morbidities, serum for SARS-CoV-2 Serology and WHO clinical progression score were balanced between both treatment groups. The median time from symptom onset was 5 days. A relatively high percentage of subjects (51.8%) was of Hispanic or Latin ethnic origin. Most of the participants were White (61.9%) and from Europe (41.9%) or Latin America (42.2%). An imbalance between treatment groups was observed regarding regions: while 14.2% of subjects were from US and 38.7% of subjects from Latin America (Argentina, Brazil, Mexico) in the Evusheld group, these were 8.9% and 45.7%, respectively in the placebo group. It cannot be excluded that regional differences in standard of care and concomitant medication might have an impact on patient clinical outcome and thus, such imbalances might potentially affect study results.

Based on the baseline and demographic data presented, an adult patient population with mild-moderate COVID-19, without previous vaccination/infection and at risk for progression to severe COVID-19 seems to be adequately represented by this clinical trial. However, numbers were low for subjects without documented risk factors for disease progression (10.4%) and seropositives at baseline (14.1%) and thus, the information on potential treatment benefit for these subgroups may be limited. Upon request, indication was restricted to patients with risk factors for disease progression.

For the primary analysis of the primary endpoint "Severe COVID-19 or Death From Any Cause Through Day 29", data of 413 subjects in the Evusheld group and 421 subjects in the placebo group were analysed (DCO 21 August 2021); Approximately 9% of subjects in the Evusheld group and 7% of subjects in the placebo group from FAS were excluded for the applied modified full analysis set.

The primary endpoint was met: There were 18 events (4.4%) of severe COVID-19 or death from any cause through day 29 in patients treated with Evusheld and 37 events (8.9%) in the respective placebo group. This led to a 50.49% (95%: CI 14.56, 71.31) relative risk reduction for developing severe COVID-19 or death from any cause in non-hospitalized adults who had been symptomatic for 7 days or less. As only few deaths occurred through day 29 (3 in the Evusheld arm and 4 in the placebo arm), the results of the primary composite endpoint were driven by the incidence of severe COVID-19.

The additionally presented 1st supportive estimand including subjects with symptom onset ≤ 5 days indicates that earlier treatment might be beneficial. This is further supported by a subgroup analysis investigating RRR in subjects treated ≤3 days after symptom onset. The chosen SmPC wording "EVUSHELD should be given as soon as possible after a positive viral test for SARS-CoV-2 and within 7 days of the onset of symptoms of COVID-19" is deemed appropriate. Presentation of results from the 1st supportive estimand in the SmPC is acceptable and provides prescribers with relevant information on benefit when treated earlier in disease course.

The presented 2nd supportive estimand indicates a higher treatment effect after day 3 post treatment. In addition, the supplementary presented Kaplan-Meier plot shows that curves begin to separate at approximately Day 4, with no apparent treatment effect within the first 3 days after application. However, the applicant claims that after IM application efficacious plasma level are reached within few hours. Thus, this result indicates that treatment effect might not be sufficient in subjects with fast onset of clinical worsening and might also support the hypothesis that treatment should occur as early as possible after mild symptom onset. The finding is in line with what has been observed with other anti-spike mAbs (also after IV application) and does not raise a certain concern.

As the primary analysis in the mFAS is not fully supported (not fully in line with the intention to treat principle) and a relevant number of subjects was excluded, the additionally presented 3rd supportive estimand investigating FAS is considered important. Here in the FAS, 6 additional events occurred in the Evsuheld group, whereas only 4 in the placebo group. The resulting RRR was 41.59% (95%: CI 5.01, 64.08). The combination of 2 different reasons for exclusion from mFAS (hospitalised or symptom onset > 7 days) somewhat impedes interpretation of results. Additionally requested analysis in the FAS were not provided. The applicant states that analysis from the FAS is not in alignment with the proposed indication. This is not fully agreed, as there is no requirement for not being hospitalised with mild-moderate disease at baseline in the indication wording. Thus, results of the third supportive estimands were additionally presented in the SmPC.

The 4th supportive estimand demonstrates a good treatment effect in seronegatives, with RRR of 61.26% (95%: CI 29.67, 78.66).

The applied event-based primary analysis resulted in overall low numbers of subjects and low numbers of primary endpoint events in the pivotal study TACKLE. Therefore, information from pre-defined subgroup analyses is limited - The study was not designed to detect treatment differences with high statistical power within subgroups and the explorative character of such an analysis needs to be emphasized. However, based on pre-defined subgroups some uncertainties arise for the therapy and the generalizability of a positive treatment effect remains somewhat questionable.

In particular, in the oldest subgroups aged ≥75 years or aged ≥80 years, placebo event rate was 20% whereas 1/3 of Evusheld treated subjects experienced an event. In an exploratory analysis the interaction between age and treatment was nominally significant, suggesting decreased treatment effect with increasing higher age. However, events are overall sparse, and the finding would neither be supported by a mechanistic rationale nor by replication in independent data. There remains uncertainty, but the finding is currently considered likely to be a chance finding.

Based on subgroup results presented, it seems like the positive treatment effect on severe COVID-19 or death from any cause trough day 29 is attributed to Latin American population only (Evusheld 5/166; placebo 24/201), whereas no treatment effect is seen in European (Evusheld 11/173; placebo 11/175) and US-American (Evusheld 2/62; placebo 2/36) population. The apparent lack of a positive treatment effect in the European population is currently not understood. Potential reasons for this finding remain speculative and might include differing efficacy against different emerging variants, regional differences in patient care/medical practice and regional differences in patient characteristics, including a higher proportion of elderly patients in Europe.

In the small group of seropositives (n=113), 4 subjects experienced an event in the Evusheld group and 1 subject in placebo group. Based on these currently available clinical data, the magnitude of treatment effect (if any) in the seropositive population with acute infection, cannot be derived. In routine clinical practice, determination of serostatus prior to treatment may not be feasible or delay treatment. As Evusheld has a favourable safety profile, a mAbs treatment irrespective of serostatus can be agreed.

For certain treatments as part of standard of care, including corticosteroids, antivirals and immune-based therapies, a higher percentage of subjects in these subgroups experienced an event in the Evusheld group compared to placebo group, however, with very low numbers overall. Thus, chance findings are possible and the potential for an additional treatment effect in corticosteroid/anti-viral/immunotherapy co-treated subjects cannot be estimated based on these data.

The key secondary endpoint analysis of "death from Any Cause or Hospitalization for COVID 19 Complications or Sequelae through Day 169" showed results (49.11% (95% CI: 14.47, 69.72; p = 0.009) RRR) that are in good accordance with the primary endpoint "Severe COVID-19 or Death from Any Cause Through Day 29" analysed at the key secondary DCO (50.38 (95% CI: 14.38, 71.25; p = 0.010) RRR). As hospitalisation was a prerequisite for classification as primary endpoint event (by use of WHO scale), it is understood that all cases that were counted as primary events were also counted as key secondary events. All but one key secondary event (death due to colorectal cancer metastatic in the Evusheld group) occurred prior to Day 29. Therefore, the informative value regarding Evusheld's effect on longer-term adverse outcomes is limited. Nevertheless, results can be considered supportive. The potential impact of unblinding and COVID-19 vaccination on this key secondary endpoint is presumed to be low. In light of only one additional event observed after day 30 (after the possibility of unblinding), the censoring approach can be concluded to have had only minor impact.

For the secondary endpoint "Incidence of respiratory failure through day 29", there were 3 events (0.7%) of respiratory failure through day 29 in patients receiving Evusheld and 11 events (2.7%) in the respective placebo group. This resulted in a 71.86% (95% CI 0.25 to 92.06) relative risk reduction for respiratory failure through day 29. Missing response data were not imputed. The reported missing events were similar in both groups but high relative to number of reported events (Evusheld: 8 events and placebo: 9 events). Thus, a potential impact of missing values on this secondary endpoint analysis cannot be excluded. Overall, results on respiratory failure can be considered supportive for a treatment effect of Evusheld on disease progression. However, data need to be interpreted with caution as the overall number of events is small.

Three (3) other secondary endpoints investigated the effect of Evusheld on COVID-19 symptom course compared to placebo: severity of participant-reported COVID-19 symptoms through Day 29 (16 symptoms scored from 0 to 4); progression of participant-reported COVID-19-associated symptoms through Day 29; return to usual health through Day 29. Information on symptom severity/progression was not further collected in hospitalized subjects. In the remaining population of non-hospitalised (not severely ill) subjects, there was only a numerical effect on "average LS mean difference in symptom severity through 29 days" regarding the symptoms cough and muscle aches. For all other symptoms no relevant difference was observed. Furthermore, the analysis of the secondary endpoint "Time to Return to

Usual Health Through Day 29" showed that the number of subjects with an event was similar in both treatment groups (Evusheld 271 out of 413 participants (65.6 %), Placebo: 267 out of 421 participants (63.4%)). Overall, no clinically relevant benefit of Evusheld compared to placebo could be derived these symptom related endpoints. The number of subjects with COVID-19 symptom progression (1 or more symptoms based on symptom severity score from 0-4) through study Day 29 was 167 (54.9%) for Evusheld versus 199 (62.2%) for placebo. Thus, this result might be interpreted as supportive; however, effect size was rather small.

Based on secondary endpoint data available for change from baseline of SARS-CoV-2 RNA from nasal swabs through day 29, it is evident that in both, the Evusheld group and the placebo group, viral RNA load declined over time between day 3 and day 15. Viral decline within the first week was enhanced by Evusheld with moderate effect size. Clinical relevance of enhanced viral load reduction has not been fully established so far.

2.4.4. Conclusions on the clinical efficacy

Evidence for efficacy of Evusheld has been generated by a single pivotal study investigating treatment effect on severe COVID-19 or death by any cause. The need to revise the study planning (including the primary analysis model, time of analysis, multiplicity adjustment) several times indicates that the study was planned and conducted with relevant uncertainty.

Evusheld demonstrated a statistically significant effect for the primary endpoint as well as signs of efficacy across secondary endpoints. The primary analysis was conducted in a modified FAS, excluding patients hospitalised or with symptom onset ≥7 days at baseline. Therefore, the 3rd supportive estimand analysed in all randomized subjects (FAS) is considered closer to a treatment policy estimand, more robust and more relevant for the regulatory decision.

The included patient population with mild-moderate disease was mainly young, Latin American and highly co-morbid. As only a patient population at risk for progression to severe COVID-19 was adequately represented by this clinical trial, indication was restricted upon request. Furthermore, with regard to the generalizability of study results some uncertainties remain for subgroups with high age, seropositivity and European region.

2.5. Clinical safety

Introduction

In addition to the existing safety data from 4210 participants that were enrolled in Phase 3 studies PROVENT and STORM CHASER, the applicant now provides clinical data from the primary analysis of the ongoing Phase 3 study TACKLE. The results of the Phase 1 study D8850C00001 were also submitted as supportive safety data.

Evusheld (AZD7442, components: AZD8895/tixagevimab and AZD1061/cilgavimab) is a monoclonal antibody with a non-host target. In both Phase 3 studies PROVENT and STORM CHASER, most frequently reported TEAEs were headache, fatigue and cough with similar percentages regarding the different treatment groups after the sequential administration of 150 mg of tixagevimab and 150 mg of cilgavimab IM. In both Phase 3 studies, the majority of participants had TEAEs that were mild to moderate in intensity. Serious adverse events occurred rarely in both treatment groups. In the PROVENT study, a slight imbalance between the treatment arms regarding cardiac disorders (coronary and thrombo-embolic events) had been observed; this is reflected in section 4.4 of the SmPC.

Adverse events that were classified as Adverse Drug Reactions were Hypersensitivity and Injection site reactions in line with available safety data and the mode of action. The hitherto collected safety data suggested a tolerable safety profile, however further (long-term) data are necessary to fully characterize the safety profile.

Table below provides an overview on the submitted study safety data.

Table 32 Studies Included in Safety Summary

Study Number/(Acronym) Sponsor/Countries	Primary Safety Objective(s)	Study Design/ Primary Safety Endpoints	Treatments, Doses, and Numbers of Participants Exposed	Population	Duration	Study Status
Phase III study						
D8851C00001 (TACKLE)/ AstraZeneca/ Argentina, Brazil, Czech Republic, Poland, Ukraine, UK, US, Germany, Hungary, Italy, Spain, Russia, Mexico, and Japan	To evaluate safety and tolerability of EVUSHELD	Phase III, RD, DB, PC, multicenter Primary safety endpoints: AEs, SAEs, safety laboratory parameters through 1 year	EVUSHELD 600 mg IM (N = 452); placebo (N = 451) At least 60% of participants at high risk[a] of progression to severe COVID-19: - aged ≥ 65 years - aged < 65 years with at least one of the following: cancer; chronic lung disease or moderate to severe asthma; obesity; hypertension; cardiovascular disease (including history of stroke), diabetes, chronic kidney disease, 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; sickle cell disease; smoking (current and former)	Outpatient adults ≥ 18 years with a documented positive SARS-CoV-2 molecular test (antigen or nucleic acid) from a sample collected ≤ 3 days prior to study entry and with ≤ 7 days of symptoms of COVID-19 at study entry, plus the presence of select symptoms within 24 hours prior to Day 1	Screening period: 1 day Treatment period: 1 day Safety follow-up: 457 days	Ongoing (enrolment complete; primary analysis complete)

Study Number/(Acronym) Sponsor/Countries	Primary Safety Objective(s)	Study Design/ Primary Safety Endpoints	Treatments, Doses, and Numbers of Participants Exposed	Population	Duration	Study Status
Phase I Study						
D8850C00001/ AstraZeneca / UK	To evaluate the safety and tolerability of EVUSHELD administered IV or IM	Phase I; FTIH, randomized DB/PC/DE, single center Primary safety endpoints: standard safety assessments	**Cohorts with the 2 mAbs administered sequentially:** **Cohort 1a:** EVUSHELD 300 mg IM (N = 10); placebo (N = 2) **Cohort 1b:** EVUSHELD 300 mg IV (N = 10); placebo (N = 2) **Cohort 2**: EVUSHELD 1000 mg IV (N = 10); placebo (N = 2) **Cohort 3:** EVUSHELD 3000 mg IV (N = 10); placebo (N = 2) **Cohort with the 2 mAbs co-administered:** **Cohort 4:** EVUSHELD 3000 mg IV (N = 10) co-administered; placebo (N = 2)	Healthy adults aged 18 to 55 years	Screening period: ≤ 27 days Treatment period: 3 days Safety follow-up: 361 days	Completed

[a] High risk was defined by any of the following:

- Persons aged 65 years and older at randomization
- Persons aged < 65 years and having at least one of the following conditions: cancer; chronic lung disease or moderate to severe asthma; obesity (BMI > 30; may be based on self-report of recent height and weight measurement); hypertension; cardiovascular disease (including history of stroke); diabetes; chronic kidney disease; 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; sickle cell disease; smoking

AE, adverse event; BMI, body mass index; COVID-19, coronavirus disease 2019; CSR, Clinical Study Report; DB, double blinded; DE, dose escalation; FTIH, first time in human; HIV, human immunodeficiency virus; IM, intramuscular; IV, intravenous; PC, placebo-controlled; RD, randomized; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory disease coronavirus 2; UK, United Kingdom; US, United States.

