# 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

## ClinicalTrials.gov Identifier: NCT05281601

## Statistical Analysis Plan: Final 3.0, 31 Jul 2023

| STATISTICAL ANALYSIS PLAN | |
|---|---|
| Study Code | D8850C00006 |
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| Date | 31-Jul-2023 |

# 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

## SPONSOR SIGNATURE PAGE

This document has been reviewed for clarity, completeness and consistency and approved and signed electronically on the final page by the following:

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## Parexel SIGNATURE PAGE

Signature(s) below confirm that the Statistical Analysis Plan was developed in accordance with Parexel SOP-GDO-WW-019 and that it is approved for release.

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| Signatory | |
|---|---|
| **Author** | PPD<br>Project Role: PPD |

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# LIST OF ABBREVIATIONS

| Abbreviation or Specialized Term | Definition |
|---|---|
| %AUCext | percentage of AUC extrapolated |
| ADA | anti-drug antibody |
| ADS1 | AZD1061ADA Evaluable Analysis Set |
| ADS2 | AZD8895 ADA Evaluable Analysis Set |
| ADS3 | AZD7442 ADA Evaluable Analysis Set |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase/transaminase |
| AST | aspartate aminotransferase/transaminase |
| AUC | area under the serum concentration-time curve |
| AUC(0-92d) | area under the serum concentration-time curve from time zero to day 92 |
| AUC0-inf | area under the serum concentration versus time curve zero to infinity |
| AUC0-last | area under the serum concentration versus time curve from time zero to time of last measurable concentration |
| AZD7442 | the product under investigation (AZD8895 and AZD1061) |
| BP | blood pressure |
| CI | confidence interval |
| CL | systemic clearance |
| CL/F | apparent total clearance |
| Clast | Last observed (quantifiable) concentration |
| Cmax | maximum serum concentration |
| Ctrough | trough serum concentration |
| COVID-19 | Coronavirus disease-2019 |
| CS | clinically significant |
| CV | Cardiovascular |
| DSMB | Data Safety Monitoring Board |
| ECG | Electrocardiogram |
| eCRF | electronic Case Report Form |
| EDC | electronic data capture |
| FAS | Full Analysis Set |
| GA | gestational age |
| gCV | geometric coefficient of variation |
| ggt | Gamma glutamyl transpeptidase |
| gmean | geometric mean |
| GMT | geometric mean titers |

| | |
|---|---|
| gSD | geometric standard deviation |
| ICF | informed consent form |
| IM | intramuscular |
| IMP | investigational medicinal product |
| IPD | Important protocol deviation |
| IRT | Interactive Response Technology |
| IV | intravenous |
| LLOQ | lower limit of quantification |
| mAb | monoclonal antibody |
| MCH | Mean corpuscular hemoglobin |
| MCHC | Mean corpuscular hemoglobin concentration |
| MCV | Mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MIS-C | multisystem inflammatory syndrome in children |
| nAb | neutralizing antibody |
| NC | not calculated |
| NCS | not clinically significant |
| NQ | not quantifiable |
| NR | not reportable |
| NS | no sample |
| PD | pharmacodynamics |
| PK | pharmacokinetics |
| PKS | PK Analysis Set |
| PT | Preferred Term |
| qRT-PCR | quantitative real-time polymerase chain reaction |
| RBC | Red blood cell |
| RT-PCR | reverse transcriptase polymerase chain reaction |
| SAE | serious adverse event |
| SAF | Safety Analysis Set |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| SD | standard deviation |
| SES | SARS-CoV-2 nAb Evaluable Analysis Set |
| SOC | System Organ Class |
| SPS | Screened population set |
| t1/2 | terminal half-life |
| t1/2λz | Half-life associated with terminal slope of a semi-logarithmic concentration-time curve |
| TEAE | treatment-emergent adverse event |
| tmax | time to reach maximum serum concentration |
| VPC | Visual Predictive Checks |
| Vss | volume of distribution at steady state |
| Vz/F | apparent volume of distribution based on terminal phase |

| | |
|---|---|
| WBC | White blood cell |
| λz | Terminal disposition rate constant/terminal rate constant |

