Amsterdam, 30 January 2025
EMA/56406/2025
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Evusheld

International non-proprietary name: AZD7442 (tixagevimab and cilgavimab)

Procedure no.: EMA/H/C/5788/P46/024

Marketing authorisation holder (MAH): AstraZeneca

## Note

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



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| Status of this report and steps taken for the assessment | | | |
|---|---|---|---|
| **Current step** | **Description** | **Planned date** | **Actual Date** |
| ☐ | Start of procedure | 02/12/2024 | 02/12/2024 |
| ☐ | CHMP Rapporteur Assessment Report | 06/01/2025 | 06/01/2025 |
| ☐ | CHMP members comments | 20/01/2025 | 20/01/2025 |
| ☐ | Updated CHMP Rapporteur Assessment Report | 23/01/2025 | N/A |
| ☒ | CHMP adoption of conclusions: | 30/01/2024 | 30/01/2024 |

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# Abbreviations

| | |
|---|---|
| ADA | Anti-drug antibodies |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| CO | Clinical Overview |
| COVID-19 | Coronavirus disease 2019 |
| CSR | Clinical Study Report |
| EMA | European Medicines Agency |
| GA | Gestational Age |
| GCP | Good Clinical Practice |
| IM | Intramuscular |
| IMP | Investigational medicinal product |
| IV | Intravenous |
| nAb | Neutralizing antibodies |
| PD | Pharmacodynamic(s) |
| PIP | Paediatric Investigation Plan |
| PK | Pharmacokinetic(s) |
| RMP | Risk Management Plan |
| SAE | Serious adverse event |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SmPC | Summary of Product Characteristics |
| SOC | System Organ Class |
| TE-ADA+ | Treatment-emergent anti-drug antibodies positive |

# 1. Introduction

On 14 October 2024, the MAH submitted a completed paediatric study for D8850C00006 (TRUST), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview was also provided.

# 2. Scientific discussion

## *2.1. Information on the development programme*

The MAH stated that Study D8850C00006 (TRUST) entitled „Open-label, Uncontrolled, Single dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety of AZD7442 in Pediatric Participants Aged ≥ 29 Weeks Gestational Age to <18 Years" is a stand-alone study.

The MAH stated that the above-mentioned study is part of a clinical development program.

## *2.2. Information on the pharmaceutical formulation used in the study*

AZD7442 comprised two drug products supplied as separate vials of AZD8895 and AZD1061. Each vial contained a solution of 100 mg/mL active ingredient (AZD8895 or AZD1061), L-histidine, L-histidine-HCl, sucrose, polysorbate 80, and Water for Injection, pH 6.0.

The label claim volume for each vial was 1.5 mL and each vial contained 150 mg (nominal) of active ingredient. The dose levels were stratified by body weight range categories (prophylaxis of COVID-19/treatment of mild to moderate COVID-19: 60 to 600 mg IM or 50 to 440 mg IV; treatment of severe COVID-19: 60 to 600 mg IV).

## *2.3. Clinical aspects*

### 2.3.1. Introduction

The MAH submitted a final report for:

- Study number: D8850C00006 (TRUST)
  Title: „Open-label, Uncontrolled, Single dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety of AZD7442 in Pediatric Participants Aged ≥ 29 Weeks Gestational Age to <18 Years"

### 2.3.2. Clinical study

**Study D8850C00006 (TRUST) „Open-label, Uncontrolled, Single dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety of AZD7442 in Pediatric Participants Aged ≥ 29 Weeks Gestational Age to <18 Years"**

**Description**

Study D8850C00006 was conducted as a part of a pediatric program for EVUSHELD and both its drug substances tixagevimab and cilgavimab based on agreed Paediatric Investigation Plans (numbers: EMEA-003079-PIP01-22, EMEA-002900-PIP01-20 and EMEA-002925-PIP01-20 for EVUSHELD, tixagevimab and cilgavimab, respectively).

**Methods**

***Study design and participants***

This was a Phase I, open-label, uncontrolled, multi-country, multicenter, single dose study to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), safety, and tolerability of AZD7442 administered via intramuscular (IM) or intravenous (IV) routes in pediatric participants aged ≥ 29 weeks gestational age (GA) (infants born between GA of 29 weeks to full term) to < 18 years. Up to 3 cohorts of participants were planned to be enrolled based on the adult indication and dose (Fig. 1):

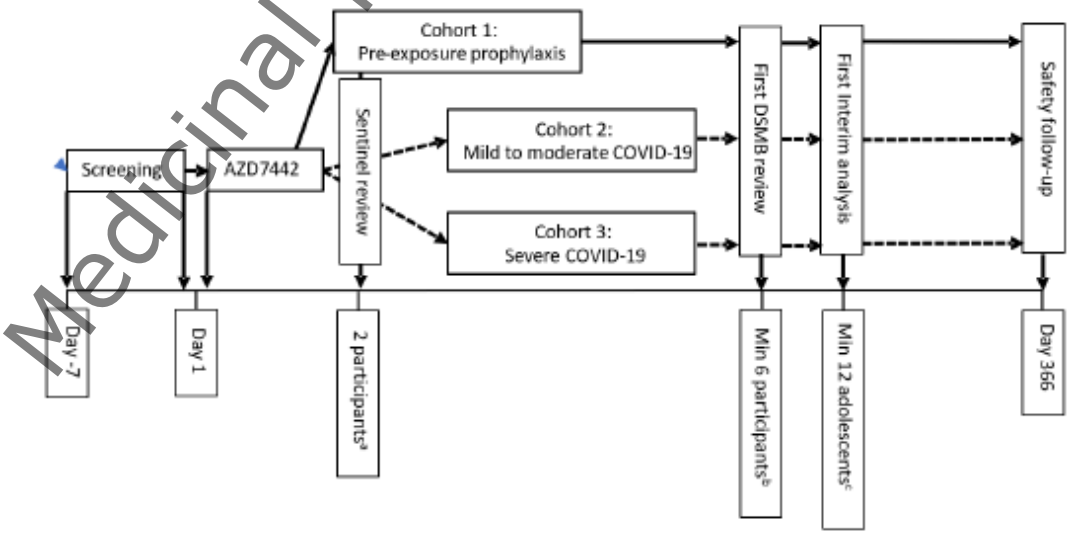
- Cohort 1: Participants who were severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) negative at screening and had not knowingly been exposed to a SARS-CoV-2 positive individual (pre-exposure prophylaxis).
- Cohort 2: Participants who were SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) positive at screening and had mild to moderate coronavirus disease 2019 (COVID-19).
- Cohort 3: Participants who were SARS-CoV-2 positive at screening and had severe COVID-19.

Both Cohort 1 and Cohort 2 were required to be at increased risk of developing severe COVID-19.

Note: The planned analyses for Cohort 3 were not conducted as Cohort 3 was not opened as part of this study.

Following a screening evaluation, which was planned to be conducted over one or more visits between Day -7 to Day 1, participants received a single dose of investigational medicinal product (IMP). After administration of the dose of IMP on Day 1, participants were monitored on site for at least 1 hour for general safety, including injection/infusion site reactions and hypersensitivity reactions (including anaphylaxis). Participants were to be followed up until Study Day 366 for safety, including recording of adverse events (AEs) and serious adverse events (SAEs), and collection of blood samples for PK, PD, and anti-drug antibodies (ADAs), and exploratory efficacy endpoints (which were expected to support the extrapolation of the efficacy data observed in adults to children). The expected maximum duration of the study for each participant, including screening, was 388 days. Planned analyses for ADA nAb to AZD7442 in serum data were not conducted for this study.

**Figure 1 Flow Chart of Study Design**



[a] The sentinel review was conducted on the first 2 participants with 24 hours of safety data.
[b] The first DSMB review was to take place once 14 days of safety data were available for ≥ 6 participants.
[c] The first interim analysis was conducted once 92 days of safety data were available for ≥ 12 adolescents. All available PK and safety data from all age groups at the data cut-off date were included in the analysis.

Cohort 1: Participants who were SARS-CoV-2 RT-PCR negative at screening and had not knowingly been exposed to a SARS-CoV-2 positive individual and who were at increased risk of developing severe COVID-19.

Cohort 2: Participants who were SARS-CoV-2 RT-PCR positive at screening and had mild to moderate COVID-19 and who were at increased risk of developing severe COVID-19. Cohort 2 was only to start recruiting if this indication is progressed in adults.

*Cohort 3: Participants who were SARS-CoV-2 RT-PCR positive at screening and had severe COVID-19. Cohort 3 was only to start recruiting if this indication had progressed in adults. Cohort 3 was not opened as part of this study.

Recruitment was planned to be paused during the sentinel review but not during the DSMB reviews. Refer to section 9.9.1.1 for details on change in the study schedule.

Pharmacokinetic sampling was kept to a minimum due to the age of the population under study: one sample on Day 1 for participants receiving an IV infusion, one sample during the first 2 weeks for all participants (at either Day 4, 8, 11, or 15, spread across participants), then one sample at Day 31, 92, 183, and 366 (i.e., the total number of samples per participant was up to 5 samples for IM administration and 6 samples for IV administration due to the additional sample taken at the end of the infusion on Day 1).

***Treatments***

AZD7442 was supplied as separate vials of AZD8895 and AZD1061. Each vial contained a solution of 100 mg/mL active ingredient (AZD8895 or AZD1061), histidine/histidine hydrochloride sucrose, PS80, pH 6.0. The dose levels were stratified by body weight range categories (prophylaxis of COVID-19/treatment of mild to moderate COVID-19: 60 to 600 mg IM or 50 to 440 mg IV; planned treatment of severe COVID 19: 60 to 600 mg IV). Investigational medicinal product (IMP) was administered as 2 consecutive IM injections (AZD8895 followed by AZD1061) or a single IV infusion (AZD8895 and AZD1061 concurrently).

Each participant received a single dose of IMP on Day 1 and the expected maximum duration of the study for each participant, including screening, was 388 days.

Table 1: Planned Doses in the Different Indications in the Pediatric PK/PD/Safety Study

| | Prophylaxis (matching adult dose of 600 mg IM) | | Treatment – Outpatient (matching adult dose of 600 mg IM) | | Treatment – Inpatient (matching adult dose of 600 mg IV) |
|---|---|---|---|---|---|
| Participant weight range | Planned IM dose (mg) | Planned IV dose (mg) | Planned IM dose (mg) | Planned IV dose (mg) | Planned IV dose (mg) |
| ≥ 1.5 to < 5 kg | 60 | 50 | 60 | 50 | 60 |
| ≥ 5 to < 15 kg | 150 | 110 | 150 | 110 | 150 |
| ≥ 15 to < 40 kg | NA[a] | 300 | NA[a] | 300 | 400 |
| ≥ 40 kg | 600 | 440 | 600 | 440 | 600 |

[a] In participants who weigh ≥ 15 to < 40 kg, IM dosing is not feasible for the treatment indication due to the maximum volume required for injection.