Patient exposure

Overall extent of exposure

The pivotal study TACKLE is an ongoing Phase III, randomized, double-blind, placebo-controlled, multicenter study is assessing the safety and efficacy of a single 600 mg dose of Evusheld IM compared to placebo for the treatment of mild to moderate COVID-19 in non-hospitalized patients. The adult participants had a positive SARS-CoV-2 molecular test, sample collected ≤ 3 days prior to study entry and with ≤7 days of symptoms of COVID-19 at study entry ('Day 1' symptom count starts from the first day of symptoms), plus the presence of select symptoms within 24 hours prior to Day 1. At least 60% of participants were at high risk of progression to severe COVID-19.

This application includes safety data from 452 participants with mild to moderate COVID-19 at 600 mg Evusheld IM; overall, 903 participants had been dosed with the IMP. As this pivotal study is ongoing, data from the full safety reporting are not available. The duration of the median safety follow up is 84 days until data cut-off (DCO) 21 August 2021; the total follow-up period is 457 days. The safety follow-up of the Phase 1 study, including 50 healthy participants, is completed and presents data up to day 361. The Safety Analysis Set consists of all participants who received at least one injection of study drug administration of Evusheld or placebo.

The extent of exposure is displayed in the table below:

Table 33 Extent of Exposure and Follow up-TACKLE and Phase I study

Study, Data cut-off	Treatments and Doses	Number of participants		Safety follow-up duration[a]
		EVUSHELD	Placebo	
TACKLE, 21Aug2021	600 mg EVUSHELD/placebo administered as 2 sequential IM injections on Day 1.	452	451	84.0 (30, 86) [b]
Study D8850C00001 (final data presented)	**Cohort 1a:** 300 mg EVUSHELD/placebo administered as 2 sequential IM injections **Cohort 1b:** 300 mg EVUSHELD/placebo administered as 2 sequential IV infusion **Cohort 2**: 1000 mg EVUSHELD/placebo administered as 2 sequential IV infusion **Cohort 3:** 3000 mg EVUSHELD/placebo administered as 2 sequential IV infusion **Cohort 4:** 3000 mg EVUSHELD/placebo administered as IV infusion (co-administration of the 2 mAbs)	50 (10 each Cohort)	10 (2 each Cohort)	361 days[c]

[a] Duration of safety follow-up in days, from Day 1 to data cut-off.
[b] Median (IQR).
[c] Follow-up in days for all 58 participants who completed the study.
IM, intramuscular; IV, intravenous; mAbs, monoclonal antibodies; IQR, interquartile.
Source: Table 14.1.8, TACKLE CSR in Module 5.3.5.1 and Section 12.1, D8850C00001 I CSR in Module 5.3.3.1.

Additional safety data until the Key Secondary DCO 14 January 2022 were presented with the responses and are discussed in the relevant sections as well as in Question 23.

Demographics and Patient Characteristics

The table below summarizes the demographic and key baseline characteristics of study participants in TACKLE. The majority of enrolled patients were classified to be at high risk of progression to severe COVID-19. The present co-morbidities at Baseline are also displayed in the followed tables.

Table 34 Demographic and Baseline Characteristics-Full Analysis Set, TACKLE

Characteristic	EVUSHELD (N = 452)	Placebo (N = 451)	Total (N = 903)
Age (years)			
n	452	451	903
Mean	46.3	45.9	46.1
SD	15.42	14.99	15.20
Min	18	18	18
Q1	34.0	34.0	34.0
Median	46.0	46.0	46.0
Q3	57.0	56.0	57.0
Max	83	86	86
Age group (years) n (%)			
>= 18-< 65	393 (86.9)	394 (87.4)	787 (87.2)
>= 65-< 75	38 (8.4)	46 (10.2)	84 (9.3)
>= 75-< 80	12 (2.7)	6 (1.3)	18 (2.0)
>= 80	9 (2.0)	5 (1.1)	14 (1.6)
< 65	393 (86.9)	394 (87.4)	787 (87.2)
>= 65	59 (13.1)	57 (12.6)	116 (12.8)
Sex n (%)			
Male	213 (47.1)	235 (52.1)	448 (49.6)
Female	239 (52.9)	216 (47.9)	455 (50.4)
Race n (%)			
White	285 (63.1)	274 (60.8)	559 (61.9)
Black or African American	16 (3.5)	20 (4.4)	36 (4.0)
Asian	30 (6.6)	21 (4.7)	51 (5.6)
American Indian or Alaska Native	100 (22.1)	115 (25.5)	215 (23.8)
Not Reported	21 (4.6)	21 (4.7)	42 (4.7)

Characteristic	EVUSHELD (N = 452)	Placebo (N = 451)	Total (N = 903)
Region n (%)			
United States	64 (14.2)	40 (8.9)	104 (11.5)
Europe	187 (41.4)	191 (42.4)	378 (41.9)
Latin America	175 (38.7)	206 (45.7)	381 (42.2)
Asia	26 (5.8)	14 (3.1)	40 (4.4)
Body Mass Index (kg/m^2) Category n (%)			
< 25	113 (25.0)	126 (27.9)	239 (26.5)
25-< 30	142 (31.4)	130 (28.8)	272 (30.1)
30-< 35	146 (32.3)	114 (25.3)	260 (28.8)
>= 35	49 (10.8)	77 (17.1)	126 (14.0)
Missing	2 (0.4)	4 (0.9)	6 (0.7)
Time from Symptom Onset (day)			
Mean	4.9	5.0	5.0
SD	1.61	1.59	1.60
Min	1	1	1
Q1	4.0	4.0	4.0
Median	5.0	5.0	5.0
Q3	6.0	6.0	6.0
Max	8	9	9
Time from Symptom Onset n (%)			
<= 5 days	268 (59.3)	265 (58.8)	533 (59.0)
> 5 days	184 (40.7)	186 (41.2)	370 (41.0)
Risk Group n (%)			
High	404 (89.4)	405 (89.8)	809 (89.6)
Low	48 (10.6)	46 (10.2)	94 (10.4)
Smoking History n (%)			
Current Smoker	100 (22.1)	94 (20.8)	194 (21.5)
Former Smoker	80 (17.7)	90 (20.0)	170 (18.8)
Never Smoker	272 (60.2)	267 (59.2)	539 (59.7)

[a] This category includes participants recruited in Mexico who identify as Native American.

All percentages are based on the number of participants with data.

For risk of progression, 'high' was derived based on the selection of any risk factors on the SCOV2RP eCRF page, and 'low' was derived based on the absence of any selection of risk factors. For any participant for which missing records exist on SCOV2RP eCRF page, and no 'Yes' response is provided for any available record, the risk of progression variable was set to the IRT captured response.

Table 35 Participant Disease Characteristics at Baseline- Full Analysis Set, TACKLE

Characteristic	EVUSHELD (N = 452)	Placebo (N = 451)	Total (N = 903)
COVID-19 co-morbidities [a] n (%)			
no co-morbidity	52 (11.5)	52 (11.5)	104 (11.5)
> = 1 co-morbidity	400 (88.5)	399 (88.5)	799 (88.5)
Serum for SARS-CoV-2 Serology n (%)			
Positive	60 (13.3)	67 (14.9)	127 (14.1)
Negative	384 (85.0)	374 (82.9)	758 (83.9)
Missing	8 (1.8)	10 (2.2)	18 (2.0)
WHO Clinical Progression Scale score n (%)			
2	396 (87.6)	398 (88.2)	794 (87.9)
3	56 (12.4)	53 (11.8)	109 (12.1)

[a] Co-morbidity = Risk factors in CRF for both adults and adolescents: SARS-CoV-2 Progression risk to COVID-19, excluding the risk factor "Person aged >=65 year" for adult participants.

All percentages are based on the number of participants with data.

COVID-19, coronavirus disease 2019; CRF, case report form; N, number of participants in treatment group; n, number of participants included in analysis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

Source: Table 14.1.4.2, TACKLE CSR in Module 5.3.5.1

Table 36 High risk Co-mobilities for Progression to Severe COVID-19 for Death-TACKLE

Co-morbidity	EVUSHELD (N = 452)	Placebo (N = 451)	Total (N = 903)
n (%)	400 (88.5)	399 (88.5)	799 (88.5)
Cancer	18 (4.0)	15 (3.3)	33 (3.7)
Chronic Lung Disease/Asthma	58 (12.8)	50 (11.1)	108 (12.0)
Obesity	195 (43.1)	193 (42.8)	388 (43.0)
Hypertension	135 (29.9)	121 (26.8)	256 (28.3)
Cardiovascular Disease	42 (9.3)	38 (8.4)	80 (8.9)
Diabetes	53 (11.7)	55 (12.2)	108 (12.0)
Chronic Kidney Disease	10 (2.2)	9 (2.0)	19 (2.1)
Immunocompromised State	22 (4.9)	23 (5.1)	45 (5.0)
Chronic Liver Disease	7 (1.5)	13 (2.9)	20 (2.2)
Sickle Cell Disease	0	0	0
Smoking	180 (39.8)	184 (40.8)	364 (40.3)

Co-morbidity = Risk factors in CRF: SARS-CoV-2 Progression risk to COVID-19, excluding the risk factor "Person aged >=65 year".

Obesity: BMI > 30; may be based on self-report of recent height and weight measurement.

BMI, body mass index; COVID-19, coronavirus disease 2019; CRF, case report form; N, number of participants in treatment group; n, number of participants included in analysis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Source: Table 14.1.4.3, TACKLE CSR in Module 5.3.5.1

Adverse events

Summary of treatment-emergent Adverse Events

An overall summary of Adverse Events and common adverse events by PT with a frequency ≥1% are displayed in the tables below.

Table 37 Overall Summary of Adverse Events in Any Category-Safety Analysis set, TACKLE

AE Category	Number (%) of Participants [a]		
	EVUSHELD (N = 452)	Placebo (N = 451)	Total (N = 903)
Participants with any AE	132 (29.2)	163 (36.1)	295 (32.7)
Any AE with outcome=death	6 (1.3)	6 (1.3)	12 (1.3)
Any SAE (including events with outcome=death)	33(7.3)	54 (12.0)	87 (9.6)
Any AE leading to study withdrawal	5 (1.1)	7 (1.6)	12 (1.3)
Any AESI	15 (3.3)	15 (3.3)	30 (3.3)
Any related AE [b]	23 (5.1)	21 (4.7)	44 (4.9)
Any related SAE [b]	0	0	0
Any related AESI [b]	15 (3.3)	15 (3.3)	30 (3.3)
Any Grade 3 or 4 AE	27 (6.0)	43 (9.5)	70 (7.8)
Any Grade 3 or 4 AESI	0	0	0
Any related Grade 3 or 4 AE [b]	0	0	0
Any related Grade 3 or 4 AESI [b]	0	0	0

[a] Participants with multiple events in the same category are counted only once in that category. Participants with events in more than one category are counted once in each of those categories.

[b] Possibly related, as assessed by the Investigator.

Includes adverse events that occurred through end of study.

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

Table 38 Number of Participants with Adverse Events, Most common ≥ 1% by Preferred Term-Safety Analysis Set, TACKLE

Preferred Term	Number (%) of Participants		
	EVUSHELD (N = 452)	Placebo (N = 451)	Total (N = 903)
Participants with any AE	132 (29.2)	163 (36.1)	295 (32.7)
COVID-19 pneumonia	26 (5.8)	49 (10.9)	75 (8.3)
Injection site pain	8 (1.8)	10 (2.2)	18 (2.0)
Insomnia	6 (1.3)	1 (0.2)	7 (0.8)
Type 2 diabetes mellitus	6 (1.3)	2 (0.4)	8 (0.9)
Diabetes mellitus inadequate control	5 (1.1)	2 (0.4)	7 (0.8)
Diarrhoea	5 (1.1)	3 (0.7)	8 (0.9)
Dizziness	5 (1.1)	0	5 (0.6)
Headache	5 (1.1)	2 (0.4)	7 (0.8)
Hypertension	3 (0.7)	7 (1.6)	10 (1.1)
COVID-19	1 (0.2)	9 (2.0)	10 (1.1)

Most common is defined according to % in at least one treatment group.

Number (%) of Participants with AEs, sorted by decreasing frequency for preferred term based on EVUSHELD group.

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

At the time of the Key Secondary DCO the rates increased in both groups to 174 (38.5%) and 196 (43.5%) participants, respectively, and were still higher in the placebo group compared with the Evusheld group (see table below).