# AMENDMENT HISTORY

| CATEGORY Change refers to: | Date | Description of change | In line with Clinical Study Protocol? | Rationale |
|---|---|---|---|---|
| Data presentation | 26-Oct-2022 | Removed reference to PK data for DSMB | Yes | Updated protocol |
| Other | 26-Oct-2022 | Minor text corrections | N/A | Typos and consistency |
| Data presentation | 26-Oct-2022 | Removed summary of AEs by maximum intensity | No | Sponsor request per AZD7442 program-level shell changes |
| Data presentation | 26-Oct-2022 | Added confidence intervalls for percentage of subjects with AEs | Yes | Sponsor request per AZD7442 program-level shell changes |
| Data presentation | 26-Oct-2022 | Clarified ECG evaluation summary to be a shift table | Yes | Clarification of presentation per AZ standard shell |
| Other | 26-Oct-2022 | Demographics: correction of estimated gestational age for prematurely born infants at birth, not study entry | Yes | Correction |
| Data presentation | 26-Oct-2022 | COVID-19 incidence will be summarized by weight categories, and route of administration, not by dose | Yes | Correction. This is a single-dose study |
| Other | 26-Oct-2022 | ADA Evaluable Analysis Sets have been clearly distinguished, defining one set each for AZD1061, AZD8895, AZD7442 | Yes | Clarification |
| Other | 26-Oct-2022 | Mis-assignment to Cohort 1 via contradictory rapid and confirmatory COVID-19 test handling explained. Added separate analysis set and repetition of COVID-19 incidence summary for this set. | Yes | Newly identified potential case of erroneous cohort assignment |
| Statistical analysis method for secondary endpoint(s) | 26-Oct-2022 | The SARS-CoV-2 viral loads will be log10-transformed before summary. | Yes | Clarification on result presentation |

| **CATEGORY Change refers to:** | **Date** | **Description of change** | **In line with Clinical Study Protocol?** | **Rationale** |
|---|---|---|---|---|
| Statistical analysis method for secondary endpoint(s) | 26-Oct-2022 | Time-to-Event summaries will include quartiles. | Yes | Addition of statistic |
| Other | 26-Oct-2022 | Clarification of vaccinations status as captured in the eCRF at baseline. | Yes | Clarification of definition |
| Other | 26-Oct-2022 | Description of use of unscheduled and repeated assessments added. | Yes | Addition of information |
| Data presentation | 26-Oct-2022 | Presentation of descriptive statistics: quartiles, minimum, maximum updated for several variables and explicitly stated where applicable. | Yes | Sponsor request per AZD7442 program-level shell changes |
| Other | 30-May-2023 | Updated information on cohorts and early stop of recruitment. | Yes | Early discontinuation of patient recruitment |
| Data presentation | 30-May-2023 | Description of nAb data added. | Yes | Clarification |

# 1 INTRODUCTION

This Phase I pediatric study will provide information on the AZD7442 PK profile, SARS-CoV-2-neutralizing antibody titers, effect on viral load, data on the safety and tolerability and generation of ADAs to AZD7442, following a single IM or IV AZD7442 dose administration in different pediatric age groups. This will be the first AZD7442 clinical study in pediatric participants aged ≥ 29 weeks GA to < 18 years.

The analyses described in this SAP are based upon the following study documents:

1. Clinical Study Protocol, Version 1.0 (October 08, 2021)
2. Clinical Study Protocol Amendment 1 (December 16, 2021)
3. Clinical Study Protocol Amendment 2 (March 03, 2022)
4. Clinical Study Protocol Amendment 3 (September 22, 2022)

The content of this SAP is compatible with the International Council for Harmonization/Food and Drug Administration E9 Guidance documents.

# 2 CHANGES TO PROTOCOL PLANNED ANALYSES

A summary of adverse events by maximum intensity was planned in protocol Section 9.4.4. This was removed per AZD7442 program-level data presentation decision.