IM, intramuscular; IV, intravenous; PD, pharmacodynamic; PK, pharmacokinetic.

***Objective(s)***

The study objectives and endpoints listed in Table 2 reflect the objectives and endpoints as described in the CSP (Version 5.0, 25 October 2023). All changes to the endpoints were documented before final CDL and are summarized in Section 9.9 of the CSR. Data for the exploratory endpoints are presented where available.

Table 2: Objectives and Endpoints

| Objectives | Endpoints |
|---|---|
| **Primary - All Cohorts** | |
| • To evaluate the serum concentrations of AZD7442 after a single IM or IV dose in pediatric participants | • Serum concentrations of AZD7442 at specified time points during the study period when administered as a single IM or IV dose<br>• Serum PK parameters (if data permits): $C_{max}$, $t_{max}$, $t_{½}$, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $t_{last}$, $\%AUC_{ex}$, and:<br>° for IM: CL/F, and $V_z/F$<br>° for IV: CL, and $V_{ss}$<br>• Model-derived predicted serum AZD7442 concentrations and $AUC_{0\text{-inf}}$ |
| • To evaluate the safety and tolerability of AZD7442 after a single IM or IV dose in pediatric participants | • TEAEs, SAEs, and AESIs<br>• Safety laboratory parameters (hematology, clinical chemistry, coagulation, and urinalysis); 12-lead safety ECG; vital signs (BP, pulse rate, tympanic membrane temperature, and respiratory rate), and physical examination [a] |
| **Secondary – All Cohorts** | |
| • To evaluate the PD of AZD7442 after a single IM or IV dose in pediatric participants [a] | • Titer of SARS-CoV-2 neutralizing antibodies [a] |
| • To evaluate the immunogenicity profile of AZD7442 after a single IM or IV dose in pediatric participants | • Incidence of ADA and neutralizing antibodies to AZD7442 in serum [b] |
| **Secondary – Cohort 1 (Prophylaxis)** | |
| • To evaluate the incidence of SARS-CoV-2 infections with or without COVID-19 symptoms after a single IM or IV dose of AZD7442 in pediatric participants | • Incidence of SARS-CoV-2 infections with and without COVID-19 symptoms |
| **Secondary – Cohort 2 and Cohort 3 (Treatment)** [a] | |
| • To quantify SARS-CoV-2 viral loads after a single IM or IV dose of AZD7442 in pediatric participants [a] | • Change from baseline to Day 8 in viral load as measured by qRT-PCR [a] |
| • To evaluate the proportion of participants with progression of COVID-19 after a single IM or IV dose of AZD7442 in pediatric participants [a] | • Proportion of participants with progression of COVID-19 through Day 29 [a] |
| • To evaluate COVID-19-related death after a single IM or IV dose of AZD7442 in pediatric participants [a] | • The incidence of COVID-19-related death occurring after dosing with IMP through 90 days [a] |
| **Secondary – Cohort 3 (Severe COVID-19)** [a] | |
| • To evaluate the time to sustained recovery from severe COVID-19 after a single IM or IV dose of AZD7442 in pediatric participants [a] | • Time to sustained recovery (defined as being discharged from the index hospitalization, followed by being alive and home for 14 consecutive days) [a] |

| | |
|---|---|
| **Exploratory** | |
| • To evaluate the concentrations of AZD7442 in nasal fluid after a single IM or IV dose in pediatric participants | • Nasal concentrations of AZD7442 at specified time points during the study period when administered as a single IM or IV dose |

[a] No objectives and endpoints related to Cohort 3 are included in this CSR, as Cohort 3 was not opened as part of this study. For details, refer to Table 11 of Section 9.9.2.2 of this CSR or Section 2 of the SAP report (Appendix 16.1.9).

[b] Planned analyses for ADA nAb to AZD7442 in serum data were not conducted for this study. Refer to Section 9.9.2.3.

***Outcomes/endpoints***

See Table 2.

***Sample size***

A complete description and justification of the methods used to determine the planned sample size, together with their derivations or the reference source, is provided in Section 9.2 of the CSP. In this study, approximately 120 participants were planned to be enrolled to achieve at least 100 evaluable participants.

The total sample size of 100 participants across all pediatric age groups and cohorts is the minimum number required to adequately characterize the AZD7442 safety profile in pediatric participants following IM or IV administration (based on FDA and EMA Pediatric Committee feedback). Furthermore, preliminary PK simulations based on adult PK data determined that with a minimum sample size of 24 participants (n = 6, per route of administration, in the 4 age groups from any cohort), and the proposed PK sampling scheme, 80% of the simulated trials estimated the geometric mean for systemic clearance with a 95% confidence interval that remained within 60% to 140% of the point estimate in each pediatric subgroup.

***Randomisation and blinding (masking)***

Not applicable.

***Statistical Methods***

Details of the most important endpoints, including primary, key secondary endpoints and exploratory endpoint, are described briefly below. All original and derived parameters as well as demographic and disposition data were listed and described using summary statistics. All safety data (scheduled and unscheduled) were presented in the data listings.

Frequency counts (n and percentages) were produced for each qualitative variable. Descriptive statistics (n, mean, SD, median, minimum, and maximum) were calculated for each quantitative variable (unless otherwise stated). Descriptive statistics were only presented if n > 3. If no participants had data at a given time point, then only n = 0 was presented. If n < 3, only the n, minimum and maximum were presented, and if n = 3, only the n, median, minimum, and maximum were presented; the other descriptive statistics were left blank. Incidence proportions of participants experiencing AEs were accompanied by the 95% exact Clopper-Pearson confidence interval.

Primary PK Endpoints:

Primary PK endpoints serum AZD7442 concentrations and PK parameters were listed and presented separately in tabular and graphical form. The analysis of these endpoints comprised of descriptive summary statistics stratified by cohort, route of administration (IM or IV), and weight categories (≥ 1.5 to < 5 kg, ≥ 5 to < 15 kg, ≥ 15 to < 40 kg, ≥ 40 kg). For PK parameters other than tmax and tlast, the following descriptive statistics were presented: n, geometric mean (gmean), geometric standard deviation (gSD), 95% confidence interval (CI) for the gmean, geometric coefficient of variation (gCV%), arithmetic mean, arithmetic SD, median, minimum, and maximum. For tmax and tlast, only n, median, minimum, and maximum were presented.

Primary Safety Endpoints:

The primary safety endpoints used were treatment-emergent adverse event (TEAE), SAE, AESI, safety laboratory parameters, ECG, vital signs, and physical examinations. The analysis of these endpoints comprised of qualitative or quantitative summary statistics.

Secondary Endpoints-All Cohorts:

- SARS-CoV-2 neutralizing antibodies: Titers of SARS-CoV-2 neutralizing antibodies were listed for the safety analysis set and summarized for the SES at each time point. Descriptive statistics for titers and fold rises included number of participants, gmean, gSD, 95% CI for the gmean, minimum, and maximum.
- ADA and nAb to AZD7442 in serum: The incidence of ADA and nAb to AZD7442 in serum were assessed and summarized for the ADA analysis set (ie, ADS1 for AZD1061, ADS2 for AZD8895, and ADS3 for AZD7442).

Note: Planned analyses for ADA nAb to AZD7442 in serum data were not conducted for this study. ADA nAb samples may be tested at a later date if requested by a health authority.

Other Secondary Endpoints

- Secondary variable – Cohort 1 (prophylaxis): To evaluate the incidence of SARS-CoV-2 infections with or without COVID-19 symptoms after a single IM or IV dose of AZD7442 in pediatric participants, when a participant developed at least one of the COVID-19 qualifying symptoms, an unscheduled visit was performed, and a SARS-CoV-2 RT-PCR test was performed to confirm that the participant was positive. Additionally, to identify symptom-free SARS-CoV-2 infections, serology testing was performed at each visit. Any positive SARS-CoV-2 test result indicating infection as well as any symptoms were reported as an AE.
- Viral load: To quantify SARS-CoV-2 viral loads after a single IM or IV dose of AZD7442 in pediatric participants, the log10-transformed observed results and changes from baseline to Day 8 in log10-transformed viral load as measured by qRT-PCR were summarized for the SAF by weight categories, dose, and route of administration.
- COVID-19 related death (Cohort 2 and Cohort 3): To evaluate COVID-19-related death through 90 days after a single IM or IV dose of AZD7442 in pediatric participants, the incidence of COVID-19-related death occurring after dosing with IMP up to Study Day 90 was tabulated by cohort, weight categories, dose, and route of administration for the SAF. All fatal events were further assessed as part of safety evaluation.
- Recovery (Cohort 3-Severe COVID-19): To evaluate the time to sustained recovery from severe COVID-19 after a single IM or IV dose of AZD7442 in pediatric participants, the time from Day

1 to discharge from the index hospital ('treating' hospital or the hospital where the participant was first admitted for COVID-19), if and only if followed by being alive and home for 14 consecutive days, was calculated.

Note: Planned analyses for Cohort 3 were not conducted as Cohort 3 was not opened as part of this study.

**Results**

***Participant flow***

The disposition of the participants in this study is summarized in Table 12 below. The first participant was enrolled on 21 March 2022 and received their AZD7442 dose on 22 March 2022.

Overall, 49 participants were screened (all participants signed the ICF), of whom 46 participants were enrolled in this study and received AZD7442. A total of 24 participants received AZD7442 via IM injection (AZD8895 followed by AZD1061 administered separately) and 22 participants received AZD7442 via a single IV infusion (AZD8895 and AZD1061 co-administered (Appendix 16.2.1.2)).

At the final analysis, 38 (82.6%) participants had completed the study and 8 (17.4%) had withdrawn from the study. The reasons for study withdrawal were, withdrawal by a parent or guardian (3 [6.5%] participants), followed by loss to follow-up and physician decision (2 [4.3%] participants each), and death (1 [2.2%] participant) (Table 12). One participant who was screened and had passed all screening assessments, withdrew consent prior to being assigned to a cohort.