Table 39 Number of Participant with Adverse Events in Any Category (Safety Analysis Set)

AE Category	Number (%) of Participants [a]					
	Primary DCO			Key Secondary DCO		
	AZD7442 (N = 452)	Placebo (N = 451)	Total (N = 903)	AZD7442 (N = 452)	Placebo (N = 451)	Total (N = 903)
Participants with any AE	132 (29.2)	163 (36.1)	295 (32.7)	**174 (38.5)**	**196 (43.5)**	**370 (41.0)**
Any AE with outcome = death	6 (1.3)	6 (1.3)	12 (1.3)	**7 (1.5)**	6 (1.3)	**13 (1.4)**
Any SAE (including events with outcome = death)	33 (7.3)	54 (12.0)	87 (9.6)	**40 (8.8)**	**61 (13.5)**	**101 (11.2)**
Any AE leading to study withdrawal	5 (1.1)	7 (1.6)	12 (1.3)	5 (1.1)	7 (1.6)	12 (1.3)
Any AESI	15 (3.3)	15 (3.3)	30 (3.3)	15 (3.3)	15 (3.3)	30 (3.3)
Any related AE [b]	23 (5.1)	21 (4.7)	44 (4.9)	23 (5.1)	21 (4.7)	44 (4.9)
Any related SAE [b]	0	0	0	0	0	0
Any related AESI [b]	15 (3.3)	15 (3.3)	30 (3.3)	15 (3.3)	15 (3.3)	30 (3.3)
Any Grade 3 or 4 AE	27 (6.0)	43 (9.5)	70 (7.8)	**31 (6.9)**	**48 (10.6)**	**79 (8.7)**
Any Grade 3 or 4 AESI	0	0	0	0	0	0
Any related Grade 3 or 4 AE [b]	0	0	0	0	0	0
Any related Grade 3 or 4 AESI [b]	0	0	0	0	0	0

[a] Participants with multiple events in the same category are counted only once in that category. Participants with events in more than one category are counted once in each of those categories.
[b] Possibly related, as assessed by the Investigator.
Text in bold indicates change from the Primary DCO to Key Secondary DCO.
Includes adverse events that occurred through the Key Secondary DCO.
Percentages are based on the total numbers of participants in the treatment group (N).
AE severity ratings and AESIs are defined in Protocol Sections 8.3.2 and 8.3.4.
MedDRA version 24.0.
AE, adverse event; AESI, adverse events of special interest; DCO, data cut-off; MedDRA, Medical Dictionary for Regulatory Activities; N, numbers of participants in the treatment group; SAE, serious AE.
Source: Table 14.3.1 and Table 14.3.1A

As for the Primary DCO, at the Key Secondary DCO the number of participants with AEs, SAEs, AEs leading to study withdrawal, Grade 3 or 4 AEs, and AESIs were either lower in the AZD7442 group or similar between the AZD7442 and placebo groups. Similarly, the number of related AEs were balanced between groups and there were no related SAEs reported. One additional death was reported in the Evusheld group; however, it was not considered related to the IMP. No Grade 3 or 4 AE was judged by the Investigator to be possibly related to IMP, see section below.

In total, 40 (8.8%) participants on AZD7442 and 61 (13.5%) participants on placebo had an SAE; 7 additional participants in each group reported SAEs since the Primary DCO. Grade 3 or 4 (severe to life-threatening) AEs were reported in 31 (6.9%) participants on AZD7442 and 48 (10.6%) participants on placebo, an increase of 4 (0.9%) and 5 (1.1%), respectively, since the Primary DCO.

Common adverse events by PT with a frequency ≥1% are displayed in the table below. Overall, the findings at Key Secondary DCO did not significantly differ from those at the Primary DCO.

Table 40 Number of Participant with Adverse Events, Most Common (≥ 1%) , by Preferred Term (Safety Analysis Set), Key Secondary DCO

Preferred Term	Number (%) of Participants		
	AZD7442 (N = 452)	Placebo (N = 451)	Total (N = 903)
Participants with any AE	174 (38.5)	196 (43.5)	370 (41.0)
COVID-19 pneumonia	26 (5.8)	49 (10.9)	75 (8.3)
COVID-19	7 (1.5)	15 (3.3)	22 (2.4)
Injection site pain	8 (1.8)	11 (2.4)	19 (2.1)
Vaccination complication	7 (1.5)	9 (2.0)	16 (1.8)
Urinary tract infection	6 (1.3)	9 (2.0)	15 (1.7)
Hypertension	5 (1.1)	10 (2.2)	15 (1.7)
Diarrhoea	8 (1.8)	5 (1.1)	13 (1.4)
Type 2 diabetes mellitus	8 (1.8)	5 (1.1)	13 (1.4)
Diabetes mellitus inadequate control	7 (1.5)	4 (0.9)	11 (1.2)
Headache	7 (1.5)	4 (0.9)	11 (1.2)
Back pain	6 (1.3)	5 (1.1)	11 (1.2)
Nasopharyngitis	4 (0.9)	5 (1.1)	9 (1.0)
Insomnia	6 (1.3)	1 (0.2)	7 (0.8)
Dizziness	5 (1.1)	1 (0.2)	6 (0.7)
Myalgia	5 (1.1)	0	5 (0.6)
Nausea	5 (1.1)	1 (0.2)	6 (0.7)
Asthenia	1 (0.2)	6 (1.3)	7 (0.8)

Most common is defined according to % in at least one treatment group.
Number (%) of Participants with AEs, sorted by decreasing frequency for preferred term based on AZD7442 group.
Participants with multiple events in the same preferred term are counted only once in that preferred term.
Includes adverse events that occurred through Key Secondary DCO.
COVID-19 AEs represent a deterioration of pre-existing COVID-19 disease.
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; MedDRA, Medical Dictionary for Regulatory Activities; N, number of participants in treatment group.
Source: Table 14.3.2.3.2A

Treatment-emergent Adverse Events by Severity

In TACKLE, a Grade 3 AE was defined as a severe event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the participant. A Grade 4 AE was defined as an event, and/or its immediate sequelae that is associated with an imminent risk of death (see table below).

Table 41 Number of Participants with Grade 3-4 Adverse Events, by System Orgam Class and Preferred Term (Safety Analysis Set), TACKLE

System Organ Class/Preferred Term	Number (%) of Participants [a]		
	EVUSHELD (N = 452)	Placebo (N = 451)	Total (N = 903)
Participants with any Grade 3 or 4 AE	27 (6.0)	43 (9.5)	70 (7.8)
Blood and lymphatic system disorders	1 (0.2)	0	1 (0.1)
Anaemia of malignant disease	1 (0.2)	0	1 (0.1)
Cardiac disorders	2 (0.4)	1 (0.2)	3 (0.3)
Acute myocardial infarction	1 (0.2)	0	1 (0.1)
Angina pectoris	1 (0.2)	0	1 (0.1)
Arrhythmia	0	1 (0.2)	1 (0.1)
Gastrointestinal disorders	0	1 (0.2)	1 (0.1)
Gastrointestinal haemorrhage	0	1 (0.2)	1 (0.1)

System Organ Class/Preferred Term	Number (%) of Participants [a]		
	EVUSHELD (N = 452)	Placebo (N = 451)	Total (N = 903)
Hepatobiliary disorders	0	2 (0.4)	2 (0.1)
Biliary colic	0	1 (0.2)	1 (0.1)
Portal vein thrombosis	0	1 (0.2)	1 (0.1)
Infections and infestations	19 (4.2)	38 (8.4)	57 (6.3)
COVID-19 pneumonia	19 (4.2)	29 (6.4)	48 (5.3)
COVID-19	0	8 (1.8)	8 (0.9)
Disseminated tuberculosis	0	1 (0.2)	1 (0.1)
Superinfection bacterial	0	1 (0.2)	1 (0.1)
Injury, poisoning and procedural complications	0	1 (0.2)	1 (0.1)
Forearm fracture	0	1 (0.2)	1 (0.1)
Metabolism and nutrition disorders	1 (0.2)	0	1 (0.1)
Hyperkalaemia	1 (0.2)	0	1 (0.1)
Nervous system disorders	1 (0.2)	4 (0.9)	5 (0.6)
Loss of consciousness	0	1 (0.2)	1 (0.1)
Migraine	0	1 (0.2)	1 (0.1)
Optic neuritis	0	1 (0.2)	1 (0.1)
Superior sagittal sinus thrombosis	0	1 (0.2)	1 (0.1)
Syncope	1 (0.2)	0	1 (0.1)
Renal and urinary disorders	1 (0.2)	1 (0.2)	2 (0.2)
Nephrolithiasis	1 (0.2)	0	1 (0.1)
Ureteric obstruction	0	1 (0.2)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	1 (0.2)	0	1 (0.1)
Pulmonary embolism	1 (0.2)	0	1 (0.1)
Vascular disorders	3 (0.7)	0	3 (0.3)
Circulatory collapse	1 (0.2)	0	1 (0.1)
Hypertensive crisis	1 (0.2)	0	1 (0.1)
Peripheral artery thrombosis	1 (0.2)	0	1 (0.1)

[a] Number (%) of Participants with a Grade 3 or 4 AE, sorted alphabetically by SOC, and within each SOC, PTs sorted by decreasing frequency.

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

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

The rate of Adverse Events with grade 3 or 4 increased minimally in both treatment groups until Key Secondary DCO and remained higher in the placebo group. Of note, two additional cases with cardiac disorders were reported in the placebo group, i.e. 3/451 (0.7%) in the placebo group and 2/452 (0.4 %) patients in the Evusheld group experienced Grade 3 or 4 AEs in the Cardiac disorders SOC. No additional severe AEs related to thrombosis or embolism were reported until Key Secondary DCO (see table below).

Table 42 Number of Participants with Grade 3-4 Adverse Events, by System Orgam Class and Preferred Term (Safety Analysis Set), Key Secondary DCO

System Organ Class/Preferred Term	Number (%) of Participants [a]		
	AZD7442 (N = 452)	Placebo (N = 451)	Total (N = 903)
Participants with any Grade 3 or 4 AE	31 (6.9)	48 (10.6)	79 (8.7)
Blood and lymphatic system disorders	1 (0.2)	1 (0.2)	2 (0.2)
Anaemia of malignant disease	1 (0.2)	0	1 (0.1)
Blood loss anaemia	0	1 (0.2)	1 (0.1)
Cardiac disorders [b]	2 (0.4)	3 (0.7)	5 (0.6)
Arrhythmia	0	2 (0.4)	2 (0.2)
Acute myocardial infarction	1 (0.2)	0	1 (0.1)
Angina pectoris	1 (0.2)	0	1 (0.1)
Cardiac failure	0	1 (0.2)	1 (0.1)
Gastrointestinal disorders	0	1 (0.2)	1 (0.1)
Gastrointestinal haemorrhage	0	1 (0.2)	1 (0.1)
Hepatobiliary disorders	0	2 (0.4)	2 (0.2)
Biliary colic	0	1 (0.2)	1 (0.1)

System Organ Class/Preferred Term	Number (%) of Participants [a]		
	AZD7442 (N = 452)	Placebo (N = 451)	Total (N = 903)
Portal vein thrombosis	0	1 (0.2)	1 (0.1)
Immune system disorders	1 (0.2)	0	1 (0.1)
Allergy to arthropod sting	1 (0.2)	0	1 (0.1)
Infections and infestations	21 (4.6)	38 (8.4)	59 (6.5)
COVID-19 pneumonia	19 (4.2)	29 (6.4)	48 (5.3)
COVID-19	0	8 (1.8)	8 (0.9)
Bacterial diarrhoea	0	1 (0.2)	1 (0.1)
Cellulitis	1 (0.2)	0	1 (0.1)
Disseminated tuberculosis	0	1 (0.2)	1 (0.1)
Gastroenteritis viral	1 (0.2)	0	1 (0.1)
Pneumonia bacterial	1 (0.2)	0	1 (0.1)
Superinfection bacterial	0	1 (0.2)	1 (0.1)
Injury, poisoning and procedural complications	1 (0.2)	2 (0.4)	3 (0.3)
Forearm fracture	0	1 (0.2)	1 (0.1)
Foreign body in gastrointestinal tact	0	1 (0.2)	1 (0.1)
Hip fracture	1 (0.2)	0	1 (0.1)
Metabolism and nutrition disorders	1 (0.2)	0	1 (0.1)
Hyperkalaemia	1 (0.2)	0	1 (0.1)
Nervous system disorders	2 (0.4)	4 (0.9)	6 (0.7)
Loss of consciousness	0	1 (0.2)	1 (0.1)
Migraine	0	1 (0.2)	1 (0.1)
Optic neuritis	0	1 (0.2)	1 (0.1)
Presyncope	1 (0.2)	0	1 (0.1)
Superior sagittal sinus thrombosis	0	1 (0.2)	1 (0.1)
Syncope	1 (0.2)	0	1 (0.1)
Psychiatric disorders	1 (0.2)	0	1 (0.1)
Bipolar disorder	1 (0.2)	0	1 (0.1)
Renal and urinary disorders	1 (0.2)	1 (0.2)	2 (0.2)
Nephrolithiasis	1 (0.2)	0	1 (0.1)
Ureteric obstruction	0	1 (0.2)	1 (0.1)

Reproductive system disorders	0	1 (0.2)	1 (0.1)
Adenomyosis	0	1 (0.2)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	1 (0.2)	1 (0.2)	2 (0.2)
Acute pulmonary oedema	0	1 (0.2)	1 (0.1)
Pulmonary embolism	1 (0.2)	0	1 (0.1)
Vascular disorders	2 (0.4)	0	2 (0.2)
Hypertensive crisis	1 (0.2)	0	1 (0.1)
Peripheral artery thrombosis	1 (0.2)	0	1 (0.1)

[a] Number (%) of participants with a Grade 3 or 4 AE, sorted alphabetically by SOC, and within each SOC, PTs sorted by decreasing order of total frequency.