Enrolment into the study has been discontinued due to FDA feedback. No participant has been included for Cohort 3, and the full analysis set will contain 46 instead of 100 participants. Planned analyses for Cohorts with no participants will not be conducted.

# 3 DATA ANALYSIS CONSIDERATIONS

## 3.1 Timing of Analyses

### 3.1.1 Interim Analysis

At least one interim analysis is planned to be conducted in this study after a minimum of 12 adolescent participants, age ≥ 12 to < 18 years old, complete the Day 92 study visit.

Additional interim analyses may be conducted to support regulatory requirements. No adjustment will be made for multiple hypotheses testing.

Please see Section 5 Interim Analysis for details on the analysis content.

### 3.1.2 Data Safety Monitoring Board

An independent DSMB will provide oversight to ensure safe and ethical conduct of the study. The DSMB will regularly meet and make any necessary recommendations to the Sponsor based on their evaluations of emerging data. In particular, the DSMB will conduct a safety evaluation once 14 days of safety data are available for 6 participants or more. Subsequent DSMB meetings will review safety data after 21, 36, 51, 66, 81 and 96 participants have been dosed with AZD7442. Data summaries will be prepared and provided to the DSMB.

Details for the DSMB and summaries to be prepared will be outlined in a DSMB Charter and a DSMB analysis plan.

## 3.2 Analysis Populations

The study population of pediatric participants aged ≥ 29 weeks gestational age to < 18 years are split into three cohorts by their COVID-19 status at study entry and dosed considering weight categories.

**Cohorts**

Cohort 1: Pediatric participants who are SARS-CoV-2 negative at baseline

Cohort 2: Pediatric participants who are SARS-CoV-2 positive at baseline and have mild to moderate COVID-19

Cohort 3: Pediatric participants who are SARS-CoV-2 positive at baseline and have severe COVID-19

In case a participant is assigned to Cohort 1 via a negative rapid COVID-19 test at screening, but the confirmatory test result is positive, the participant stays assigned to Cohort 1.

Cohort 3 will be empty due to discontinuation of enrolment. No change to enrolment in Cohort 1 and 2 was made.

**Route of IMP administration**

IM: Participants will receive a single dose of AZD7442 given via IM (AZD8895 followed by AZD1061 administered separately)

IV: Participants will receive a single IV infusion (AZD8895 and AZD1061 co-administered) based on the participant's body weight

**Age groups**
The participants' ages will be categorized into the following categories using age information captured during the randomization procedure.

1. ≥ 12 years to < 18 years
2. ≥ 6 years to < 12 years
3. ≥ 1 years to < 6 years
4. ≥ 29 week gestational age to < 1year
    a. ≥ 1 month to < 1 year
    b. ≥ 29 week gestational age to < 1 month

**Weight categories**

1. ≥ 1.5 to < 5 kg
2. ≥ 5 to < 15 kg
3. ≥ 15 to < 40 kg
4. ≥ 40 kg

## 3.3 General Considerations

### 3.3.1 General Study Level Definitions

All original and derived parameters as well as demographic and disposition data will be listed and described using summary statistics. All safety data (scheduled and unscheduled) will be presented in the data listings.

Summaries will be based on the visit schedule, but unscheduled and repeated assessments captured will be used for definition of baseline or for identification of worst post-baseline evaluations. If there is an unscheduled and a scheduled assessment with the same date, the unscheduled assessment will be assumed to be a repetition and the scheduled result used for summaries.

Frequency counts (number of participants [n] and percentages) will be produced for each qualitative variable. Descriptive statistics (n, mean, SD, median, minimum and maximum) will be calculated for each quantitative variable (unless otherwise stated). Descriptive statistics will only be presented if n > 3. If no participants have data at a given time point, n = 0 will be presented. If n < 3, only the n, minimum and maximum will be presented, and if n = 3, only the n, median, minimum and maximum will be presented; the other descriptive statistics will be left blank.

The CI to a geometric mean will be determined by log-transforming the observations, calculating the 95% confidence limits to the arithmetic mean of the transformed data and back-transforming the confidence limits with the exponential function.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator. The denominator should be clearly presented in each table.