**Table 12 Participant Disposition**

| | Cohort 1 n (%) | Cohort 2 n (%) | Total n (%) |
|---|---|---|---|
| Participants screened | NA | NA | 49 |
| Participants who did not receive investigational medicinal product | NA | NA | 3 |
| Screen failure | NA | NA | 2 |
| Withdrawal by subject | NA | NA | 1 |
| Participants who received investigational medicinal product | 44 (100) | 2 (100) | 46 (100) |
| Participants completed study | 37 (84.1) | 1 (50.0) | 38 (82.6) |
| Participants withdrawn from study after receiving investigational medicinal product | 7 (15.9) | 1 (50.0) | 8 (17.4) |
| Death | 1 (2.3) | 0 | 1 (2.2) |
| Lost to follow-up | 2 (4.5) | 0 | 2 (4.3) |
| Physician decision | 2 (4.5) | 0 | 2 (4.3) |
| Withdrawal by parent/guardian | 2 (4.5) | 1 (50.0) | 3 (6.5) |

Investigational medicinal product: AZD8895 and AZD1061 (comprising AZD7442) as a single IV infusion or as 2 separate IM injections matching the adult dose of 600 mg based on the participants weight and Cohort (1: prophylaxis, 2: mild/moderate COVID-19). Screened participants are those who signed informed consent. Percentages are based on number of participants who received investigational medicinal product.
Source: Table 14.1.1

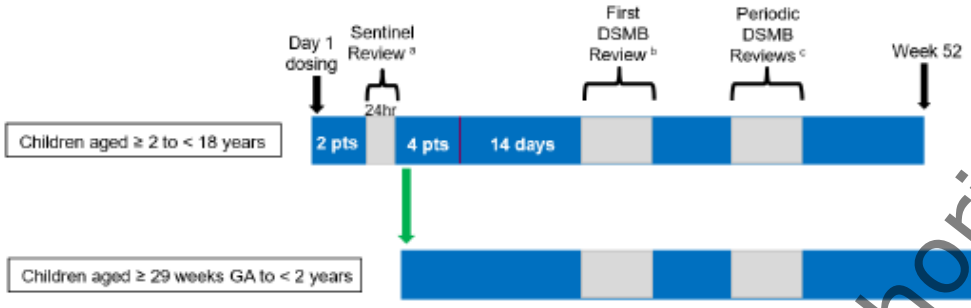
***Recruitment***

The study was conducted by 52 investigators (Principal Investigators and sub-Investigators) at 11 sites in 5 countries. The first subject was enrolled on 21 March 2022, the last subject last visit was scheduled on 16 April 2024. The date of premature stop of enrollment was 31 March 2023; it was per regulatory authority feedback and reduced benefit-risk assessments of EVUSHELD. The analyses presented in this report are based on the final clinical data lock date of 21 May 2024.

Recruitment was started with Cohort 1; Cohorts 2 and 3* were planned to be added if the indications were progressed in adults (Fig. 2). If recruitment in a cohort had not been initiated, the minimum number of participants in the other cohort(s) were allowed to be increased such that there was a minimum of 6 participants receiving IV administration and a minimum of 6 participants receiving IM administration of the IMP in each of the 4 main age categories.

*Note: The planned analyses for Cohort 3 were not conducted as Cohort 3 was not opened as part of this study. This decision was made due to the lack of progress in the indication for severe COVID-19 among adults.

**Figure 2 Recruitment and Safety Review During the Study**




a Sentinel review: Two participants aged ≥ 2 to < 18 years from Cohort 1 were dosed and monitored for 24 hours post-dose (Sentinel Cohort). Recruitment was paused while the International Co-ordinating Investigator, the AstraZeneca Global Safety Physician, and the AstraZeneca Global Clinical Head reviewed the safety data from the Sentinel Cohort. Once the 24-hour safety data review of the Sentinel Cohort was complete, and the safety of AZD7442 was confirmed in the sentinel group, recruitment started in the remaining pediatric participants, including those aged ≥ 29 weeks GA to < 2 years.

b First DSMB Review: The review was conducted when 6 participants from any age group (including the 2 sentinel participants) had at least 14 days of safety data (all available safety data from all participants were included in the DSMB review). Recruitment continued during the DSMB review.

c Periodic DSMB Reviews: For this study, cumulative safety data were reviewed after 21 participants were recruited and another meeting was held post-DCO after 42 participants were recruited. Cumulative safety data were planned to further be reviewed after the following number of participants have been recruited: 51, 66, 81, and 96. However, DSMB recognized the premature stop of enrollment based on the FDA feedback. Subsequent DSMB meetings to review safety data were planned to occur quarterly.

***Baseline data***

The demographic and key baseline characteristics of study participants are summarized in Table 15.

The mean (± SD) age of participants was 9.9 years (± 5 years) and most of the participants were ≥12 to < 18 years of age (21 [45.7%] participants). There were 15 (32.6%) participants ≥ 6 to < 12 years of age and 10 (21.7%) participants ≥ 1 to < 6 years of age in this study. There were no participants younger than 1 year old enrolled in the study. More participants were female (25 [54.3%] participants), White (29 [63.0%] participants) and Not Hispanic or Latino (34 [73.9%] participants). Most of the participants were from the United States of America (37 [80.0%] participants).

At baseline, 26 (56.5%) participants had not received a COVID-19 vaccine and 20 (43.5%) participants were COVID-19 vaccinated.

**Table 15 Demographics and Baseline characteristics (Safety Analysis Set)**

| | Statistic | Cohort 1 N = 44 | Cohort 2 N = 2 | Total N = 46 |
|---|---|---|---|---|
| **Age (years)** | | | | |
| Overall | n | 44 | 2 | 46 |
| | Mean | 10.3 | NA | 9.9 |
| | SD | 4.8 | NA | 5.0 |
| | Median | 10.0 | NA | 10.0 |
| | Min | 1 | 1 | 1 |
| | Max | 17 | 3 | 17 |
| 0 to < 12 years | n | 23 | 2 | 25 |
| | Mean | 6.3 | NA | 6.0 |
| | SD | 3.1 | NA | 3.2 |
| | Median | 8.0 | NA | 6.0 |
| | Min | 1 | 1 | 1 |
| | Max | 10 | 3 | 10 |
| ≥ 12 years | n | 21 | 0 | 21 |
| | Mean | 14.6 | NA | 14.6 |
| | SD | 1.4 | NA | 1.4 |
| | Median | 14.0 | NA | 14.0 |
| | Min | 12 | NA | 12 |

| | Statistic | Cohort 1 N = 44 | Cohort 2 N = 2 | Total N = 46 |
|---|---|---|---|---|
| | Max | 17 | NA | 17 |
| **Age group** | | | | |
| ≥ 12 years to < 18 years | n (%) | 21 (47.7) | 0 | 21 (45.7) |
| ≥ 6 years to < 12 years | n (%) | 15 (34.1) | 0 | 15 (32.6) |
| ≥ 1 years to < 6 years | n (%) | 8 (18.2) | 2 (100) | 10 (21.7) |
| ≥ 29 weeks gestational age to < 1 year | n (%) | 0 | 0 | 0 |
| ≥ 1 month to < 1 year | n (%) | 0 | 0 | 0 |
| ≥ 29 weeks gestational age to < 1 month | n (%) | 0 | 0 | 0 |
| **Age (years) by weight category** | | | | |
| ≥ 1.5 to < 5 kg | n | 0 | 0 | 0 |
| ≥ 5 to < 15 kg | n | 4 | 2 | 6 |
| | Mean | 1.3 | NA | 1.5 |
| | SD | 0.5 | NA | 0.8 |
| | Median | 1.0 | NA | 1.0 |
| | Min | 1 | 1 | 1 |
| | Max | 2 | 3 | 3 |
| ≥ 15 to < 40 kg | n | 19 | 0 | 19 |
| | Mean | 8.1 | NA | 8.1 |
| | SD | 3.4 | NA | 3.4 |
| | Median | 8.0 | NA | 8.0 |
| | Min | 2 | NA | 2 |
| | Max | 17 | NA | 17 |
| ≥ 40 kg | n | 21 | 0 | 21 |
| | Mean | 14.0 | 0 | 14.0 |
| | SD | 2.2 | NA | 2.2 |
| | Median | 14.0 | NA | 14.0 |
| | Min | 8 | NA | 8 |
| | Max | 17 | NA | 17 |
| **Sex** | | | | |
| Female | n (%) | 25 (56.8) | 0 | 25 (54.3) |
| Male | n (%) | 19 (43.2) | 2 (100) | 21 (45.7) |
| **Race** | | | | |
| Asian | n (%) | 1 (2.3) | 0 | 1 (2.2) |
| Black or African American | n (%) | 11 (25.0) | 0 | 11 (23.9) |
| Multiple | n (%) | 2 (4.5) | 0 | 2 (4.3) |
| Not Reported | n (%) | 2 (4.5) | 1 (50.0) | 3 (6.5) |

| | Statistic | Cohort 1 N = 44 | Cohort 2 N = 2 | Total N = 46 |
|---|---|---|---|---|
| White | n (%) | 28 (63.6) | 1 (50.0) | 29 (63.0) |
| **Ethnicity** | | | | |
| Hispanic or Latino | n (%) | 10 (22.7) | 0 | 10 (21.7) |
| Not Hispanic or Latino | n (%) | 33 (75.0) | 1 (50.0) | 34 (73.9) |
| Missing | n (%) | 1 (2.3) | 1 (50.0) | 2 (4.3) |
| **Country** | | | | |
| Argentina | n (%) | 0 | 0 | 0 |
| Belgium | n (%) | 2 (4.5) | 1 (50.0) | 3 (6.5) |
| Brazil | n (%) | 2 (4.5) | 0 | 2 (4.3) |
| Germany | n (%) | 2 (4.5) | 1 (50.0) | 3 (6.5) |
| Mexico | n (%) | 0 | 0 | 0 |
| Poland | n (%) | 0 | 0 | 0 |
| Spain | n (%) | 0 | 0 | 0 |
| Ukraine | n (%) | 0 | 0 | 0 |
| United Kingdom of Great Britain and Northern Ireland | n (%) | 1 (2.3) | 0 | 1 (2.2) |
| United States of America | n (%) | 37 (84.1) | 0 | 37 (80.4) |
| **Height (cm) by weight category** | | | | |
| Overall | n | 44 | 2 | 46 |
| | Mean | 138.9 | NA | 136.3 |
| | SD | 28.9 | NA | 30.7 |
| | Median | 142.1 | NA | 142.0 |
| | Min | 71 | 72 | 71 |
| | Max | 200 | 90 | 200 |
| ≥ 1.5 to < 5 kg | n | 0 | 0 | 0 |
| ≥ 5 to < 15 kg | n | 4 | 2 | 6 |
| | Mean | 79.1 | NA | 79.7 |
| | SD | 8.7 | NA | 8.9 |
| | Median | 76.8 | NA | 76.8 |
| | Min | 71 | 72 | 71 |
| | Max | 91 | 90 | 91 |
| ≥ 15 to < 40 kg | n | 19 | 0 | 19 |
| | Mean | 125.0 | NA | 125.0 |
| | SD | 12.2 | NA | 12.2 |
| | Median | 126.0 | NA | 126.0 |
| | Min | 102 | NA | 102 |
| | Max | 146 | NA | 146 |