[b] For further details on Cardiac disorders see Section 12.3.2 on SAEs and Participant narratives in Section 14.4. A summary of the AE angina pectoris is described below this table.

Participants with multiple events of the same preferred term are counted only once in that preferred term.
Participants with events in more than one preferred term within the same SOC were counted only once in that SOC row.
Includes adverse events that occurred through the Key Secondary DCO.
AE severity ratings are defined in Protocol Section 8.3.2.
COVID-19 AEs represent a deterioration of pre-existing COVID-19 disease.
MedDRA version 24.0.
AE, adverse event; COVID-19; coronavirus disease 2019; DCO, data cut-off; MedDRA, Medical Dictionary for Regulatory Activities; N, number of participants in treatment group; PT, preferred term; SAE, serious adverse event; SOC, system organ class.
Source: Table 14.3.3.3A

Treatment-emergent Adverse Events with Possible Relationship

The proportion of participants with AEs that were possibly related to the IMP were similar between the total Evusheld group and the pooled placebo group (5.1% vs. 4.7%), see table below (Table 14.3.1.4.)

Table 14.3.2.4 Number of Participants with Adverse Events, Assessed by Investigator as Possibly Related to IMP by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class / Preferred Term	Number (%) of Participants[a] AZD7442 (N=452)	Placebo (N=451)	Total (N=903)
Participants with any possibly related AE[b]	23 (5.1)	21 (4.7)	44 (4.9)
Cardiac disorders	0	1 (0.2)	1 (0.1)
Palpitations	0	1 (0.2)	1 (0.1)
General disorders and administration site conditions	19 (4.2)	14 (3.1)	33 (3.7)
Injection site pain	8 (1.8)	10 (2.2)	18 (2.0)
Injection site erythema	2 (0.4)	2 (0.4)	4 (0.4)
Energy increased	1 (0.2)	2 (0.4)	3 (0.3)
Injection site discomfort	2 (0.4)	1 (0.2)	3 (0.3)
Injection site bruising	1 (0.2)	1 (0.2)	2 (0.2)
Injection site haematoma	1 (0.2)	1 (0.2)	2 (0.2)
Pyrexia	2 (0.4)	0	2 (0.2)
Asthenia	0	1 (0.2)	1 (0.1)
Injection site hypoaesthesia	1 (0.2)	0	1 (0.1)
Injection site induration	1 (0.2)	0	1 (0.1)
Injection site inflammation	1 (0.2)	0	1 (0.1)
Injection site nodule	1 (0.2)	0	1 (0.1)
Injection site warmth	0	1 (0.2)	1 (0.1)
Malaise	1 (0.2)	0	1 (0.1)
Musculoskeletal and connective tissue disorders	0	1 (0.2)	1 (0.1)
Pain in extremity	0	1 (0.2)	1 (0.1)
Nervous system disorders	2 (0.4)	2 (0.4)	4 (0.4)
Dizziness	2 (0.4)	0	2 (0.2)

Nervous system disorders *(continued)*			
Dysaesthesia	0	1 (0.2)	1 (0.1)
Headache	0	1 (0.2)	1 (0.1)
Skin and subcutaneous tissue disorders	2 (0.4)	5 (1.1)	7 (0.8)
Rash	1 (0.2)	1 (0.2)	2 (0.2)
Dermatitis allergic	0	1 (0.2)	1 (0.1)
Erythema	1 (0.2)	0	1 (0.1)
Prurigo	0	1 (0.2)	1 (0.1)
Pruritus	0	1 (0.2)	1 (0.1)
Rash pruritic	0	1 (0.2)	1 (0.1)
Vascular disorders	0	1 (0.2)	1 (0.1)
Hypertension	0	1 (0.2)	1 (0.1)

a. Number (%) of participants with possibly related AE, sorted alphabetically by SOC, and within each SOC, PTs sorted by decreasing order of total frequency.
b. Possibly related, as assessed by the investigator.
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 only terms with at least one possibly related AE.
Includes adverse events that occurred through end of study.
Percentages are based on the total numbers of participants in the treatment group (N).
IMP Investigational medicinal product.
MedDRA version 24.0.

At the Key Secondary DCO, Adverse events considered possibly related to IMP were and unchanged from the Primary DCO.

Serious adverse event/deaths/other significant events

Serious adverse events

The table below summarises all patients who experienced a serious adverse event (SAE) including fatal events. The analysis of SAEs, having a focus on cardiac and thrombo-embolic events, shows that the number of patients with SAEs was numerically lower in the Evusheld group compared with the placebo group. Overall, 3 patients experienced cardiac events, 1/451 (0.2%) in the placebo group, and 2/452 (0.4%) in the Evusheld group (Acute myocardial infarction, acute myocardial infarction and acute left ventricular failure); 2 of these patients died (see section below), the other patient recovered.

Thromboembolic SAEs were reported in 4 participants: 2/451 (0.4%) in the placebo group and 2 in the AZD7442 group (0.4%). SAEs in the Evusheld group were COVID-19 pneumonitis and Pulmonary embolism (recovered) and peripheral artery thrombosis (recovered).

None of these SAEs were assessed as possibly related to IMP by the Investigator.

Table 43 Serious Adverse Events, by System Organ Class and Preferred Term – Safety Analysis Set, TACKLE

System Organ Class/Preferred Term	Number (%) of Participants [a]		
	EVUSHELD (N = 452)	Placebo (N = 451)	Total (N = 903)
Participants with any SAE	33 (7.3)	54 (12.0)	87 (9.6)
Blood and lymphatic system disorders	1 (0.2)	0	1 (0.1)
Anaemia of malignant disease	1 (0.2)	0	1 (0.1)
Cardiac disorders	2 (0.4)	1 (0.2)	3 (0.3)
Acute myocardial infarction	2 (0.4)	0	2 (0.2)
Acute left ventricular failure	1 (0.2)	0	1 (0.1)

System Organ Class/Preferred Term	Number (%) of Participants [a]		
	EVUSHELD (N = 452)	Placebo (N = 451)	Total (N = 903)
Arrhythmia	0	1 (0.2)	1 (0.1)
Gastrointestinal disorders	0	2 (0.4)	2 (0.2)
Gastrointestinal haemorrhage	0	1 (0.2)	1 (0.1)
Oesophageal varices haemorrhage	0	1 (0.2)	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)
Hepatobiliary disorders	0	2 (0.4)	2 (0.2)
Biliary colic	0	1 (0.2)	1 (0.1)
Portal vein thrombosis	0	1 (0.2)	1 (0.1)
Infections and infestations	25 (5.5)	47 (10.4)	72 (8.0)
COVID-19 pneumonia	23 (5.1)	37 (8.2)	60 (6.6)
COVID-19	1 (0.2)	9 (2.0)	10 (1.1)
Appendicitis	1 (0.2)	0	1 (0.1)
Disseminated tuberculosis	0	1 (0.2)	1 (0.1)
Post-acute COVID-19 syndrome	0	1 (0.2)	1 (0.1)
Septic shock	0	1 (0.2)	1 (0.1)
Superinfection bacterial	0	1 (0.2)	1 (0.1)
Injury, poisoning and procedural complications	0	2 (0.4)	2 (0.2)
Forearm fracture	0	1 (0.2)	1 (0.1)
Jaw fracture	0	1 (0.2)	1 (0.1)
Musculoskeletal and connective tissue disorders	1 (0.2)	0	1 (0.1)
Immobilisation syndrome	1 (0.2)	0	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)
Nervous system disorders	1 (0.2)	3 (0.7)	4 (0.4)
Loss of consciousness	0	1 (0.2)	1 (0.1)
Optic neuritis	0	1 (0.2)	1 (0.1)
Superior sagittal sinus thrombosis	0	1 (0.2)	1 (0.1)
Syncope	1 (0.2)	0	1 (0.1)
Renal and urinary disorders	2 (0.4)	1 (0.2)	3 (0.3)
Chronic kidney disease	1 (0.2)	0	1 (0.1)

System Organ Class/Preferred Term	Number (%) of Participants [a]		
	EVUSHELD (N = 452)	Placebo (N = 451)	Total (N = 903)
Nephrolithiasis	1 (0.2)	0	1 (0.1)
Ureteric obstruction	0	1 (0.2)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	1 (0.2)	1 (0.2)	2 (0.2)
Pneumothorax	0	1 (0.2)	1 (0.1)
Pulmonary embolism	1 (0.2)	0	1 (0.1)
Vascular disorders	3 (0.7)	0	3 (0.3)
Circulatory collapse	1 (0.2)	0	1 (0.1)
Hypertensive crisis	1 (0.2)	0	1 (0.1)
Peripheral artery thrombosis	1 (0.2)	0	1 (0.1)

[a] Number (%) of Participants with an SAE, 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 one preferred term within the same SOC will be counted only once in that SOC row.

Includes adverse events that occurred through end of study.

AE severity ratings and AESIs are defined in the Protocol (see Appendix 16.1.1, Section 8.3.2 and Section 8.3.4, TACKLE CSR in Module 5.3.5.1).

MedDRA version 24.0.

COVID-19, coronavirus disease 2019; N, Number of participants in treatment group, PT, referred term; SAE, Serious adverse event, SOC, system organ class.

Source Table 14.3.4.1, TACKLE CSR in Module 5.3.5.1

Until the Key Secondary DCO 7 (1.5%) participants in each group reported additional SAEs, reporting the following PTs (more than 1 PT may have been reported by a participant):

- AZD7442 group: cholecystitis chronic (2 participants), bipolar disorder, circulatory collapse cellulitis, colorectal cancer metastatic, gastroenteritis viral, hip fracture, pneumonia bacterial, presyncope.
- Placebo group: arrhythmia, blood loss anaemia, cardiac failure, bacterial diarrhoea, diabetic retinopathy, sinusitis, foreign body in gastrointestinal tract, intravertebral disc protrusion, abortion spontaneous, disorientation, acute pulmonary oedema, adenomyosis.

As mentioned above, the number of participants with Cardiac disorders SOC SAEs was 2/452 (0.4%) in the AZD7442 group and 3/451 (0.7%) in the placebo group, i.e. 2 additional SAEs were reported between both DCOs in the placebo group. All cardiac related SAEs occurred in participants with elevated cardiovascular risk (eg, age > 65 years, cardiac history, and hypertension) and were confounded by medical history. None of the Cardiac disorders SAEs were assessed as possibly related to IMP by the Investigator. No further thromboembolic events were reported.

Deaths

The table below summarizes all participants who experienced a SAE with subsequent fatal outcome during the TACKLE study. At the time of DCO, a total of 12/451 (1.3%) participants had died, 6/452 (1.3%) in the Evusheld group and 6/451 (1.3%) in the placebo group. None of the AEs leading to death were assessed as possibly related to IMP by the Investigator.

There were 3 non-COVID-19 deaths in the EVUSHELD group, 1 (0.2%) due to acute left ventricular failure (), 1 (0.2%) due to sudden cardiac death (), and 1 (0.2%) due to progression of malignant neoplasm ().

Table 44 Number of Participants with Adverse Events with Outcome of Death, by System Orgam Class and Preferred Term (Safety Analysis Set), TACKLE

System Organ Class/Preferred Term	Number (%) of Participants [a]		
	EVUSHELD (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.

12 deaths are reported in this table, while the disposition table reports 11 deaths. The discrepancy is due to one patient experiencing an AE which lead to death before DCO, while death occurred after DCO.

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

Participants with events in more than one 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.

All participants who died are recorded below, with relevant data on their treatment history in the study, and the Investigator's opinion on the likelihood of a causal relationship between death and study treatment.

Table 45 Individual Data for Death- Full Analysis Set, TACKLE

Individual Data for Death (FAS), Primary Analysis DCO

Planned treatment	AE Preferred term	Primary cause of death	Secondary cause of death	Considered related to IMP by Investigator
AZD7442 600 mg	COVID-19 pneumonia	Respiratory failure due to COVID-19 pneumonia	Unknown cause of death	N
AZD7442 600 mg	Acute left ventricular failure	Acute left ventricular failure	Acute myocardial infarction	N
AZD7442 600 mg	Malignant neoplasm progression	Cancer of the middle third of the stomach	Cachexia	N
AZD7442 600 mg	COVID-19	Respiratory distress	NA	N
AZD7442 600 mg	Sudden cardiac death	Sudden cardiac death	NA	N
AZD7442 600 mg	COVID-19 pneumonia	COVID-19, pneumonia	NA	N
Placebo	COVID-19 pneumonia	Bilateral pneumonia due to COVID-19	NA	N
Placebo	COVID-19 pneumonia	Respiratory failure	NA	N
Placebo	Septic shock	Septic shock	Unknown	N
Placebo	COVID-19	Progression of covid19	Hypoxemia	N
Placebo	COVID-19 pneumonia	COVID-19	Unknown	N
Placebo	COVID-19 pneumonia	Not reported	Not reported	N

[a] AE was ongoing at time of database lock, and was reported as outcome death after database lock.

AE, adverse event; COVID-19, coronavirus disease 2019; DCO, data cut-off; FAS, full analysis set; N, No; NA, not applicable.

Source: Appendix 16.2.3.1, Appendix 16.2.5.1, Appendix 16.2.6.1.2, and Appendix 16.2.7.1

At the time of the Key Secondary DCO, 7/452 (1.5%) participants in the AZD7442 group and 6/451 (1.3%) participants in the placebo group had an SAE with an outcome of death, thus one death following metastatic colorectal cancer in the AZD7442 group was reported between the Primary and Key Secondary DCOs which was considered unrelated by the Investigator (see table below).