Rounding should be the last operation in the treatment of data. There should be no rounding of intermediate results during the calculation of any derived value. Zeros at the end of a number should be retained.

All statistical analyses and production of tables, figures, and listings will be performed using SAS® version 9.4 or higher. All other requirements and specifications for programming and presentation of TFLs will be specified in the TFL shells document.

### 3.3.2 Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to the dose of IMP. These can be assessments from screening, Visit 1 or unscheduled or repeated assessments prior to IMP administration.

### 3.3.3 Change from Baseline

Change from baseline will be defined as the value post-dosing minus the baseline defined, for each timepoint.

Percent change from baseline will be calculated as:

Percent change from baseline = ([visit value – baseline value]/baseline value) ×100

### 3.3.4 Study Day

Study Day 1 is defined as the date of first dose of IMP.

For visits (or events) that occur on or after first dose of study treatment, study day is defined as (date of visit [event] – date of first dose of study treatment + 1). For visits (or events) that occur prior to first dose, study day is defined as (date of visit [event] – date of first dose of IMP). There is no study day 0 defined for this study.

### 3.3.5 Handling of Missing Data

In general, other than the below there will be no imputation of missing data unless explicitly stated.

In case of missing data in collection of AE start date or start time, that is not reported as unknown:

- AEs with start date/time at the time of or after dosing (for each specific treatment/dose) until Follow-Up Visit will be assigned to the specific treatment/dose.
- AEs with completely unknown start dates will be imputed with the date and time of dosing, unless the end date is known and prior to dosing; in that case the start date will be imputed as the date of Screening and a time of 00:00.
- AEs with unknown start times, but with start date known, will be imputed with a time of 00:00, unless the start date corresponds to the dosing date. In this case the start time will be imputed with the time of dosing. If this results in a start date/time after end date/time of the AE, then the time will also be imputed with 00:00.
- Missing day: impute with the 1st of the month, unless the month and year in which the AE started is a month and year in which IMP was administered, then the day will be imputed with the first day on which IMP was administered in that month. If this results in a start date after the end date, then the day will be imputed with the first day of the month.
- Missing month: impute with the 1st month in which IMP was administered. If this results in a start date after the end date of the AE, then the month will be imputed with JAN. If the known year part is not a year in which IMP was administered, then the month will also be imputed with JAN.
- Missing day and month: impute with the day and month of dosing. If this results in a start date after end date, then the day and month will be imputed with 01JAN. If the year is not a year in which IMP was administered, then the day and month will also be imputed with 01JAN.
- Missing year: impute with the year of dosing
- Missing times will be imputed as 00:00 h or with the time of dosing for events starting on a dosing day.

When imputing a start date, care should be taken to ensure the start date is sensible, ie, prior to the end date.

### 3.3.6 Visit Window

Scheduled visits will be analysed as captured in the electronic case report forms. Early discontinuation visits will be mapped to the chronologically closest not-performed visit.

### 3.3.7 Handling of Unscheduled Visits

#### 3.3.7.1 For Tables, Listings and Figures

Subject data listings will include data obtained from unscheduled visits chronologically.

By-visit summaries will not include unscheduled visits. Across-visits summaries, eg, summaries of occurrences will include unscheduled assessments.

#### 3.3.7.2 For Pharmacokinetic Analysis

In case a serum PK sample is drawn at an unscheduled visit, PK analysis will include the unscheduled concentrations.

### 3.3.8 Multiplicity/Multiple Comparisons

No hypotheses are planned to be formally tested using inferential statistics in this study so multiplicity is not a concern.

### 3.3.9 Handling of Protocol Deviations in Study Analysis

Protocol deviations will be captured and presented as described in Section 4.1.3. The protocol deviations and their categorization to "important" or "non-important" are pre-defined as far as possible before inclusion of the first participant. Final categorization of protocol deviations and actions for analysis will be done continuously during the study but finalized prior to the final analysis and any interim analysis.

For details on definition of protocol deviations, please refer to the study-specific Protocol Deviation Specification.