| | Statistic | Cohort 1 N = 44 | Cohort 2 N = 2 | Total N = 46 |
|---|---|---|---|---|
| ≥ 40 kg | n | 21 | 0 | 21 |
| | Mean | 162.7 | NA | 162.7 |
| | SD | 12.2 | NA | 12.2 |
| | Median | 161.3 | NA | 161.3 |
| | Min | 142 | NA | 142 |
| | Max | 200 | NA | 200 |
| **Weight (kg) by weight category** | | | | |
| Overall | n | 44 | 2 | 46 |
| | Mean | 41.85 | NA | 40.53 |
| | SD | 22.25 | NA | 22.65 |
| | Median | 37.40 | NA | 34.90 |
| | Min | 9.1 | 10.0 | 9.1 |
| | Max | 94.7 | 12.6 | 94.7 |
| ≥ 1.5 to < 5 kg | n | 0 | 0 | 0 |
| ≥ 5 to < 15 kg | n | 4 | 2 | 6 |
| | Mean | 10.18 | NA | 10.55 |
| | SD | 1.42 | NA | 1.49 |
| | Median | 9.70 | NA | 10.05 |
| | Min | 9.1 | 10.0 | 9.1 |
| | Max | 12.2 | 12.6 | 12.6 |
| ≥ 15 to < 40 kg | n | 19 | 0 | 19 |
| | Mean | 26.83 | NA | 26.83 |
| | SD | 5.58 | NA | 5.58 |
| | Median | 25.10 | NA | 25.10 |
| | Min | 18.2 | NA | 18.2 |
| | Max | 39.2 | NA | 39.2 |
| ≥ 40 kg | n | 21 | 0 | 21 |
| | Mean | 61.49 | NA | 61.49 |
| | SD | 14.71 | NA | 14.71 |
| | Median | 55.60 | NA | 55.60 |
| | Min | 46.6 | NA | 46.6 |
| | Max | 94.7 | NA | 94.7 |
| **BMI (kg/m²)** | | | | |
| Overall | n | 44 | 2 | 46 |
| | Mean | 20.09 | NA | 19.97 |
| | SD | 5.52 | NA | 5.44 |
| | Median | 18.43 | NA | 18.43 |
| | Min | 13.6 | 15.5 | 13.6 |

| | Statistic | Cohort 1 N = 44 | Cohort 2 N = 2 | Total N = 46 |
|---|---|---|---|---|
| | Max | 35.2 | 19.3 | 35.2 |
| **COVID-19 vaccination status at baseline** | | | | |
| Non-vaccinated | n (%) | 24 (54.5) | 2 (100) | 26 (56.5) |
| Vaccinated | n (%) | 20 (45.5) | 0 | 20 (43.5) |

Investigational medicinal product: AZD8895 and AZD1061 (comprising AZD7442) as a single IV infusion or as 2 separate IM injections matching the adult dose of 600 mg based on the participant's weight and cohort (Cohort 1: prophylaxis, 2: mild/moderate COVID-19).
Age is the participant's age at screening.
Source: Table 14.1.5.1, Table 14.1.6

The most frequently reported medical histories in participants were asthma (19 [41.3%] participants), seasonal allergies (6 [13.0%] participants), allergic rhinitis, obesity, gastrostomy, and insomnia (5 [10.9%] participants each).

***Numbers analysed***

There were no concerns regarding study conduct based on protocol deviations, compliance with IMP, or prohibited concomitant medications that would be expected to affect any study outcome or interpretation of results.

The analysis sets and the number of participants in each analysis set are summarized in Table 14 below. Definitions of the analysis sets are given in Section 9.8.2 of the CSR. Of the 49 participants who were screened in this study (i.e., signed the ICF), 3 participants did not receive IMP so 46 were included in the SAF. Of all 46 participants who received AZD7442, 44 participants were included in the PKS, and 42 participants each were included in ADS1, ADS2, and ADS3. Two participants were excluded from the PKS as no PK sample was available and 4 participants each were excluded from the ADA analysis sets since there was no evaluable AZD8895 and AZD1061 ADA (Appendix 16.2.3.1). A total of 43 participants were included in the SARS-CoV-2 nAb Evaluable Analysis Set, while 3 participants were excluded from the analysis set since there were no quantifiable serum titer observations post-dose.

**Table 14 Analysis Sets (Screened Population Set)**

| | Cohort 1 N = 44 n (%) | Cohort 2 N = 2 n (%) | Total N = 49 n (%) |
|---|---|---|---|
| Screened Population Set | 44 (100) | 2 (100) | 49 (100) |
| Safety Analysis Set | 44 (100) | 2 (100) | 46 (93.9) |

| | | | |
|---|---|---|---|
| Excluded from Safety Analysis Set | 0 | 0 | 3 (6.1) |
| No IMP received | 0 | 0 | 3 (6.1) |
| Full Analysis Set | 44 (100) | 2 (100) | 46 (93.9) |
| Excluded from Full Analysis Set | 0 | 0 | 3 (6.1) |
| No IMP received | 0 | 0 | 3 (6.1) |
| Modified Full Analysis Set | 44 (100) | 2 (100) | 46 (93.9) |
| Excluded from Modified Full Analysis Set | 0 | 0 | 3 (6.1) |
| Not part of FAS population set | 0 | 0 | 3 (6.1) |
| PK Analysis Set | 43 (97.7) | 1 (50.0) | 44 (89.8) |
| Excluded from PK Analysis Set | 1 (2.3) | 1 (50.0) | 5 (10.2) |
| No PK sample available | 1 (2.3) | 1 (50.0) | 5 (10.2) |
| AZD8895 ADA Evaluable Analysis Set | 41 (93.2) | 1 (50.0) | 42 (85.7) |
| Excluded from AZD8895 ADA Evaluable Analysis Set | 3 (6.8) | 1 (50.0) | 7 (14.3) |
| Not AZD8895 ADA evaluable | 3 (6.8) | 1 (50.0) | 7 (14.3) |
| AZD1061 ADA Evaluable Analysis Set | 41 (93.2) | 1 (50.0) | 42 (85.7) |
| Excluded from AZD1061 ADA Evaluable Analysis Set | 3 (6.8) | 1 (50.0) | 7 (14.3) |
| Not AZD1061 ADA evaluable | 3 (6.8) | 1 (50.0) | 7 (14.3) |
| AZD7442 ADA Evaluable Analysis Set | 41 (93.2) | 1 (50.0) | 42 (85.7) |
| Excluded from AZD7442 ADA Evaluable Analysis Set | 3 (6.8) | 1 (50.0) | 7 (14.3) |
| Not AZD1061 and AZD8895 ADA evaluable | 3 (6.8) | 1 (50.0) | 7 (14.3) |
| SARS-CoV-2 nAb Evaluable Analysis Set | 42 (95.5) | 1 (50.0) | 43 (87.8) |
| Excluded from SARS-CoV-2 nAb Evaluable Analysis Set | 2 (4.5) | 1 (50.0) | 6 (12.2) |
| No quantifiable serum titer observation post-dose | 2 (4.5) | 1 (50.0) | 6 (12.2) |

Investigational medicinal product: AZD8895 and AZD1061 (comprising AZD7442) as a single IV infusion or as 2 separate IM injections matching the adult dose of 600 mg based on the participant's weight and cohort (Cohort 1: prophylaxis, 2: mild/moderate COVID-19).
The same participant could have been excluded from an analysis set for more than one reason.
The total counts include participants who signed informed consent but discontinued before cohort assignment.
Data Source: Table 14.1.4

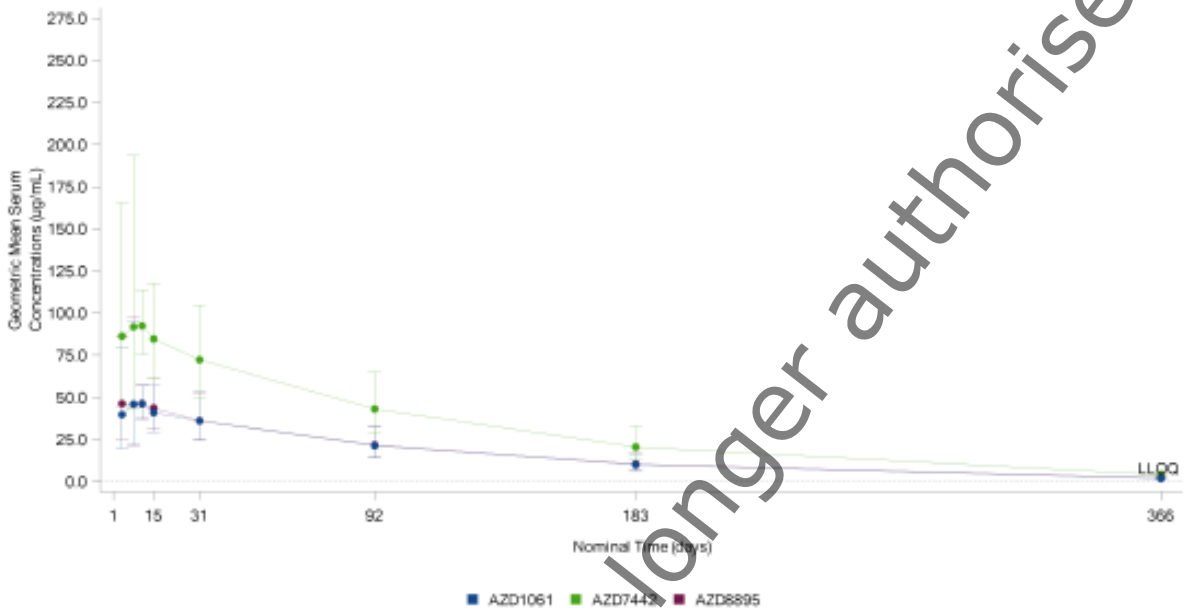
***Pharmacokinetic results***

For serum drug concentration-time profiles, Cohort 1 and 2 data were combined due to limited Cohort 2 IV PK data (N = 1) and no apparent difference in PK between Cohort 1 and 2.