TABLE 45 B

Individual Data for Death (FAS), Key Secondary Analysis DCO

Planned treatment	SAE Preferred term	Primary cause of death	Secondary cause of death	Considered related to IMP by Investigator
AZD7442 600 mg	COVID-19 pneumonia	Respiratory failure due to COVID-19 pneumonia	Unknown cause of death	N
AZD7442 600 mg	Acute left ventricular failure	Acute left ventricular failure	Acute myocardial infarction	N
AZD7442 600 mg	Gastric cancer [a]	Cancer of the middle third of the stomach	Cachexia	N
AZD7442 600 mg	COVID-19	Respiratory distress	NA	N
AZD7442 600 mg	Sudden cardiac death	Sudden cardiac death	NA	N
AZD7442 600 mg	COVID-19 pneumonia	COVID-19, pneumonia	NA	N
AZD7442 600 mg	**Colorectal cancer metastatic**	**Colorectal cancer IVst/cT3N0M1 (hep)/pT3N2b worsening**	**Multiple organ failure**	**N**
Placebo	COVID-19 pneumonia	Bilateral pneumonia due to COVID-19	NA	N
Placebo	COVID-19 pneumonia	Respiratory failure	NA	N
Placebo	Septic shock	Septic shock	Unknown	N
Placebo	COVID-19	Progression of COVID-19	Hypoxemia	N
Placebo	COVID-19 pneumonia	COVID-19	Unknown	N
Placebo	COVID-19 pneumonia	COVID-19	Not reported	N

[a] Reported previously as Malignant neoplasm progression.

Text in bold indicates the death that occurred between the Primary DCO and Key Secondary DCO.

COVID-19, coronavirus disease 2019; DCO, data cut-off; FAS, full analysis set; N, No; NA, not applicable; SAE, serious adverse event.

Source: Appendix 16.2.3.1A, Appendix 16.2.5.1A, Appendix 16.2.6.1.2A, and Appendix 16.2.7.1A

Adverse Events of Special Interest

The overall number of participants who experienced Adverse events of special interest (AESI) are listed in the table below. Overall, AESIs were balanced between the treatment groups.

Table 46 Number of Participants with Adverse Events of Special Interest by Category and Preferred Term (Safety Analysis Set), TACKLE

System Organ Class/Preferred Term	Number (%) of Participants [a]		
	EVUSHELD (N = 452)	Placebo (N = 451)	Total (N = 903)
Participants with any AESI	15 (3.3)	15 (3.3)	30 (3.3)
General disorders and administration site conditions	14 (3.1)	13 (2.9)	27 (3.0)
Injection site pain	8 (1.8)	10 (2.2)	18 (2.0)
Injection site erythema	2 (0.4)	2 (0.4)	4 (0.4)
Injection site discomfort	2 (0.4)	1 (0.2)	3 (0.3)
Injection site bruising	1 (0.2)	1 (0.2)	2 (0.2)
Injection site haematoma	1 (0.2)	1 (0.2)	2 (0.2)
Injection site induration	1 (0.2)	0	1 (0.1)
Injection site inflammation	1 (0.2)	0	1 (0.1)
Injection site nodule	1 (0.2)	0	1 (0.1)
Injection site warmth	0	1 (0.2)	1 (0.1)
Skin and subcutaneous tissue disorders	1 (0.2)	2 (0.4)	3 (0.3)
Dermatitis allergic	0	1 (0.2)	1 (0.1)
Erythema	1 (0.2)	0	1 (0.1)
Rash	0	1 (0.2)	1 (0.1)

[a] Number (%) of participants with an AESI, 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 one preferred term within the same SOC will be counted only once in that SOC row.

Includes adverse events that occurred through end of study.

AESIs include injection site reactions, and anaphylaxis and other serious hypersensitivity reactions, including immune complex disease. See details in the Protocol (see Appendix 16.1.1, Section 8.3.4, TACKLE CSR in Module 5.3.5.1).

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AESI, adverse events of special interest; N, number of participants in treatment group; PT, preferred term; SOC, system organ class.

Source: Table 14.3.6.1, TACKLE CSR in Module 5.3.5.1

At the Key Secondary DCO, the number of participants with AESIs was 15 (3.3%) in both groups, and unchanged from the Primary DCO.

Adverse Drug Reactions

Hypersensitivity, injection related, and injection site reactions were analyzed due to a possible causal relationship with Evusheld based on its mechanism of action. Potential risks associated risks are also anaphylaxis and Antibody-dependent enhancement (ADE). True hypersensitivity reactions were observed very rarely throughout the study and balanced between treatment groups. Overall, no amendment of SmPC section 4.8 as to the frequency of observed adverse reactions is deemed necessary.

Table 47 Summary n(%) of Hypersensitivity and Injection Site Reaction, TACKLE

Preferred Term[a]	Number (%) of Participants	
	EVUSHELD (N = 452)	Placebo (N =451)
Hypersensitivity [b]	2 (0.4)	3 (0.7)
Rash	2 (0.4)	3 (0.7)
Urticaria	0	0
Injection site reaction [b]	11 (2.4)	11 (2.4)
Injection site erythema	2 (0.4)	2 (0.4)
Injection site induration	1 (0.2)	0
Injection site pain	8 (1.8)	10 (2.2)
Injection site pruritus	0	0
Injection site reaction	0	0
Injection related reaction	0	0

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

[b] Grouped terms.

AE, adverse event, AESI, adverse events of special interest; eCRF, electronic Case Report Forms, N, number of participants in treatment group; PT, preferred term; SOC, system organ class.

Laboratory findings

Hematology

In TACKLE, hematology and coagulation parameters were to be measured at Day 1, Day 3, Day 6, Day 15, Day 29, Day 169 and Day 366. None of the studies showed apparent differences between treatment groups in mean hematology or coagulation parameters over time, or in shifts from normal to high/low in individual parameters. In addition, there were no individual clinically important abnormalities.

Clinical Chemistry

In TACKLE, clinical chemistry parameters (sodium, potassium, urea, creatinine, albumin, calcium, phosphate, glucose, and CRP) were also to be measured at Day 1, Day 3, Day 6, Day 15, Day 29, Day 169 and Day 366. None of the studies showed apparent differences between treatment groups in mean clinical chemistry parameters over time, or in shifts from normal to high/low in individual parameters.

Urinalysis

In TACKLE, urinalysis (glucose, protein, and blood) were to be measured at Day 1, Day 6, Day 15, Day 29, Day 169 and Day 366. None of the studies showed apparent differences between treatment groups in mean urinal analysis parameters over time, or in shifts from normal to high/low in individual parameters.

No notable differences between the treatment groups in clinical chemistry, clinical hematology, coagulation, urinalysis or liver enzymes (ALT and AST) versus total bilirubin.

Vital signs

In TACKLE, Vital signs (BP, pulse rate, oral temperature, and respiratory rate) were to be measured prior to study start and at Day 1, Day 3, Day 6, Day 15, Day 29, Day 85, Day 169 and Day 366; furthermore,

Triplicate 12-lead ECG was to be measured prior to study start and at Day 29 and Day 366. Clinically significant ECG abnormalities were reported for 5 participants in the EVUSHELD group and 2 participants in the placebo group. Of these, the ECG abnormalities were reported as AEs in one participant in the EVUSHELD group (at Day 29); atrioventricular block first degree and nodal rhythm. Both AEs were reported as mild in severity, non-serious, were assessed by the Investigator as not related to IMP and were not associated with any clinical symptoms or other AEs. The participant was a 38-year-old Asian male smoker with no prior cardiac history or concomitant medications at baseline, no other AEs on study and had otherwise normal QTc, QTcF and QTcB values at the time of the events.

Vital signs (BP, pulse rate, oral temperature, and respiratory rate) were measured at different time points. There were no treatment-related effects on vital signs or ECGs observed following administration of Evusheld until the Key Secondary DCO.

Safety in special populations

Intrinsic factors

Study participants were mostly patients with a high risk of progression to severe COVID-19, i.e. 89.6% were defined to be as high-risk based on the following criteria:

- Persons aged 65 years and older at randomization
- Persons aged < 65 years and having at least one of the following conditions: obesity with BMI > 30, smoking, cancer, diabetes, cardiovascular disease including history of stroke, chronic lung disease or moderate to severe asthma, hypertension, chronic kidney disease, 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, sickle cell disease.

The table below provides a summary of TEAEs in this subgroup:

Table 48 Number of Participants with Adverse Events in any Category, High Risk Subgroup (Safety Analysis Set), TACKLE

AE Category	Number (%) of Participants [a]		
	EVUSHELD (N = 404)	Placebo (N = 405)	Total (N = 809)
Participants with any AE	119 (29.5)	144(35.6)	263 (32.5)
Any AE with outcome = death	6 (1.5)	6 (1.5)	12 (1.5)
Any SAE (including events with outcome = death)	31 (7.7)	48 (11.9)	79 (9.8)
Any AE leading to study withdrawal	5 (1.2)	7 (1.7)	12 (1.5)
Any AESI	13 (3.2)	10 (2.5)	23 (2.8)
Any related AE [b]	20 (5.0)	16 (4.0)	26 (4.4)
Any related SAE [b]	0	0	0
Any related AESI [b]	13 (3.2)	10 (2.5)	23 (2.8)
Any Grade 3 or 4 AE	25 (6.2)	39 (9.6)	64 (7.9)
Any Grade 3 or 4 AESI	0	0	0
Any related Grade 3 or 4 AE [b]	0	0	0
Any related Grade 3 or 4 AESI [b]	0	0	0

[a] Participants with multiple events in the same category are counted only once in that category. Participants with events in more than one category are counted once in each of those categories.

[b] Possibly related, as assessed by the Investigator.

Includes adverse events that occurred through end of study.

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

AE severity ratings and AESIs are defined in the Protocol (see Appendix 16.1.1, Section 8.3.2 and Section 8.3.4, TACKLE CSR in Module 5.3.5.1).

AE, adverse event; AESI, adverse events of special interest; N, numbers of participants in the treatment group; SAE, serious AE.

Extrinsic Factors

Based on the mechanism of action, PK/PD results, and AEs presented in the tables, there is no reason to believe that the safety profile of Evusheld will be affected by diet, concomitant medication use or other extrinsic factors.

Safety related to Drug-drug interactions

No interaction studies have been conducted. There is a theoretical risk that Evusheld may interfere with COVID-19 vaccines of Evusheld. Data from animal studies reported that prior administration did not alter the cellular or the humoral immune responses elicited by subsequent COVID-19 vaccinations. The available clinical safety data did not reveal any additional safety concerns for the participants who were exposed to Evusheld in PROVENT and STORM CHASER and then subsequently received COVID-19 vaccines. Based on these results, Evusheld is not anticipated to interfere with vaccine safety or efficacy.

Discontinuation due to adverse events

Table below summarizes the TEAEs that lead to study discontinuation in the overall and high-risk subpopulation and excluding TEAEs after unblinding of the study subjects.

Table 49 Number of Participants with Adverse Events leading to Discontinuation of Study, by System Organ Class and Preferred Term (Safety Analysis Set)

Table 14.3.5.1 Number of Participants with Adverse Events Leading to Discontinuation of Study, by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class / Preferred Term	Number (%) of Participants[a]		
	AZD7442 (N=452)	Placebo (N=451)	Total (N=903)
Participants with any AE leading to discontinuation of study	5 (1.1)	7 (1.6)	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)	1 (0.2)	2 (0.2)
Asthenia	0	1 (0.2)	1 (0.1)
Sudden cardiac death	1 (0.2)	0	1 (0.1)
Infections and infestations	2 (0.4)	6 (1.3)	8 (0.9)
COVID-19 pneumonia	1 (0.2)	4 (0.9)	5 (0.6)
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)

Table 14.3.5.1.1 Number of participants with Adverse Events Leading to Discontinuation from Study, by System Organ Class and Preferred Term (Safety Analysis Set - High Risk Group)

System Organ Class / Preferred Term	Number (%) of Participants[a]		
	AZD7442 (N=404)	Placebo (N=405)	Total (N=809)
Participants with any AE leading to discontinuation of study	5 (1.2)	7 (1.7)	12 (1.5)
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)	1 (0.2)	2 (0.2)
Asthenia	0	1 (0.2)	1 (0.1)
Sudden cardiac death	1 (0.2)	0	1 (0.1)
Infections and infestations	2 (0.5)	6 (1.5)	8 (1.0)
COVID-19 pneumonia	1 (0.2)	4 (1.0)	5 (0.6)
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)

Table 14.3.5.1.2 Number of Participants with Adverse Events Leading to Discontinuation of Study, by System Organ Class and Preferred Term - Excluding AEs After Unblinding (Safety Analysis Set)

System Organ Class / Preferred Term	Number (%) of Participants[a]		
	AZD7442 (N=452)	Placebo (N=451)	Total (N=903)
Participants with any AE leading to discontinuation of study	5 (1.1)	7 (1.6)	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)	1 (0.2)	2 (0.2)
Asthenia	0	1 (0.2)	1 (0.1)
Sudden cardiac death	1 (0.2)	0	1 (0.1)
Infections and infestations	2 (0.4)	6 (1.3)	8 (0.9)
COVID-19 pneumonia	1 (0.2)	4 (0.9)	5 (0.6)
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 an AE leading to discontinuation, 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 through end of study.
N Number of participants in treatment groups.
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Few patients discontinued the study due to adverse events. Slightly more participants of the placebo group discontinued the study (1.6% vs. 1.1%). In the Evusheld group, all early study terminations were results of fatal, unrelated adverse events (see above). In the placebo group, reasons were related to

COVID-19. Results were consistent with the high-risk group and after unblinding. The number was unchanged until Key Secondary DCO.

Supportive data

Supportive safety data come from Phase 1 study D8850C00001, a randomized, double-blind, placebo-controlled, dose escalation study to evaluate the safety, tolerability, and PK of EVUSHELD in healthy adults aged 18 to 55 years of age. Interim results of this study were presented in the initial marketing authorization. Participants were followed up until Day 361 for safety, including recording of AEs and SAEs, and collection of blood samples for PK and ADAs.