Following a single IM or IV administration of AZD7442, serum concentrations of AZD8895 and AZD1061 were very similar. Following IM administration, geometric mean serum AZD7442 concentrations were highest on Day 11, then declined over time. Following IV administration, geometric mean serum concentrations were highest at the earliest available timepoint, and then declined over time. Inter-participant variability (gCV%) in AZD7442 serum concentrations across time ranged from 20.35% to 78.24%, with similar variability for IM and IV administration.

**Figure 3** **Geometric Mean (± gSD) Serum Concentrations of AZD8895, AZD1061, and AZD7442 Versus Nominal Time, Intramuscular Administration (Linear Scale) (Pharmacokinetic Analysis Set**

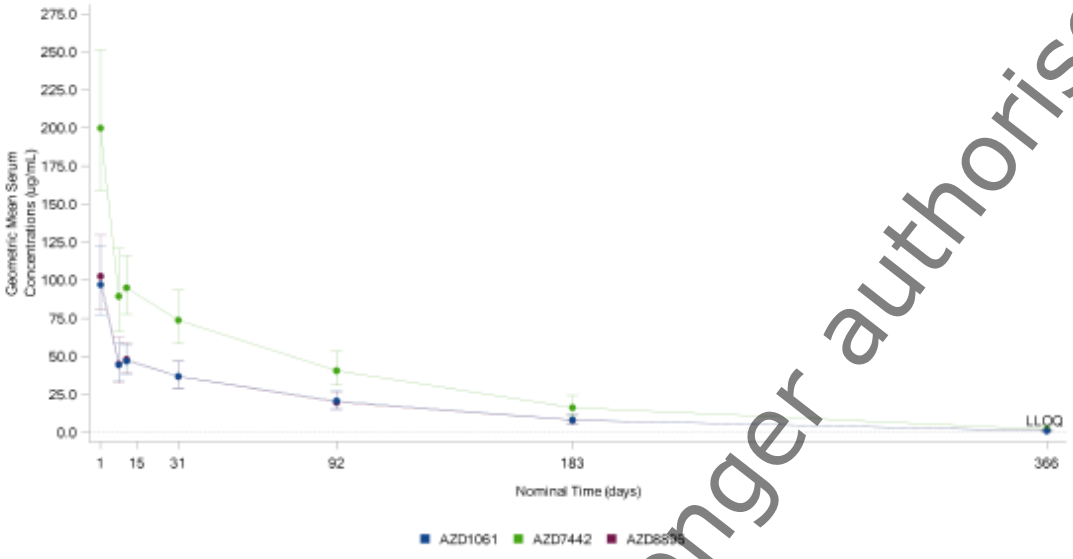
Cohort: Cohort 1
Route of Administration: Intramuscular
Weight Category: Overall




Investigational medicinal product: AZD8895 and AZD1061 (comprising AZD7442) as 2 separate IM injections matching the adult dose of 600 mg based on the participant's weight and cohort (Cohort 1: prophylaxis).
Vertical lines represent gmean ± gSD.
gmean - gSD: exp[mean(log(PK Concentration)) – SD(log(PK Concentration))]
gmean + gSD: exp[mean(log(PK Concentration)) + SD(log(PK Concentration))]
Source: Figure 14.2.1.3 and 14.2.1.1

**Figure 5** **Geometric Mean (± gSD) Serum Concentrations of AZD8895, AZD1061, and AZD7442 Versus Nominal Time, Intravenous Administration (Linear Scale) (Pharmacokinetic Analysis Set)**

Cohort: Total
Route of Administration: Intravenous
Weight Category: Overall




Investigational medicinal product: AZD8895 and AZD1061 (comprising AZD7442) as a single IV infusion matching the adult dose of 600 mg based on the participant's weight and cohort (Cohort 1: prophylaxis and Cohort 2: Mild to moderate COVID-19).
Vertical lines represent gmean ± gSD.
gmean - gSD: exp[mean(log(PK Concentration)) – SD(log(PK Concentration))]
gmean + gSD: exp[mean(log(PK Concentration)) + SD(log(PK Concentration))]
Source: Figure 14.2.1.3 and 14.2.1.1

**Primary Endpoint: Serum PK Parameters of AZD7442**

Cohort 1 and 2 data were combined due to limited Cohort 2 IV PK data (N = 1) and no apparent difference in PK between Cohort 1 and 2.

**Table 16 Overall Summary of PK Parameters for AZD8895, AZD1061, and AZD7442 When Administered Intramuscularly (Pharmacokinetic Analysis Set)**

| PK Parameter | Statistic | AZD8895 N = 24 | AZD1061 N = 24 | AZD7442 N = 24 |
|---|---|---|---|---|
| $AUC_{(0-92)}$ (day*ug/mL) | n | 23 | 23 | 23 |
| | Geometric mean | 2852 | 2796 | 5654 |
| | Geometric CV% | 39.45 | 41.03 | 39.95 |
| $AUC_{inf}$ (day*ug/mL) | n | 22 | 22 | 22 |
| | Geometric mean | 5619 | 5374 | 11000 |
| | Geometric CV% | 37.76 | 38.82 | 38.03 |
| $AUC_{last}$ (day*ug/mL) | n | 23 | 23 | 23 |
| | Geometric mean | 5019 | 4856 | 9884 |
| | Geometric CV% | 42.35 | 43.77 | 42.84 |
| CL/F (L/day) | n | 22 | 22 | 22 |
| | Geometric mean | 0.04707 | 0.04921 | 0.04807 |
| | Geometric CV% | 74.17 | 76.75 | 75.26 |
| $C_{last}$ (ug/mL) | n | 24 | 24 | 24 |
| | Geometric mean | 2.998 | 2.569 | 5.577 |
| | Geometric CV% | 114.3 | 112.3 | 113.0 |
| $C_{max}$ (ug/mL) | n | 24 | 24 | 24 |
| | Geometric mean | 47.44 | 45.07 | 92.47 |
| | Geometric CV% | 44.63 | 44.81 | 44.22 |
| $C_{trough}$ (ug/mL) | n | 22 | 22 | 22 |
| | Geometric mean | 10.44 | 10.07 | 20.53 |
| | Geometric CV% | 50.53 | 51.16 | 50.63 |
| $MRT_{inf}$ (day) | n | 22 | 22 | 22 |
| | Geometric mean | 122.6 | 116.5 | 119.7 |
| | Geometric CV% | 25.06 | 22.01 | 23.57 |
| Vz/F (L) | n | 22 | 22 | 22 |
| | Geometric mean | 5.533 | 5.374 | 5.475 |
| | Geometric CV% | 98.99 | 98.45 | 98.74 |
| $t_{½λz}$ (day) | n | 22 | 22 | 22 |
| | Geometric mean | 81.48 | 75.70 | 78.95 |
| | Geometric CV% | 25.89 | 21.77 | 24.21 |
| $t_{max}$ (day) | n | 24 | 24 | 24 |
| | Median | 10.88 | 10.88 | 11.44 |
| | Min | 0.76 | 0.76 | 0.76 |
| | Max | 32.73 | 32.73 | 32.73 |

Investigational medicinal product: AZD8895 and AZD1061 (comprising AZD7442) as 2 separate IM injections matching the adult dose of 600 mg based on the participant's weight and cohort (Cohort 1: prophylaxis).
Source: Table 14.2.2.1, Table 14.2.2.2, Table 14.2.2.3.

**Table 17** **Overall Summary of PK Parameters for AZD8895, AZD1061, and AZD7442 When Administered Intravenously (Pharmacokinetic Analysis Set)**

| PK Parameter | Statistic | AZD8895 N = 20 | AZD1061 N = 20 | AZD7442 N = 20 |
|---|---|---|---|---|
| $AUC_{(0\text{-}92)}$ (day*ug/mL) | n | 19 | 19 | 19 |
| | Geometric mean | 3346 | 3328 | 6679 |
| | Geometric CV% | 17.92 | 17.91 | 17.50 |
| $AUC_{inf}$ (day*ug/mL) | n | 18 | 18 | 18 |
| | Geometric mean | 5341 | 5328 | 10680 |
| | Geometric CV% | 23.08 | 21.39 | 21.91 |
| $AUC_{last}$ (day*ug/mL) | n | 20 | 20 | 20 |
| | Geometric mean | 4616 | 4634 | 9257 |
| | Geometric CV% | 36.99 | 34.83 | 35.69 |
| CL (L/day) | n | 18 | 18 | 18 |
| | Geometric mean | 0.02656 | 0.02663 | 0.02658 |
| | Geometric CV% | 26.50 | 26.46 | 26.19 |
| $C_{last}$ (ug/mL) | n | 20 | 20 | 20 |
| | Geometric mean | 2.063 | 1.911 | 3.980 |
| | Geometric CV% | 205.0 | 220.5 | 212.0 |
| $C_{max}$ (ug/mL) | n | 20 | 20 | 20 |
| | Geometric mean | 96.85 | 91.67 | 188.7 |
| | Geometric CV% | 27.05 | 27.81 | 27.01 |
| $C_{trough}$ (ug/mL) | n | 17 | 17 | 17 |
| | Geometric mean | 7.868 | 7.995 | 15.88 |
| | Geometric CV% | 43.84 | 41.02 | 42.17 |
| $MRT_{inf}$ (day) | n | 18 | 18 | 18 |
| | Geometric mean | 93.39 | 92.34 | 92.85 |
| | Geometric CV% | 21.62 | 20.04 | 20.68 |
| $V_{ss}$ (L) | n | 18 | 18 | 18 |
| | Geometric mean | 2.481 | 2.459 | 2.468 |
| | Geometric CV% | 30.21 | 32.18 | 30.87 |
| $t_{½λz}$ (day) | n | 18 | 18 | 18 |
| | Geometric mean | 66.13 | 63.31 | 64.67 |
| | Geometric CV% | 23.46 | 22.48 | 22.59 |
| $t_{max}$ (day) | n | 20 | 20 | 20 |
| | Median | 0.01 | 0.01 | 0.01 |
| | Min | 0.01 | 0.01 | 0.01 |
| | Max | 9.95 | 9.95 | 9.95 |

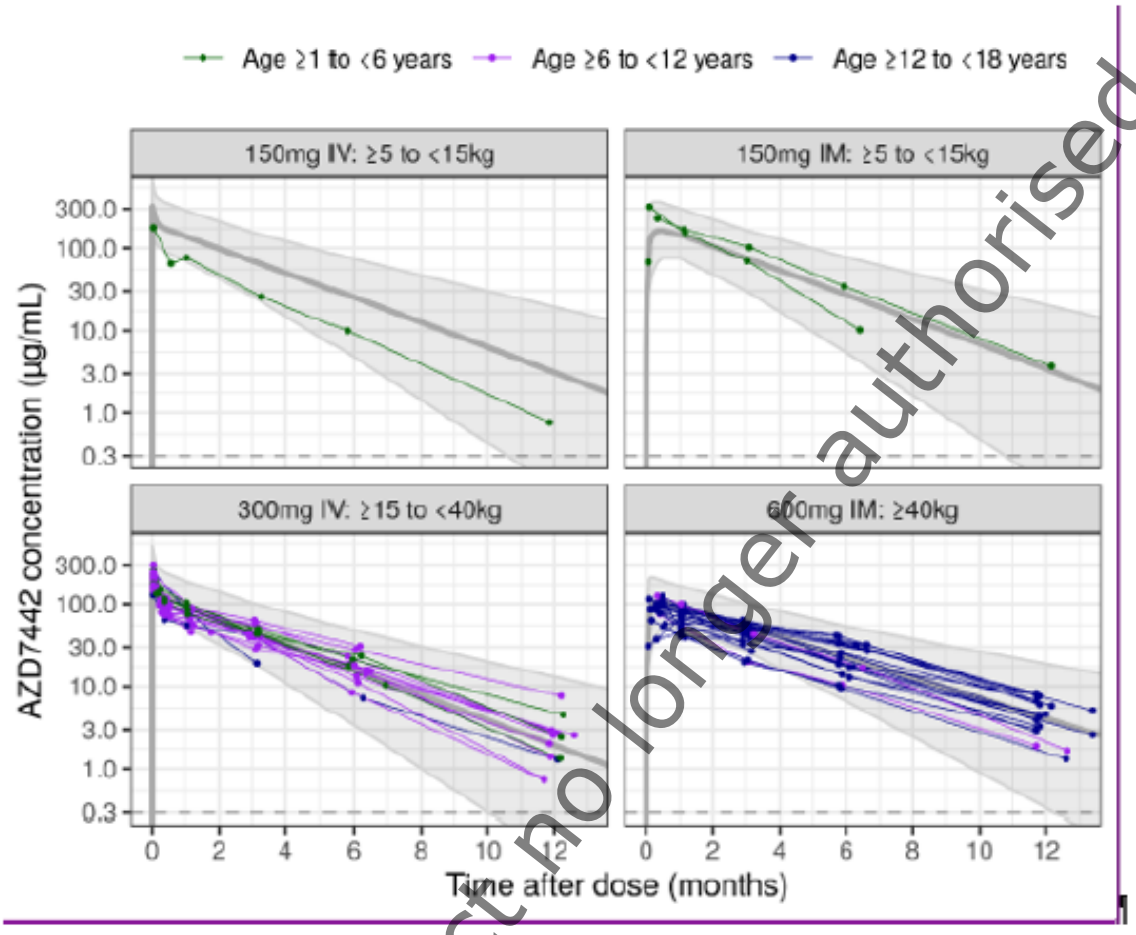
Investigational medicinal product: AZD8895 and AZD1061 (comprising AZD7442) as a single IV infusion matching the adult dose of 600 mg based on the participant's weight and cohort (Cohort 1: prophylaxis and Cohort 2: Mild to moderate COVID-19).
Source: Table 14.2.2.1, Table 14.2.2.2, Table 14.2.2.3



**Primary Endpoint: Comparison of Observed Serum Concentrations With Population PK Predictions**

Available PK data from this study (D8850C00006) were compared to the predicted serum concentrations for each weight-band dose group (Figure 7). The predictions were derived as specified in the pediatric investigation plan, using the AZD7442 population PK model with addition of a maturation function fit to data for the similar half-life-extended (via the YTE-modification) mAb, nirsevimab. PK data for nirsevimab are available in infants, allowing for estimation of the effect of post-menstrual age on clearance of YTE mAbs in young children. The weight-based dose bands in this study were selected to provide comparable serum concentrations at 6 months to a 600 mg IM dose in adults. The observed PK data from this study generally fall within the 90% prediction intervals of the population PK model predictions for each dose group and for both IM and IV administration. This supports the appropriateness of the AZD7442 doses studied in this clinical study. Additionally, the results suggest that the proposed population PK model structure is sufficient to predict AZD7442 PK in children and adolescents one to 18 years of age.

**Figure 7** **Comparison of Observed and Predicted Serum AZD7442 Concentrations in Study D8850C00006 by Age and Weight Group**




Gray solid line: median predicted concentration.
Ribbon: 90% prediction interval.
Colored lines and points: observed PK data.
Colors indicate age group for each participant.
Predictions made with the AZD7442 population PK model (2023), modified with the nirsevimab maturation function.
Simulations were performed for 1000 participants per dose group, with 10 replicates per participant, using the most common category for categorical model covariates (male, no diabetes) and anterolateral thigh as the site of administration for IM cohorts.
Participant ages and weights were drawn from the Centers for Disease Control and Prevention growth charts, as specified in the pediatric investigation plan.
Source: AstraZeneca Data on File (will be available upon request)

**Exploratory Endpoint: Nasal AZD7442 Concentrations**

Following a single IM or IV administration of AZD7442, nasal concentrations of AZD8895 and AZD1061 were similar. Following IM administration, geometric mean nasal AZD7442 concentrations were highest on Day 8, then declined over time. Inter-participant variability (gCV%) in AZD7442 nasal concentrations across time was high and ranged from 50.32% to 451.5%, with similar variability for IM and IV administration.

***Pharmacodynamic endpoints***

**Secondary Endpoint: Titer of SARS-CoV-2 Neutralizing Antibodies (All Cohorts)**

Samples for neutralizing antibody titers were collected pre-dose as well as at days 31, 92, 183, and 366.

In Cohort 1 after IM administration, the geometric mean titer of SARS-CoV-2 nAb in serum at baseline was 1703 (gSD 4.689). On Day 31, the geometric mean titer showed a peak of 52720 (gSD 3.168) and there was a decrease in the geometric mean titer thereafter. By Day 366 the geometric mean titer was 1699 (gSD 2.155) (cf. Tables 14.2.8.1 and 14.2.8.2 in the CSR).

In Cohorts 1 and 2 after IV administration the geometric mean titer of SARS-CoV-2 nAb in serum at baseline was 658.2 (gSD 3.821) and 0 respectively. On Day 31, SARS-CoV-2 nAb titer increased (geometric mean titer of 52720 [gSD 3.168] for Cohort 1, 19800, 19800 [min/max] for Cohort 2) and decreased thereafter.

Among non-vaccinated participants, after IM administration (Cohort 1), the geometric mean titer peaked on Day 31 with a geometric mean titer of 43420 (gSD 3.910) and decreased thereafter with a Day 366 geometric mean titer of 1545 (gSD 2.418). A similar trend was seen for the non-vaccinated participants after IV administration (Cohorts 1 and 2).

Among vaccinated participants, after IM administration (Cohort 1), the geometric mean titer peaked on Day 31 with a geometric mean titer of 75870 (gSD 1.612) and decreased thereafter with a Day 366 geometric mean titer of 2083 (gSD 1.518). A similar trend was seen for the non-vaccinated participants after IV administration (Cohorts 1 and 2).

As expected, throughout the study, the geometric mean titer value was generally higher for the vaccinated participants compared with non-vaccinated participants. The geometric mean titers peaked on Day 31 and decreased thereafter with the lowest post-baseline value on Day 366.

**Secondary Endpoint: SARS-CoV-2 Viral Loads (Cohort 2)**

There was not enough data to conduct this analysis and no meaningful conclusions can be drawn.

**Secondary Endpoint: Anti-drug Antibody Results**

Of the 46 participants who received AZD7442, 42 were ADA evaluable for ADA to AZD7442; 23 participants who received AZD7442 by IM injection and 19 participants who received AZD7442 by IV infusion. In Cohort 1, ADA prevalence (% ADA positive) to AZD7442 was 8.7% (2 out of 23 ADA-evaluable participants) and 11.1% (2 out of 18 ADA-evaluable participants) in the IM and IV group, respectively. In Cohort 2, both participants received AZD7442 by IV infusion; the one participant who was ADA evaluable was ADA negative. In Cohort 1, ADA incidence (% TE-ADA+) to AZD7442 was 4.3% (1 out of 23) and 5.6% (1 out of 18) in the IM and IV group, respectively. ADA responses in Cohort 1 were similar for both IM and IV routes with low prevalence, incidence, and low ADA titer values of 80 and 160 for the 2 participants who were categorized as TE-ADA+ (Table 18).

**Anti-drug Antibody Effect on Pharmacokinetics**

The number of TE-ADA+ participants were too few to formally assess the impact of ADA on PK.

**Anti-drug Antibody Effect on Pharmacodynamics**

The number of TE-ADA+ participants were too few to formally assess the impact of ADA on PD.

**Anti-drug Antibody Effect on Safety**

There were 2 TE-ADA+ participants in the study both with low ADA titers of 160 and 80 with reported AEs, which were mostly infections. None of the ADA+ participants reported any injection site reactions or any other AESI. There was no apparent impact of ADA on safety; however, the number of TE-ADA+ participants was too few for a formal assessment.

**Secondary Endpoint-Incidence of SARS-CoV-2 Infections After Dosing with AZD7442**

Overall, there were 13 participants who had a SARS-CoV-2 infection after receiving AZD7442, including 10 participants under PT COVID-19 (SOC-infections and infestations), and 3 participants under PT SARS-CoV-2 test positive (SOC-investigations).

A total of 16 (36.4%) participants in Cohort 1 had symptoms of COVID-19 (symptoms recorded following administration of AZD7442 on Day 1). The symptoms reported were abdominal pain, body aches, chills, congestion, cough, diarrhea, muscle aches, difficulty breathing, fatigue, fever, headache, nausea, new loss of smell, new loss of taste, poor appetite/feeding problems, runny nose, shortness of breath, sore throat, and vomiting. All the symptoms were of mild or moderate severity. Of these 16 participants, 10 had confirmed COVID-19 infections. Participants who reported COVID-19 symptoms were included in this summary even if COVID-19 infection was not confirmed.

Of the 44 participants, 30 participants were positive for SARS-CoV-2 serology test at baseline (29 from Cohort 1 and 1 from Cohort 2).

**Secondary Endpoint-Proportion of Participants With Progression of COVID-19 Through Day 29 (Cohort 2-Treatment)**

There were no participants with progression of COVID-19 through Day 29 in Cohort 2.