Adverse events

TEAEs were generally mild or moderate in intensity; there were no AEs of severe intensity. 26/50 (52.0%) participants receiving Evusheld reported at least one AE. No deaths, SAEs or TEAS leading to treatment discontinuation were reported (see table below).

Table 50 Number of Participants with Adverse Events in any category (Safety Analysis Set)

Table 14.3.1.1 Number of subjects with adverse events in any category (Safety analysis set)

	Number (%) of subjects*						
AE category	AZD7442 300 mg, IM (N = 10)	AZD7442 300 mg, IV (N = 10)	AZD7442 1000 mg, IV (N = 10)	AZD7442 3000 mg, IV (N = 10)	AZD7442 3000 mg, IV co-administered (N = 10)	AZD7442 Total (N = 50)	Placebo (N = 10)
Any AE	2 (20.0)	5 (50.0)	6 (60.0)	7 (70.0)	6 (60.0)	26 (52.0)	8 (80.0)
Any AE with outcome = death	0	0	0	0	0	0	0
Any SAE (including events with outcome = death)	0	0	0	0	0	0	0
Any AE leading to discontinuation of IMP	0	0	0	0	0	0	0
Any AE leading to dose interruption	0	0	0	1 (10.0)	0	1 (2.0)	0
Any AE leading to dose reduction	0	0	0	0	0	0	0
Any AE leading to withdrawal from study	0	0	0	0	0	0	0

The table below displays the number of participants with TEAE, by preferred term and maximum reported intensity.

Table 51 Number of Participants with Adverse Events by Preferred Term and Maximum Reported Intensity (Safety Analysis Set), Phase I study

Preferred Term [b]	Number (%) of Participants [a]						
	300 mg EVUSHELD, IM (N = 10)	300 mg EVUSHELD, IV (N = 10)	1000 mg EVUSHELD, IV (N = 10)	3000 mg EVUSHELD, IV (N = 10)	3000 mg EVUSHELD, IV co-administered (N = 10)	Total EVUSHELD (N = 50)	Pooled Placebo (N = 10)
Headache	0	2 (20.0)	2 (20.0)	3 (30.0)	0	7 (14.0)	2 (20.0)
Back pain	0	0	1 (10.0)	1 (10.0)	1 (10.0)	3 (6.0)	1 (10.0)
Diarrhoea	0	1 (10.0)	1 (10.0)	0	1 (10.0)	3 (6.0)	0
Fatigue	0	0	1 (10.0)	0	2 (20.0)	3 (6.0)	0
Abdominal distension	0	2 (20.0)	0	0	0	2 (4.0)	0
Abdominal pain	0	2 (20.0)	0	0	0	2 (4.0)	0
Myalgia	0	0	1 (10.0)	1 (10.0)	0	2 (4.0)	0
Nasopharyngitis	1 (10.0)	0	1 (10.0)	0	0	2 (4.0)	0
Toothache	0	0	2 (20.0)	0	0	2 (4.0)	0
Abdominal discomfort	0	0	1 (10.0)	0	0	1 (2.0)	0
Application site irritation	0	0	1 (10.0)	0	0	1 (2.0)	0
Arthralgia	0	0	0	1 (10.0)	0	1 (2.0)	0
COVID-19	0	0	0	0	1 (10.0)	1 (2.0)	0
Constipation	0	0	0	1 (10.0)	0	1 (2.0)	0
Coronavirus infection	1 (10.0)	0	0	0	0	1 (2.0)	0
Dizziness	0	0	0	0	1 (10.0)	1 (2.0)	0
Energy increased	0	1 (10.0)	0	0	0	1 (2.0)	0
Heavy menstrual bleeding	0	0	0	1 (10.0)	0	1 (2.0)	0
Hypoaesthesia	0	0	0	0	1 (10.0)	1 (2.0)	0
Ligament sprain	0	0	1 (10.0)	0	0	1 (2.0)	0
Lymphadenitis	0	1 (10.0)	0	0	0	1 (2.0)	0
Malaise	0	1 (10.0)	0	0	0	1 (2.0)	0
Memory impairment	1 (10.0)	0	0	0	0	1 (2.0)	0
Muscle strain	0	0	0	0	1 (10.0)	1 (2.0)	0
Musculoskeletal discomfort	0	0	0	0	1 (10.0)	1 (2.0)	0
Myxoid cyst	0	0	0	0	1 (10.0)	1 (2.0)	0
Nail infection	0	1 (10.0)	0	0	0	1 (2.0)	0
Nasal congestion	0	0	0	1 (10.0)	0	1 (2.0)	1 (10.0)
Nausea	0	1 (10.0)	0	0	0	1 (2.0)	0
Oral herpes	0	0	0	1 (10.0)	0	1 (2.0)	0
Pain in extremity	0	1 (10.0)	0	0	0	1 (2.0)	0
Rhinorrhoea	0	0	0	1 (10.0)	0	1 (2.0)	0
Rotator cuff syndrome	0	0	0	1 (10.0)	0	1 (2.0)	0
Seasonal allergy	0	0	0	1 (10.0)	0	1 (2.0)	0
Tooth infection	0	0	0	1 (10.0)	0	1 (2.0)	0
Tooth repair	0	0	1 (10.0)	0	0	1 (2.0)	0
Tremor	0	1 (10.0)	0	0	0	1 (2.0)	0
Urinary tract infection	0	1 (10.0)	0	0	0	1 (2.0)	1 (10.0)
Dysmenorrhoea	0	0	0	0	0	0	1 (10.0)
Injury	0	0	0	0	0	0	1 (10.0)

Oropharyngeal pain	0	0	0	0	0	0	2 (20.0)
Palpitations	0	0	0	0	0	0	1 (10.0)
Paraesthesia	0	0	0	0	0	0	1 (10.0)
Vessel puncture site pain	0	0	0	0	0	0	1 (10.0)
Vitreous floaters	0	0	0	0	0	0	1 (10.0)
Vulvovaginal candidiasis	0	0	0	0	0	0	1 (10.0)

[a] Each participant is represented with the maximum reported intensity only for each preferred term. Participants with events in more than one preferred term are counted once in each of those preferred terms.

[b] Sort: Preferred term in decreasing order of frequency in the Total EVUSHELD column. In case of ties, alphabetical preferred term.

Each participant is counted only once (by their maximum reported intensity) within a treatment group in this overall summary.

Summary includes AEs starting on or after the first administration of IMP.

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AE, adverse event; COVID-19, coronavirus disease 2019; IM, intramuscular; IMP, investigational medicinal product; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; N, number of participants in Safety Analysis Set; %, number of participants in each category expressed as a percentage of N.

Source: Table 14.3.1.3, D8850C00001 CSR in Module 5.3.3.1

Use in Pregnancy and Lactation

There are limited data from the use of Evusheld in pregnant women. In line with ICH S6, 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, or the effects of the drug on milk production. There are no data on the effects of tixagevimab and cilgavimab on human fertility.

Up to the January 2022 DCO, 3 pregnancies were reported during the study, 2 for placebo and one for AZD7442. The outcome of 2 of the pregnancies was unknown at the time of this report, one pregnancy in a women assigned to the placebo group ended in a miscarriage 154 days after administration of the study drug.

Overdose

Evusheld is administered IM as single dose by medical professionals, therefore the risk of overdosing is deemed low. In the Phase I clinical trials, doses up to 3000 mg intravenously (1500 mg each of tixagevimab and cilgavimab) have been administered without dose-limiting toxicity.

Withdrawal and Rebound

Due to the single dose nature of Evusheld, there is no risk of withdrawal. To date, there are no data to support the occurrence of ADE of infection following administration.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No studies on the effects of Evusheld on the ability to drive or use machines have been performed; however, based on the AE profile observed, Evusheld appears to have no or negligible influence on the ability to drive or use machines.

Post marketing experience

Cumulatively, until 28◦February◦2022, 100 case reports (33 serious and 67 non-serious) with 258 events have been received. The sources include serious and non-serious reports from spontaneous sources and serious adverse reactions from non-interventional post-authorization/marketing studies.

Of the 100 reports, 98 reports were received from United States, 1 from France and 1 from Germany.

The most commonly reported SOCs were general disorders and administration site conditions (62), Nervous system disorders (36), Gastrointestinal disorders (20), Investigations (19), and Respiratory, thoracic and mediastinal disorders (19).

Most commonly reported PTs were Headache (18), Fatigue (16), Chills (11), COVID-19 (11) and Pyrexia (6). There have been 3 reports of cases with fatal outcome. The first case was headache, second case sudden death and third case brain death and subarachnoid haemorrhage. All events were confounded by patients' medical history and provided limited information precluding appropriate medical assessment.

Serious hypersensitivity including anaphylaxis is a potential risk and included under Section 4.4 (Warnings and Precautions) of Evusheld Core Data Sheet (CDS). Cumulatively, 5 reports with 9 events of serious hypersensitivity have been received. The events are being closely monitored as part of ongoing surveillance.

Cardiac and thromboembolic events are considered a potential risk for EVUSHELD and are closely monitored as a part of ongoing safety surveillance. Cumulatively, 7 serious reports with 8 events have been received from spontaneous sources and early access program. The reports included PTs, each, of Acute myocardial infarction, Cardiac arrest, Cardiac disorder, Palpitations, Haemorrhagic stroke, Transient ischaemic attack, Pulmonary embolism and Deep vein thrombosis. In all of these cases, the patients had one or several relevant risk factors (such as age, obesity, hypertension, malignancies), relevant medical history (such as transient ischaemic attack, atrial fibrillation etc), were confounded by concomitant medications, or had limited information:

- A spontaneous report of cardiac arrest (PT: cardiac arrest) was received from a health care professional in the regarding a >60-year-old subject with medical history included atrial fibrillation, hypertension, stage 3 chronic kidney disease, pneumoconiosis and lung transplant. Thirteen days after EVUSHELD administration, the patient was in normal sinus rhythm and hemodynamically stable and had a cardiac arrest later that day.
- A spontaneous report of an acute anterior ST-elevation myocardial infarction (PT: acute myocardial infarction) was received from a health care professional in the regarding a 60 to 70-year-old subject with medical history of hypertension, non-Hodgkin's lymphoma, and obesity. One day after EVUSHELD administration, the patient experienced an acute anterior ST-elevation myocardial infarction (PT: acute myocardial infarction). The outcome was reported as resolved.
- A report of massive haemorrhagic cerebrovascular accident (PT: haemorrhagic stroke) was received from a health care professional regarding an > 80 -year-old subject enrolled in early access program with medical history of pulmonary embolism, hypertension, congenital mitral valve incompetence, hypogammaglobulinemia, aortic rupture, pneumococcal sepsis. Co-suspect medications included apixaban and immunoglobulins. Nineteen days after EVUSHELD administration and 4 days after the patient was hospitalized for monthly infusion of immunoglobulins, the patient died following massive haemorrhagic cerebrovascular accident.
- A report of deep vein thrombosis (PT: deep vein thrombosis) and pulmonary embolism (PT: pulmonary embolism) was received from a health care professional regarding a 70 to 80 -year-old subject enrolled in early access program in with medical history of chronic lymphocytic leukaemia,

breast cancer, radiotherapy, endometrial cancer, autoimmune thyroiditis, haemolytic anaemia. Three days after EVUSHELD administration, the patient experienced deep vein thrombosis and pulmonary embolism. The outcome of the events was reported as recovered.

- A report of transient ischemic attack (PT: transient ischaemic attack) was received from a health care professional regarding an > 80 -year-old subject enrolled in early access program in with medical history of breast cancer, renal transplant, transient ischaemic attack, substance use, hypertension, hypercholesterolaemia, and chronic obstructive pulmonary disease. One day after the EVUSHELD administration, the patient experienced transient ischemic attack and was reported to have recovered on the same day.
- A report of septal hyperpnoea (PT: cardiac disorder) was received from a health care professional regarding a 70 to 80 -year-old subject enrolled in the early access program in with a medical history of diabetes mellitus type 2, hypertension, nephropathy and hypercholesterolaemia. The patient was reported to have a fall, pulmonary oedema and septal hyperpnoea one day after receiving EVUSHELD.
- A consumer report of (PT: palpitations) was received from a 40 to 50 -year-old subject. Five minutes after EVUSHELD administration, the patient had an allergic reaction and reported that her "heart was racing" (PT: palpitations), "had chest pain in waves" (PT: chest pain), probably had ischemia (preferred term: ischaemia). The patient also reported nausea. She was treated with famotidine and diphenhydramine intravenously and was observed in the emergency room for a couple of hours. The patient recovered from the events after approximately 30 minutes.

2.5.1. Discussion on clinical safety

The applicant initially provided clinical safety data from the primary analysis of the ongoing Phase 3 study TACKLE with a data cut-off (DCO) of 21 August 2021 together with the results of the Phase 1 study D8850C00001 as supportive safety data. With the responses to the first List of Questions, the applicant provided updated safety data analyses based on the Key Secondary Data Cut-Off of 14 January 2022. The safety follow-up is currently still ongoing.

Beside the hitherto collected post-marketing data, the safety database comprises clinical data from 4210 participants that were enrolled in Phase 3 studies PROVENT and STORM CHASER (prophylaxis setting). In both Phase 3 studies PROVENT and STORM CHASER, most frequently reported TEAEs were headache, fatigue and cough with similar percentages regarding the different treatment groups after the sequential administration of 150 mg of tixagevimab and 150 mg of cilgavimab IM. In both Phase 3 studies, the majority of participants had TEAEs that were mild to moderate in intensity. Serious adverse events occurred rarely in both treatment groups. In the PROVENT study, a slight imbalance between the treatment arms regarding cardiac disorders (coronary and thrombo-embolic events) had been observed; this is reflected in section 4.4 of the SmPC. Adverse events that were classified as Adverse Drug Reactions were Hypersensitivity and Injection site reactions in line with available safety data and the mode of action. The hitherto collected safety data suggested a tolerable safety profile, however further (long-term) data are necessary to fully characterize the safety profile.

In TACKLE, 903 patients were randomized 1:1 to one of both treatment arms and received 300 mg tixagevimab and 300 mg cilgavimab or matching placebo as subsequent IM injections. The safety follow-up is currently limited to 170 days, the overall follow-up is planned for 457 days. Thus, final results are expected after the read out of the completed safety follow-up. The 58 patients enrolled in the First-in-human study D8850C00001 completed the safety follow-up of 361 days.

Overall, the demographic and patient characteristics were fairly balanced between the treatment groups, however, elderly participants ≥65 years are considered underrepresented with 12.8% compared with the age structure of the European (20%≥65 years) and US population (16%≥65 years). Elderly >65 years are at higher risk for more serious COVID-19 due to immunosenescence. The majority were considered high-risk participants with ≥1 co-morbidity at baseline, had negative serum serology for SARS-CoV-2, were White and resided in Europe or Latin America. COVID-Symptoms were present for 5 days (mean) and classified as ambulatory mild disease based on WHO Clinical Progression Scale. Uses of this scale has challenges as regards quantification of subjective symptoms, the variability in the use of life support measures based on co-morbidities and different therapeutic approaches etc., however, as it focuses on variables relevant to most subjects in COVID trials it is considered useful to identify and follow-up a study population within these trials. Most common risk factors were obesity, hypertension, diabetes, chronic lung disease/asthma, and these were balanced across the treatment arms. The chosen risk factor are considered relevant to define a high-risk population in need for rapid treatment. The overall study population is relatively similar to the PROVENT population as regards the percentage distribution of the diverse risk factors. However, in TACKLE the population was younger (mean 46 vs. 57 years), and more patients were classified to be at high risk of progression to severe COVID-19 (89.6% vs. 77.5%).

The proportion of patients who experienced treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) and TEAEs leading to early study termination was smaller in the Evusheld group compared with the placebo group. Adverse events of special interest (AESIs) and TEAEs with fatal outcome were balanced between both treatment groups. Slightly more treatment related TEAEs were observed in the Evusheld group. No treatment-related SAE was reported, and related AESI were also balanced.

TEAEs that occurred more frequently in the placebo group were COVID-19 pneumonia and COVID-19. In the Evusheld group, Diabetes mellitus, Insomnia and Dizziness were more frequently reported, however, differences were modest between both treatment groups. Grade 3/4 TEAEs were rare, more often reported in the placebo group and no specific pattern is apparent. A subgroup analysis of TEAEs was requested for the non-high risk group; within this population the Evusheld group reported AEs less frequently and thus, seemed to have a more favorable safety profile, however, patients numbers are limited.

Pyrexia was reported in 2 subjects in Evusheld group and none in placebo (0.2% vs 0%) and both cases were considered related by the investigator. The applicant provided information of time-to-onset relative to Evusheld administration and time to resolution. Following the assessment of the supplementary data, PT 'pyrexia' as ADR for Evusheld is not supported. The same applies for PTs 'fatigue' and 'cough'.

Serious Adverse events occurred more frequently in the placebo group. Due to an observed small imbalance of cardiac SAEs in the PROVENT study, special focus laid on the analysis of cardiac disorders. The applicant clarified that at the time of Key Secondary DCO of 14 January 2022, the number of participants with Cardiac disorders SAEs was 2/452 (0.4%) in the EVUSHELD and 3/451 (0.7%) in the placebo arm; 2 of these in the placebo group were reported between the Primary and Key Secondary DCOs. Thus, no imbalance is currently present that would necessitate amendments of the PI.

Thromboembolic SAEs were reported in 4 participants: 2 in the Evusheld group (Pulmonary embolism and peripheral artery thrombosis), and 2 in the placebo group (Portal vein thrombosis and superior sagittal sinus thrombosis). The applicant provided additional information on all thromboembolic events (including non-serious AEs) occurring in TACKLE study. Recent data suggest that these events were related to confounding factors resulting from comorbidities. There is no nonclinical evidence by which Evusheld would impact the risk of cardiovascular or thromboembolic events. Non-clinical and clinical data do not allow at this point to draw a strong conclusion regarding the association between Evusheld and thromboembolic events.

Deaths due to serious adverse events were rare and numerically balanced between the treatment groups. Reasons for death in the Evusheld group were acute left ventricular failure, sudden cardiac death, and progression of gastric cancer, COVID-19 pneumonia, and respiratory distress due to COVID-19. At Key secondary DCO, one additional death had occurred in the Evusheld group following metastatic colorectal cancer. None of these serious adverse events was considered related to the study drug by the investigators; this assessment can be accepted regarding the narratives.

AESI were very rarely observed throughout this study until the Key Secondary DCO. Individual cases of injection site reactions were reported with similar frequencies across both treatment arms. Antibody-dependent enhancement of disease is a concern to disease control which has been reported in vitro and in vivo for different viruses with distinct features such as preferential replication in macrophages, ability to establish persistence, and antigenic diversity (Dengue, Zika, SARS-CoV-1). However, based on current knowledge, a potential pathological relevance of ADE during SARS-CoV-2 infection seems unlikely (Arvin et al., 2020, Zhou et al., 2021). In synopsis with the available safety data that suggest that no clinical evidence for ADE in association with Evusheld administration is present, it is acknowledged that the specific investigation of ADE was not performed.

The results of the clinical laboratory and vital signs evaluations presented in the CRS suggest that no clinically relevant changes in laboratory findings were observed throughout the clinical study until the Key secondary DCO, neither in the overall nor in the high-risk study population.

The safety results of the high-risk group are consistent with the overall study population, which is plausible as 89.6% of the participants are included in this 'subgroup'. In Phase 1 study D8850C00001, more TEAEs were reported in the placebo group (80% vs. 52%). Overall, there were no clinically meaningful imbalances in AEs across treatment groups and TEAEs that were possibly related to the study drug. Taking into account the lack of SAEs, deaths or premature study discontinuation, it seems that Evusheld was well tolerated in healthy adults. No specific safety concerns arise from this treatment setting.

The applicant was asked to discuss the inclusion of PT 'Dizziness' and 'Pyrexia' in section 4.8, however, as discussed by the applicant, a causal association between both TEAEs and Evusheld has not been established which is agreed. Based on the provided safety data, no further amendment of SmPC section 4.8 is deemed necessary.

Overall, few patients discontinued the study due to adverse events. Slightly more participants of the placebo group discontinued the study (1.6% vs. 1.1%). In the Evusheld group, all early study terminations were results of fatal, unrelated adverse events (see above). In the placebo group, reasons were related to COVID-19. Results were consistent with the high-risk group and after unblinding.

No data on drug-drug interaction is available from the TACKLE study and no interaction studies had been conducted in the PROVENT or STORM CHASER studies. This is reflected in the SmPC.

Data on pregnant women were provided upon request. Individual cases were reported with unknown outcome apart from one case. This information is considered of no consequence for the PI.

The safety results of the TACKLE study are consistent with those of PROVENT and STORM CHASER Evusheld seems to be well-tolerated if administered for the treatment of COVID-19 in non-hospitalized patients. This is in line with the benign safety profile for other monoclonal antibodies directed against external targets.

2.5.2. Conclusions on clinical safety

The overall safety profile of Evusheld 600 mg IM for the treatment of mild to moderate COVID-19 seems consistent with that reported in participants who had received 300 mg EVUSHELD for COVID-19 prophylaxis. All 'other concerns' related to the characterization of the study population and the safety profile were solved.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version 2.0 with this application.

The PRAC considered that the risk management plan version 2.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 2.0 with the following content:

Safety concerns

Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	Use in pregnant women

Pharmacovigilance plan

Ongoing and planned additional pharmacovigilance activities

Study [Status]	Summary of objectives	Safety concerns addressed	Milestones	Due dates for EMA
Category 1 -– Not applicable				
Category 2 –– Not applicable				
Category 3 - Required additional pharmacovigilance activities –				
Study Code:- D8850R00006: A post-authorization Observational Study of Women exposed to EVUSHELD During Pregnancy **Status:** Planned	To evaluate obstetric, neonatal and infant outcomes among women exposed to EVUSHELD during pregnancy	Use in pregnant women	Protocol submission Final Report	30/09/2022 31/12/2027

Risk minimisation measures

Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
None	NA	NA
Important potential risks		
None	NA	NA
Missing information		
Use in pregnant-women	Routine Risk Minimization Measures: SmPC Section 4.6 and Package Leaflet Section 2	Additional Pharmacovigilance Activities: A post-authorization Observational Study of Women exposed to EVUSHELD During Pregnancy Final Report: 31/12/2027

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1,4.2,4.4, 4.8,4.9,5.1,5.2,6.3, 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make some editorial changes.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

2.7.2. Additional monitoring

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

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

2.7.3. Quick Response (QR) code

The review of the QR code request submitted by the MAH is presented in a separate attachment to this report.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The symptoms of COVID-19, if present, differ with severity of disease. The symptoms most frequently associated with symptomatic mild to moderate illness include fever, cough, fatigue, muscle or body aches, headache, sore throat, nasal congestion, shortness of breath or difficulty breathing, nausea, vomiting, diarrhea, and a loss in sense of taste or smell. COVID-19 is a systemic disease affecting not just the respiratory tract but also in myocardial, renal, neurologic, gastrointestinal, and pharyngeal tissues and where hACE2 receptors have been identified (Gupta et al 2020). Patients may progress to severe pneumonia or develop acute respiratory distress syndrome, which is the primary cause for respiratory failure, and direct organ damage by the virus likely contributes to multiorgan failure. Some people who recover from COVID-19 go on to suffer from symptoms long-term. Mortality risk factors associated with COVID 19 include age > 60 years (significantly greater for those 80 years and older), male sex, and chronic medical conditions including hypertension, diabetes, obesity, and cardiovascular disease (Zhou et al 2020a).

3.1.2. Available therapies and unmet medical need

As transmission continues and different variants of SARS-CoV-2 emerge, cases of severe disease and hospitalization, and in some countries, mortality, remain high. Breakthrough infections of fully vaccinated individuals continue to emerge both in the general population (Hacisuleyman et al 2021) and in high risk populations (Agha et al 2021, ACIP 2021). The latest variant of concern, the highly mutated Omicron variant and its lineages, has increased transmissibility versus the original and Delta strains (Garcia-Beltran et al 2022), with BA.4/5 fast becoming the dominant strain worldwide (WHO 2022b). Early data suggests that vaccine effectiveness is reduced against Omicron B.1.1.529 (Dejnirattisai et al 2021; Regev-Yochay et al 2022) and therefore is likely leading to breakthrough disease in a COVID-19 vaccinated/recovered population as well as in those who remain unvaccinated or unresponsive to vaccines. Despite the reduced severity seen with Omicron infections (Lauring et al 2022), certain individuals remain an increased risk of severe disease and includes, but is not limited to, the elderly, cancer patients as well as those with ongoing chronic health conditions. Globally, there is still a critical need to reduce hospitalizations and reduce the impact of COVID-19 on healthcare systems. Therefore, preventing progression of mild to moderate COVID-19 to severe disease remains a significant clinical need.

Clinical management of COVID-19 is based on supportive care and there are limited approved/authorized effective treatment interventions, which include antivirals as well as mAbs (eg, in some markets: remdesivir [VELKURY], PF07321332/ritonavir [PAXLOVID], regdanvimab [REGKIRONA], casirivimab and imdevimab [RONAPREVE], and sotrovimab [XEVUDY]), which results in healthcare resources being stretched (Tangcharoensathien et al 2021). Recent in vitro antiviral resistance studies have demonstrated that some mAbs in late clinical development, do not offer significant neutralization of the emergent SARS-CoV-2 Omicron subvariants and as a consequence are no longer available in some markets. Evusheld remains one of the only mAb products to retain neutralizing activity against the Omicron variant authentic virus in vitro, with comparable activity against Omicron BA.2 to the original strain (Case et al 2022) and also some residual activity against BA.4/5 although this seems to be more limited (Takashita et al 2022).

As the pandemic continues, and new variants emerge, there is a need for additional effective therapeutic antibodies that target different epitopes on the spike protein, and for people ineligible for antivirals, to prevent COVID-19 disease progression and its serious complications (Kim et al 2020).

Clinical benefit is likely to be achieved by treating patients early in their disease course while the disease is primarily driven by replication of SARS-CoV-2, before the innate immune/inflammatory response is triggered, and the disease progresses to severe illness requiring hospitalization. However, treatments available specifically in the outpatient setting are limited. Overall, despite effective vaccination programs, COVID-19 remains a global threat with significant numbers of patients contracting the disease. Early intervention is critical to prevent progression to severe disease, especially for those who are at high risk of severe COVID-19. There are limited treatment options available and, as variants emerge, there is a risk that treatments that are currently effective may not remain so, therefore further options that are effective against current variants are needed, including those available in the outpatient setting.

3.1.3. Main clinical study

Study D8851C00001 (TACKLE), an ongoing Phase III, randomized, double-blind, placebo-controlled, parallel-group, AstraZeneca-sponsored study in the treatment of mild to moderate COVID-19 provides key data supporting the efficacy and safety of Evusheld in this application. Approximately 90% of participants met the protocol definition of being at high risk of progression to severe COVID-19.

This Application includes the final CSR for the AstraZeneca-sponsored Phase I FTIH study (Study D8850C00001). An overview of these studies is provided in the table below.

Table 52 Studies with Evusheld included in the application.