**Secondary Endpoint-The Incidence of COVID-19-related Death Occurring After Dosing With IMP Through 90 Days (Cohort 2-Treatment)**

There were no COVID-19-related deaths that occurred after dosing with IMP through 90 days in Cohort 2.

***Safety results***

**Extent of Exposure**

A high study completion rate was observed, overall, 46 participants were dosed with IMP (24 participants had IM administration and 22 participants had IV administration) and 38 (82.6%) participants completed the study. A total of 24 participants received a single dose of the IMP administered by IM injections (AZD8895 followed by AZD1061 administered separately) and 22 participants received a single dose of the IMP administered by IV infusion (AZD8895 and AZD1061 co-administered). The IMP dose that each participant received was based on the participant's body weight and dosing weight band (see Table 8 of CSP Version 5.0 [Appendix 16.1.1]).

In Cohort 1, 44 participants received IMP and the median (min, max) number of days in study from dosing was 442.0 days (104 days, 469 days). In Cohort 2, 2 participants received IMP and the number of days in study from dosing was for 37 days for one participant and 356 days for the other (Table 14.4.5).

**Categories of Adverse Events**

A summary of AEs by category and study cohort for any route of administration is provided in Table 19.

**Table 19 Overall Summary of Adverse Events in Any Category (Safety Analysis Set)**

| | Cohort 1<br>n (%) [CI] | Cohort 2<br>n (%) [CI] | Total<br>n (%) [CI] |
|---|---|---|---|
| **Route of administration: overall** | | | |
| N | 44 | 2 | 46 |
| AE | 39 (88.6) [75.4, 96.2] | 2 (100) [15.8, 100] | 41 (89.1) [76.4, 96.4] |
| SAE | 8 (18.2) [8.2, 32.7] | 1 (50.0) [1.3, 98.7] | 9 (19.6) [9.4, 33.9] |
| Severe AE | 6 (13.6) [5.2, 27.4] | 0 | 6 (13.0) [4.9, 26.3] |
| AESI | 1 (2.3) [0.1, 12.0] | 0 | 1 (2.2) [0.1, 11.5] |
| SAE with outcome death | 1 (2.3) [0.1, 12.0] | 0 | 1 (2.2) [0.1, 11.5] |
| AE leading to study discontinuation | 0 | 0 | 0 |
| Possibly related AE [a] | 3 (6.8) [1.4, 18.7] | 0 | 3 (6.5) [1.4, 17.9] |
| Possibly related SAE [a] | 0 | 0 | 0 |
| Possibly related Severe AE [a] | 0 | 0 | 0 |
| Possibly related AESI [a] | 1 (2.3) [0.1, 12.0] | 0 | 1 (2.2) [0.1, 11.5] |

| | Cohort 1<br>n (%) [CI] | Cohort 2<br>n (%) [CI] | Total<br>n (%) [CI] |
|---|---|---|---|
| | | | |
| **Route of administration: intramuscular** | | | |
| N | 24 | 0 | 24 |
| AE | 20 (83.3) [62.6, 95.3] | 0 | 20 (83.3) [62.6, 95.3] |
| SAE | 4 (16.7) [4.7, 37.4] | 0 | 4 (16.7) [4.7, 37.4] |
| Severe AE | 4 (16.7) [4.7, 37.4] | 0 | 4 (16.7) [4.7, 37.4] |
| AESI | 1 (4.2) [0.1, 21.1] | 0 | 1 (4.2) [0.1, 21.1] |
| SAE with outcome death | 0 | 0 | 0 |
| AE leading to study discontinuation | 0 | 0 | 0 |
| Possibly related AE [a] | 2 (8.3) [1.0, 27.0] | 0 | 2 (8.3) [1.0, 27.0] |
| Possibly related SAE [a] | 0 | 0 | 0 |
| Possibly related Severe AE [a] | 0 | 0 | 0 |
| Possibly related AESI [a] | 1 (4.2) [0.1, 21.1] | 0 | 1 (4.2) [0.1, 21.1] |
| | | | |
| **Route of administration: Intravenous** | | | |
| N | 20 | 2 | 22 |
| AE | 19 (95.0) [75.1, 99.9] | 2 (100) [15.8, 100] | 21 (95.5) [77.2, 99.9] |
| SAE | 4 (20.0) [5.7, 43.7] | 1 (50.0) [1.3, 98.7] | 5 (22.7) [7.8, 45.4] |
| Severe AE | 2 (10.0) [1.2, 31.7] | 0 | 2 (9.1) [1.1, 29.2] |
| AESI | 0 | 0 | 0 |
| SAE with outcome death | 1 (5.0) [0.1, 24.9] | 0 | 1 (4.5) [0.1, 22.8] |
| AE leading to study discontinuation | 0 | 0 | 0 |
| Possibly related AE [a] | 1 (5.0) [0.1, 24.9] | 0 | 1 (4.5) [0.1, 22.8] |
| Possibly related SAE [a] | 0 | 0 | 0 |
| Possibly related Severe AE [a] | 0 | 0 | 0 |
| Possibly related AESI [a] | 0 | 0 | 0 |

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

Investigational medicinal product: AZD8895 and AZD1061 (comprising AZD7442) as a single IV infusion or as 2 separate sequential IM injections matching the adult dose of 600 mg based on the participant's weight and cohort (Cohort 1: prophylaxis, 2: mild/moderate COVID-19).

The table includes adverse events with an onset date on or after the date of first dose of investigational medicinal product until the final safety assessment.

Participants with multiple occurrences in the same category are counted once per category regardless of the number of occurrences.

Source: Table 14.3.1.1.



**Adverse Events by System Organ Class and Preferred Term**

A summary of AEs by SOC and PT for any route of administration is provided by cohort in Table 20 of the CSR.

Overall, 41 (81.9%) participants experienced at least 1 AE in the study. Most AEs were mild to moderate in severity, with 6 (13.0%) participants (Cohort 1) having severe AEs. Adverse events considered related to AZD7442 by the Investigator were reported in 3 (6.5%) participants (Cohort 1) (Table 19). Serious AEs were reported in 8 (18.2%) participants in Cohort 1 and 1 (50.0%) participant in Cohort 2, but none of the SAEs were considered related to the IMP by the Investigator (Table 19 of CSR).

AE of special interest (AESI) was reported in 1 (2.2%) participant (Cohort 1, IM route of IMP administration) and was considered related to the IMP by the Investigator (Table 19). There was 1 death due to device related sepsis (Cohort 1, IV route of IMP administration) which was not considered related to the IMP by the Investigator. No other deaths occurred (Table 19, Appendix 16.2.7.1). There were no AEs resulting in study discontinuation reported for any of the participants. There was no major difference in AEs trends between the IV and IM routes of administration.

**Adverse Events by Severity**

The majority of AEs were mild or moderate in severity. Overall, 6 (13.6%) participants from Cohort 1 had severe AEs (Grade 3, Grade 4, or Grade 5) including 4 (16.7%) participants from the IM group and 2 (10%) participants from the IV group. One (2.3%) participant had a serious AE leading to death (Grade 5). All of the Grade 3 and above AEs were considered not related to the IMP as assessed by the Investigator.

**Adverse Events by Relationship to the IMP**

Adverse events considered possibly related to IMP by the Investigator were reported in 3 (6.8%) participants in Cohort 1 and none from Cohort 2. These related AEs were most frequently reported in the SOC of 'Gastrointestinal Disorders' (n=2, 4.3% overall); all other SOC's had AEs reported in 1 participant each. These include one participant with injection site swelling, dizziness, nausea (IM administration); one participant with nausea and vomiting (IM administration) and one participant with stoma site reaction (IV administration). All possibly related AEs were mild in intensity, except for the AE of nausea that was moderate in intensity. These AEs were resolved, with all of them subsiding within 1-2 days (Listing 16.2.7.1.1). There were no clinically meaningful differences in the reported possibly related AEs between IM and IV dosing (Table 21 of CSR).

**Deaths**

Overall, 1 (2.2%) participant died during the study.

One participant with a complex medical history, including severe intellectual disability, chronic kidney disease stage 5, insulin-resistant diabetes, and prolonged QT syndrome, was enrolled in a clinical trial for AZD7442, receiving a 300 mg IV infusion for pre-exposure prophylaxis of COVID-19. On Day 54 post-administration, the participant developed symptoms of cough, fever, and diarrhea, rapidly progressing to severe respiratory complications. On Day 58, the participant was diagnosed with a metapneumovirus lower respiratory tract infection, resulting in acute respiratory distress requiring mechanical ventilation and intensive care management. Despite intensive therapeutic interventions, including reintubation, bilevel positive airway pressure (BiPAP) support, and multiple vasoactive agents, the participant developed a Pseudomonas lower respiratory tract infection with left-sided lung collapse on Day 67, followed by respiratory failure necessitating intubation on Day 79. The participant's clinical status further declined with the onset of central line-associated bloodstream infection on Day 89, leading to sepsis and ultimately resulting in death on Day 104. Throughout the clinical course, the investigational product, AZD7442, was evaluated by both the Investigator and AstraZeneca's medical team and was determined to be unrelated to the serious adverse events. The participant's pre-existing comorbid conditions were identified as the primary contributors to the fatal outcome (Appendix 16.2.7.1).

**Serious Adverse Events**

All participants who had an SAE are listed in Appendix 16.2.7.1 and SAEs are summarized in Table 14.3.4.1 of the CSR. A total of 25 SAEs, ranging from Grade 1 to Grade 5 severity were reported in 9 (19.6%) participants. None of the SAEs were assessed as related to the IMP. All of the SAEs were

reported in 1 participant each. The number of SAEs reported was comparable between participants who received IMP through the IV or IM route of administration (Table 22 of the CSR). None of the SAEs were related to the IMP as determined by the Investigator or Sponsor.

**Discontinuations of Investigational Medicinal Product due to Adverse Events**

No discontinuations of IMP due to an AE were reported in this study (Table 14.3.5.1 of the CSR).

**Other Significant Adverse Events**

**Adverse Events of Special Interest**

The protocol-defined AESIs for AZD7442 were anaphylaxis and other serious hypersensitivity reactions (including immune complex disease), injection site and infusion site reactions, MIS-C, as well as thrombotic events, heart failure, and cardiac ischemia. The AESIs by SOC and PT are presented in Table 23 of the CSR.

One (2.2%) participant in Cohort 1, who received AZD7442 via the IM route, developed an AESI of injection site swelling. The AE started on Study Day 1 and resolved on Study Day 2. The injection site swelling was of Grade 1 severity and was assessed as possibly related to AZD7442 by the Investigator (Appendix 16.2.7.1).