Study/Sponsor/Status	Phase	Population	Success Criteria	Dose/Route of EVUSHELD and Number of Participants Exposed	Countries
D8851C00001 (TACKLE)/ AstraZeneca/ Ongoing (recruitment complete)[a]	III	Adults with mild to moderate COVID-19[b]	Statistically significantly lower incidence of the composite endpoint of either severe COVID-19 or death from any cause through Study Day 29 for EVUSHELD 600 mg IM than placebo	600 mg IM (N = 452), placebo (N = 451)	Argentina, Brazil, Czech Republic, Germany, Hungary, Italy, Japan, Mexico, Poland, Russian Federation, Spain, UK, Ukraine, and US
D8850C00001/ AstraZeneca/ Complete[c]	I	Healthy adult volunteers	Not applicable	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] First participant randomized 29 January 2021

[b] Mild to moderate COVID-19 population (TACKLE): outpatient adults (≥ 18 years) with a documented positive SARS-CoV-2 molecular test (antigen or nucleic acid) from a sample collected ≤ 3 days prior to study entry and with ≤ 7 days of symptoms of COVID-19 at study entry ('Day 1' symptom count starts from the first day of symptoms), plus the presence of select symptoms within 24 hours prior to Day 1. At least 60% of participants were to meet the protocol definition of being at high risk of progression to severe COVID-19 as defined in Section 4.1.

[c] First participant enrolled 18 August 2020

COVID-19, coronavirus disease 2019; IM, intramuscular; IV, intravenous; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; UK, United Kingdom; US, United States

3.2. Favourable effects

The percentage of subjects who experienced severe COVID-19 (defined as selected symptoms of pneumonia or signs of hypoxia plus score ≥5 on WHO COVID-19 progression scale) or death from any cause was reduced by Evusheld compared to placebo in the pivotal study TACKLE (primary endpoint):

- Treatment with Evusheld compared with placebo led to a 50.49% (95% CI: 14.56 to 71.31) RRR for developing severe COVID-19 or death from any cause in non-hospitalized adults who had been symptomatic for 7 days or less (modified FAS).

The study achieved statistically significant results in 4 supportive estimands:

- Treatment with Evusheld compared with placebo led to a 66.93% (95% CI: 31.11, 84.12) RRR for developing severe COVID-19 or death from any cause through Day 29 in non-hospitalized participants dosed ≤ 5 days from symptom onset (first supportive estimand).
- Treatment with Evusheld compared with placebo led to a 62.98% (95% CI: 29.45, 80.57) RRR for developing severe COVID-19 or death from any cause from Day 4 through Day 29 in non-hospitalized participants dosed ≤ 7 days from symptom onset (second supportive estimand).
- Treatment with Evusheld compared with placebo led to a 41.59% (95% CI: 5.01, 64.08) RRR for developing severe COVID-19 or death from any cause from through Day 29 in all randomized participants (third supportive estimand).
- Treatment with Evusheld compared with placebo led to a 61.26% (95% CI: 29.67, 78.66) RRR for developing severe COVID-19 or death from any cause from through Day 29 in non-hospitalized participants, who are seronegative at baseline, dosed ≤ 7 days from symptom onset (fourth supportive estimand).

The percentage of subjects who experienced death from any cause or hospitalization for COVID-19 complications or sequelae during the 168-day post-dose period (Day 1 to Day 169) was reduced by Evusheld compared to placebo in the pivotal study TACKLE (key secondary endpoint):

- Treatment with Evusheld compared with placebo led to a 49.11% (95% CI: 14.47, 69.72) RRR for the composite endpoint of either death or hospitalization for COVID-19 complications or sequelae through Day 169.

Evusheld treatment demonstrated a favourable effect on the secondary endpoint "Incidence of respiratory failure (defined as requirement for mechanical ventilation, ECMO, non-invasive ventilation, or high-flow nasal cannula oxygen delivery) through day 29":

- Treatment with Evusheld compared with placebo resulted in a 71.86% (95% CI 0.25 to 92.06) relative risk reduction for respiratory failure through day 29.

3.3. Uncertainties and limitations about favourable effects

Various design changes were conducted in the ongoing study. Some of the subjects were unblinded in the ongoing study and prior to key secondary endpoint analysis.

No adolescents, pregnant or breast-feeding women were included. Limited data on elderly is available.

The number of events was overall small. Furthermore, available data do not suffice to establish efficacy in several sub-populations.

The additional information for longer follow-up gained from the key secondary endpoint is considered small, as only one additional event was observed after the observation period for the primary endpoint.

A tendency for a negative effect of Evusheld was seen in relevant subgroups including subjects at highest age (above 75 years), seropositives, in patients infected with the alpha variant and subjects from European region.

No data are available on efficacy in previously vaccinated subjects. Furthermore, for these half-life extended antibodies there is a theoretical risk for PD interaction of Evusheld with subsequent COVID-19 vaccination (impaired cellular or humoral immune response) that has not been addressed in clinical trials.

Viral sequencing data from clinical trials are too limited to allow conclusion on clinical efficacy in treatment against certain VOC/VOI. No clinical data on latest variants of concern (including omicron sub-variants) are available.

Unfavourable effects

In the placebo arm, 6 (1.3%) patients and in the Evusheld arm, 7 (1.5%) patients died during the study as a result of serious adverse events. Reasons for death in the Evusheld group were acute left ventricular failure (1, 0.2%), sudden cardiac death (1, 0.2%), progression of gastric cancer (1, 0.2%), COVID-19 pneumonia (2, 0.4%), respiratory distress due to COVID-19 (1, 0.2%), and metastatic colorectal cancer (1, 0.2%). In the placebo group, 3 (0.7%) participants died due to COVID-19 pneumonia and respiratory failure, and 2 due to COVID-19 and septic shock, one cause was unknown.

Antibody-dependent disease enhancement was not investigated in the pivotal study.

3.4. Uncertainties and limitations about unfavourable effects

The proportion of patients that experienced any common treatment-emergent adverse event or any serious adverse event was higher in the placebo arm compared with the Evusheld arm. These differences remained until the Key Secondary DCO.

Adverse events of special interest were numerically balanced between the treatment groups.

SAEs were observed with a higher frequency in the placebo group. No treatment-related SAE was reported.

Severe TEAEs were rare, more often reported in the placebo group and no specific adverse events pattern is apparent. None of SAEs with a fatal outcome were considered related to the study drug.

The safety follow-up is currently restricted to 170 days, the overall follow-up is planned for 457 days.

The available data (in vitro, non-clinical, clinical) do not raise a concern regarding antibody-dependent disease enhancement for the time being. Available clinical data on anti-drug antibody formation after Evusheld administration is currently limited.

No clinical data is available for adolescents, and very limited data concerning pregnant, breastfeeding and elderly patients.

3.5. Effects Table

Table 53: Effects Table for Evusheld in treatment of adults and adolescents (aged 12 years and older weighing at least 40 kg) with COVID-19, who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID 19 (data cut-off: 21 August 2021 for efficacy and 14 January 2022 for safety)

Effect	Short description	Unit	Evusheld	PBO	Strength of evidence/ Uncertainties	References
Favourable Effects						
Severe COVID-19 or death from any cause by day 29	Percentage of subjects meeting the endpoint definition	%	5.4	9.2	difference (95% CI): 5.01 to 64.08; p-value 0.028/ Effect driven by Latin-American population; Efficacy in latest VOCs and seropositives unknown; Small	TACKLE third supportive estimand[a]

Effect	Short description	Unit	Evusheld	PBO	Strength of evidence/ Uncertainties	References
					number of events	
			4.4	8.9	difference (95% CI): 14.56 to 71.31; p-value 0.010 / Confirmed by all supportive analyses; Effect driven by Latin-American population; Efficacy in latest VOCs and seropositives unknown; Small number of events	TACKLE, primary analysis[b]
Unfavourable Effects						
Deaths	SAE with subsequent fatal outcome	%	1.5	1.3	No treatment-related SAEs	TACKLE Safety Analysis Set[c]
SAE	Any SAE	%	8.8	13.5	Limited follow-up data. Subject numbers balanced between groups within SOCs and PTs. No possibly related SAEs observed. No imbalance of cv or thromboembolic events.	TACKLE Safety Analysis Set[c]
Grade 3 / 4 TEAE	Any Grade 3 or 4 TEAE	%	6.9	10.6	Limited follow-up data. Subject numbers balanced between groups within SOCs and PTs. No possibly related Gr. 3/4 TEAEs observed.	TACKLE Safety Analysis Set[c]

Abbreviations: AE: Adverse Event, CI: confidence interval; cv: cardiovascular; PBO: placebo; TACKLE: pivotal phase 3 study, TEAE: treatment-emergent Adverse Event, PT: Preferred Term, SAE: Serious Adverse Event, VOCs: variants of concern

Notes:
a: in all randomized participants (FAS)
b: in non-hospitalized participants dosed ≤ 7 days from symptom onset (modified FAS)
c: the Safety Analysis Set consists of all participants who received at least one injection of study drug administration (verum or placebo) and is summarized according to the actual treatment received.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The primary endpoint of the pivotal study TACKLE, a composite of either severe COVID-19 or death from any cause through study Day 29, is a relevant measure of overall clinical status in patients with mild to moderate COVID-19 at baseline. Evusheld demonstrated a statistically significant effect with moderate effect size for this important endpoint. The supportive analyses confirmed the significance of the results related to the primary endpoint.

With regard to the generalizability of study results some uncertainties remain for the pre-specified subgroups with high-age (above 75 years), seropositivity and European region.

The results of the key secondary endpoint, as a measure of clinical worsening, can be considered supportive. There were signs of efficacy across secondary endpoints investigating development of COVID-19 symptoms. However, considering the magnitude of effect, observations on COVID-19 symptoms are considered of limited clinical relevance.

Efficacy data until day 29 are considered most relevant for the treatment of mild-moderate COVID-19.

Potential bias resulting from inadequate planning and partial unblinding did not have the potential to impact study results to an extent that would make the entire conclusion on efficacy questionable.

Lacking efficacy data in adolescents ≥40 kg may be compensated by popPK modelling. Based on theoretical considerations, adolescents are expected to profit from treatment in a similar way like adult patients. Currently available data and theoretical considerations did not identify specific safety issues.

Treatment of pregnant women was currently not investigated in the clinical trial setting. Lack of cross-reactivity in human foetal tissues suggests low risk to developing foetuses in pregnant women administered Evusheld. Nevertheless, currently available information without any clinical data is too limited to make a general treatment recommendation. Use in pregnancy is subject to Additional Pharmacovigilance Activities. Based on biological plausibility no risk for the breastfed infant is anticipated. Treatment in breast feeding women may be considered when clinically indicated.

There is a theoretical risk for PD interaction of Evusheld with COVID-19 vaccines (impaired cellular or humoral immune response) that has not been addressed in clinical trials. As clinical trial data for subsequently SARS-CoV-2 vaccinated individuals are lacking, treatment decisions or timing of such decisions will need to be based on local/national guidelines.

As no clinical efficacy data will be obtained for recent/upcoming viral variants, estimates on efficacy will need to rely on in vitro information and modelling/simulations. Information from clinical trials on efficacy against certain VOCs is limited. The risk of viral resistance will be adequately addressed post approval by "other forms of routine pharmacovigilance activities for lack of efficacy". Post-authorisation reviews of genomic databases such as GISAID for emerging Variants of Interest and Variants of Concern and subsequent phenotypic evaluation by use of in vitro assays are planned.

The submitted and currently available safety data resulting from the pivotal TACKLE study suggest a good tolerability and low immunogenic potential of Evusheld in the investigated adult (high-risk) population as the incidence of treatment-emergent adverse events, serious adverse events or adverse events leading to early study discontinuation was overall lower in the Evusheld group compared with the placebo group. Furthermore, no specific adverse event cluster was observed in the Evusheld group that would qualify for the determination of additional adverse drug reactions. Effects in patients with assumed immunosenescence (>65 years) and those classified as not being at high risk for developing severe COVID-19 are considered underrepresented, limiting the informative value of the data in these patients. The unfavourable effects seen in the TACKLE study population are similar to those of the PROVENT study keeping in mind, that the TACKLE population was overall younger and less prone to severe disease courses.

Deaths due to serious adverse events were rare, almost numerically balanced between the treatment groups and all considered unrelated to the study drug; this assessment is concurred for the time being. In contrast to the observations in the PROVENT study, serious cardiac adverse events were slightly more frequently observed in the placebo group of the TACKLE study, thus, no cardiac adverse effects of Evusheld are currently assumed based on the available safety data. No new thromboembolic events were

reported until the Key Secondary DCO; non-clinical and clinical data do not allow at this point to draw a strong conclusion regarding the association between Evusheld and thromboembolic events.

The hitherto known safety profile should be further characterised. Currently safety data in adolescents are lacking and sparse in pregnant/breastfeeding women and elderly. Long-term safety data are limited to 170 days and are expected to be updated after completion of the follow-up phase. Cardiac and thromboembolic events are continuously monitored.

3.6.2. Balance of benefits and risks

The effect of Evusheld on overall clinical status in mild to moderately ill COVID-19 patients at increased risk for progression to severe disease was considered to be clinically relevant. A single dose administration of Evusheld demonstrated a good safety profile with a manageable risk of hypersensitivity/application-related reactions that does not raise a specific concern. As all the requested changes were implemented in the SmPC; the benefit-risk balance is considered positive.

3.6.3. Additional considerations on the benefit-risk balance

None

3.7. Conclusions

The overall B/R of Evusheld is positive.

The following measures are considered necessary to address issues related to pharmacology:

- Bioanalytical reports for the determination of AZD8895 and AZD1061 human serum concentrations in TACKLE are currently outstanding and should be provided as soon as available (Q4, 2022) (**REC**).
- Final TACKLE CSR should be provided as soon as available. (**REC**).

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adults and adolescents (aged 12 years and older weighing at least 40 kg) with COVID-19, who do not require supplemental oxygen and are at increased risk of progressing to severe COVID-19. As a consequence, sections 4.1, 4.2, 4.4,4.8, 4.9, 5.1, 5.2 ,6.3, 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to make some editorial changes. Version 2.0 of the RMP has also been submitted.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion - "Evusheld/H/C/005788/II/0001"