There was one event of anaphylaxis reported after administration of asparaginase and not after IMP administration and therefore not reported as an AESI.

No other AESIs were reported by any of the other participants.

**Adjudicated Cardiovascular Events**

There were no participants with positively adjudicated CV events, hence no data on demographics, medical history, and time to onset of CV event are presented.

**Clinical Laboratory Evaluation**

Summary tables and figures pertaining to this section are presented in Section 14.3 of the CSR (Table 14.3.7.1 to Table 14.3.7.4) and Appendix 16.2.8.1.

There were no notable differences between the 2 cohorts for hematology, clinical chemistry, coagulation, and urinalysis parameters. There were no trends in mean changes over time for clinical chemistry, hematology, or coagulation parameters.

**Vital Signs, Electrocardiograms, Physical Findings, and Other Observations Related to Safety**

There were no notable observations related to vital signs results reported for any of the participants and no meaningful changes over time were observed in mean vital signs parameters.

There were no notable ECG results reported for any of the participants and no meaningful changes over time were observed.

### 2.3.3. Discussion on clinical aspects

The applicant submitted results from a Phase I, open-label, uncontrolled, multi-country, multicenter, single dose study that evaluated the pharmacokinetics (PK), pharmacodynamics (PD), safety, and tolerability of AZD7442 administered via intramuscular (IM) or intravenous (IV) routes in pediatric participants aged ≥ 29 weeks gestational age (GA) (infants born between GA of 29 weeks to full term) to < 18 years. The study was conducted by 52 investigators (Principal Investigators and sub-Investigators) at 11 sites in 5 countries between March 2022 and April 2024, however, enrolment was

prematurely stopped in March 2023. The analyses presented in this report are based on the final clinical data lock date of 21 May 2024.

The primary objective was to evaluate the serum concentrations, safety and tolerability of AZD7442 after a single IM or IV dose. Secondary objectives included PD and immunogenicity evaluations for all cohorts and specific evaluations for the single cohorts, e.g. incidences of infections (cohort 1), quantification of viral loads, proportion of participants with progression of COVID-19, and COVID-19-related death after single-dose administrations (cohorts 2 and 3).

Participants were assigned to 3 cohorts, i.e. cohort 1 included participants negative for SARS-CoV-2, who had not knowingly been exposed to the virus, cohort 2 included SARS-CoV-2 positive participants at screening with a mild-to-moderate disease. Cohort 3 had been planned to enroll participants who were SARS-CoV-2 positive at screening with severe COVID-19, however, analyses were never performed for this cohort. Cohort 1 included 44, and cohort 2 two participants. Thus, the full analysis set includes 46 participants.

After the planned single dose administrations, PK, PD, safety and immunogenicity assessments were performed and subjects were followed up until day 366. 46 out of 49 screened participants were enrolled and treated. Participants were aged 1-<18 years and in a body weight range of 9.1 to 94.7 kg. In total, 43.5% of the subjects had previously received COVID-19 vaccines. The majority completed the study. Two study participants were excluded from the PK analysis set for acceptable reasons (no sample obtained).

*Pharmacokinetic results*

A weight-band dosing approach was conducted in the present study (see table 1 in this assessment report); doses ranging from 50 mg to 600 mg were planned to be applied in the different weight groups. According to PIP documents, the weight-based dose bands in this study were selected to provide comparable serum concentrations at 6 months to a 600 mg IM dose in adults based on estimates from popPK model.

Given the studied population, PK sampling was sparse for the individual participant (max 6 samples); sampling days were spread across participants. PK samples were available for study days 1, 4, 8, 15, 31, 92, 183, and 366. Bioanalytical methods already used in the adult pivotal studies were applied. Results were planned to be presented by cohort, route of administration and weight categories. As cohort 2 IV data were limited (2 participants) the presentation of concentration vs time profiles in combination with cohort 1 IV data can be agreed.

Considering graphical presentation, serum concentration-time curves were comparable for the 2 antibodies AZD8895 and AZD1061 after both, IM and IV dosing. Serum concentration-time curves for both antibodies combined (AZD7442; Evusheld) are presented within the same figures. Considering all weight categories combined, inter-participant variability (gCV%) of Evusheld concentrations was moderate to high (20.35% to 78.24%) at the different timepoints investigated.

Primary Endpoint: Serum PK Parameters of AZD7442

PK parameters for AZD8895, AZD1061, and AZD7442 (Evusheld; combination of AZD8895 and AZD1061) were calculated for all weight categories combined and for each route of administration. After IM dosing, Cmax was reached after approximately 11 days in median; serum concentrations of the antibodies declined afterwards. A geometric mean t1/2λz of 64.67 and 78.95 days was found for Evusheld after IV and IM dosing, respectively. Inter-participant variability (gCV%) was moderate for Cmax and AUCinf of Evusheld (21.91% to 44.22%).

Compared to predicted Cmax in adult population receiving the 600mg dose, mean Cmax was higher in the present pediatric population with the chosen weight-based dose bands (92.47 µg/ml vs 53.9 µg/mL). Also, at later timepoints (day 30 and day 180) the mean concentration in the present study was higher as compared to adult data from pivotal studies.

Primary Endpoint: Comparison of Observed Serum Concentrations With Population PK Predictions

Observed serum concentrations were compared with predictions from an Evusheld popPK model. As previously discussed in the EMA/PDCO Summary Report, the previously assessed Evusheld popPK model was applied, but with addition of a maturation function. Therefore, the nirsevimab maturation function on clearance was added to the Evusheld popPK model; Nirsevimab carries the same half-life extension modification (YTE) as both components of Evusheld. With the data presented it is anticipated the maturation function was applied for prediction in the age group ≥1 to< 6 years (10 children of the present study). The full modelling report has not been provided with this submission, thus, more detailed assessment is not feasible for the time being.

With the model applied, individual concentration values were mainly contained within the 90% prediction interval for all weight groups investigated (≥ 5 to < 15 kg, ≥ 15 to < 40 kg, ≥ 40 kg). The applicant concludes that the proposed population PK model structure is sufficient to predict AZD7442 PK in children and adolescents one to 18 years of age. This statement cannot be fully supported, as the lower body weight range is not well covered by presented data. There were only 3 subjects in the ≥ 5 to < 15 kg weight group, with the lightest subject having a body weight of 9.1 kg. Thus, adequacy of the applied model for PK prediction in children at the lower limit of the body weight range cannot be comprehensively assessed. Of note, no participants in the planned weight group of ≥ 1.5 to < 5 kg were included in the present study, thus predictions for infants cannot be verified with data available.

As stated in the EMA/PDCO Summary Report, the aim of the investigated dose levels was to maintain exposure above the target level of 2.1µg/ml. Evusheld concentrations were above this level in all subjects for at least 6 months. Overall, the proposed doses in the pediatric populations result in serum concentrations above the predicted efficacious level demonstrated to be effective in adults.

*Pharmacodynamic results*

The PD markers that were measured in the study served for the purpose of supporting the assumption of a similar exposure-response relationship in adults and children.

From the documentation provided, it is not clear which assay has been used for analysis of neutralizing titers (live virus vs pseudovirus neutralization; wild type vs variant specific), thus any comparison with adult data is meaningless for the time being. Results are shown by vaccination status, route of application and age group. As expected, vaccinated subjects showed higher titer at baseline and throughout the study as compared to non-vaccinated subjects. For both, vaccinated and non-vaccinated subjects, neutralizing titer peaked at day 31 and declined afterwards. Of note, a neutralizing titer threshold that is associated with prophylactical protection or efficacious treatment of COVID-19 has not been established for Evusheld.

SARS-CoV-2 viral loads were not analysed as only 2 participants were treated in cohort 2.

*Immunogenicity results*

ADA positivity rates were low. In Cohort 1, ADA incidence (% TE-ADA+) to AZD7442 was 4.3% (1 out of 23) and 5.6% (1 out of 18) in the IM and IV group, respectively.

The applicant decided to omit the previously planned analyses for ADA nAb to AZD7442 in serum.

Due to limited data, analysis of PK, efficacy or safety parameters by ADA status was not feasible.

Overall, the limited immunogenicity data from the present study do not raise a certain concern.

*Efficacy results*

The prophylaxis and treatment related endpoints in this study were not meant to establish efficacy independently but to support the extrapolation of the efficacy data observed in adults to children.

During the study, 13 participants had a SARS-CoV-2 infection after receiving AZD7442. None of them progressed to severe COVID-19 or death.

The high number of break-through infections was not further discussed by the applicant. However, the study was prematurely stopped as variants that are not susceptible to Evusheld became dominant.

*Safety results*

The safety results suggest that Evusheld was well tolerated. Most TEAEs were mild to moderate and reported TEAEs were typical for the studied population, i.e. upper respiratory tract infection and associated symptoms. Adverse events considered related to AZD7442 were injection site and injection related reactions, however, they were overall individually observed. There was 1 death due to device related sepsis considered unrelated to the study drug; based on the narrative, it seems likely, that the Evusheld administration is not responsible for the fatal outcome. Overall 9 participants (19.6%) experienced events of Grade 3 severity or higher, however, none were considered related to Evusheld. No cardiovascular or serious hypersensitivity events were reported. There were no new or unexpected safety findings observed throughout the study that were associated with Evusheld treatment.

# 1. Overall conclusion and recommendation

The presented study was prematurely stopped, as variants non-susceptible to Evusheld became dominant. Thus, the planned sample size was not fulfilled; No data were available for the lowest planned weight group (≥ 1.5 to < 5 kg); Only 2 subjects were included in Cohort 2, investigating treatment of mild to moderate COVID-19; Some previously planned analyses were not conducted (viral load, impact of ADA on PK, PD, safety).

With data available, the PK of Evusheld in the pediatric age range of 1 to <18 years was reasonably well characterized. However, clinical PK data were limited especially for younger age groups. Available data on Evusheld exposure indicate that the applied weight-banded dosing seems overall valid - measured Evusheld concentrations were overall within the 90% prediction interval from the applied popPK model. However, there are limitations with regard to lower body weights (only 3 subjects in the ≥ 5 to < 15 kg weight group, lightest subject with 9.1 kg). As no modelling report has been provided, a more detailed assessment is not feasible for the time being. Evusheld SmPC currently states *The PK of tixagevimab and cilgavimab in individuals < 18 years old has not been evaluated.*

The limited immunogenicity data from the present study do not raise a certain concern.

There were no new unexpected safety findings associated with Evusheld treatment observed throughout the study. No update of the Product Information is considered necessary.

There will be no post-approval variation with the paediatric data.

☒ **PAM Fulfilled:**

No regulatory action required.