# 4 STATISTICAL ANALYSIS

This section provides information on definitions, derivation and analysis/data presentation per domain.

## 4.1 Study Population

The domain study population covers subject disposition, analysis sets, protocol deviations, demographics, baseline characteristics, medical history, prior and concomitant medication, and study drug compliance.

### 4.1.1 Analysis Sets

#### 4.1.1.1 Definitions and Derivations

Before database lock for the final or interim analysis, protocol deviation categories and the analyses populations will be produced for review. An analysis set classification meeting will be arranged to discuss the outputs and to decide which participants and/or participant data will be excluded from certain analyses. Decisions made regarding the exclusion of participants and/or participant data from analyses will be documented and approved by the sponsor.

**Table 1: Analysis sets**

| Population/Analysis Set | Description |
|---|---|
| Screened Population Set (SPS) | All participants who signed the ICF.<br>Unless otherwise stated, this set will be used for the presentation of disposition data. |
| Full Analysis Set (FAS) | All participants who received the IMP, irrespective of their protocol adherence and continued participation in the study. 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 (mFAS) | All participants who are in the FAS, excluding participants who were assigned to Cohort 1 by rapid COVID-19 test, but have a positive confirmatory test. |
| Safety Analysis Set (SAF) | All participants who have received IMP. |
| PK Analysis Set (PKS) | 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. |
| AZD1061 ADA Evaluable Analysis Set (ADS1) | A participant is AZD1061 ADA evaluable if in the SAF and having a non-missing baseline AZD1061 ADA result and at least one non-missing post-baseline AZD1061 ADA result. |
| AZD8895 ADA Evaluable Analysis Set (ADS2) | A participant is AZD8895 ADA evaluable if in the SAF and having a non-missing baseline AZD8895 ADA result and at least one non-missing post-baseline AZD8895 ADA result. |
| AZD7442 ADA Evaluable Analysis Set (ADS3) | All participants who are AZD8895 ADA evaluable and/or AZD1061 ADA evaluable. |
| SARS-CoV-2 nAb Evaluable Analysis Set (SES) | All participants in the Safety Analysis Set from whom blood samples were assumed not to be affected by factors such as protocol violations, and who had at least one quantifiable serum titer observation post dose. |

Generally, all listings will be prepared based on the SAF unless otherwise stated. Disposition data will be listed for the SPS.

#### 4.1.1.2 Presentation

A listing will be provided presenting each subject's inclusion in each analysis set and cohort. The number of subjects in each analysis set will be summarized qualitatively by cohort.

### 4.1.2 Subject Disposition and Completion Status

#### 4.1.2.1 Definitions and Derivations

A clear accounting of the disposition of all participants who enter the study will be provided, from screening to study completion including potential re-screening.

For each subject, the dates for each visit they participated in will be listed.

#### 4.1.2.2 Presentation

Participant disposition will be summarized and will include the following information: number of participants screened, randomized and dosed, number and percentage of participants completing the study and the number and percentage of participants who were withdrawn (including primary reason for withdrawal). The summary will be done overall and by cohort.

Participant discontinuations will be listed including the date of study exit, duration of participation and primary reason for discontinuation.

Participants and/or data excluded from the PK analysis set (see Section 4.1.1) will be listed including the reason for exclusion.

The analysis set to be used for these summaries and listings is the SPS (see Section 4.1.1).

### 4.1.3 Protocol Deviations

#### 4.1.3.1 Definitions and Derivations

Important deviations from the protocol (IPDs) may lead to the exclusion of participants or data from the PKS or SES. Deviations will be assessed and classified during the study and finalized before database lock. IPDs include those deviations from the protocol that are likely to have an impact on the perceived safety of study treatments or outcome assessment.

IPDs will include the following at a minimum:

- Violation of key inclusion and/or exclusion criteria.
- Administration of prohibited concomitant medications that are expected to influence the outcome of this study.
- Deviations from planned dose or administration procedure of the IMP.
- Relevant time window deviations expected to influence key safety and/or PK assessments.

All important protocol deviations will be listed. A qualitative summary table will be provided.

#### 4.1.3.2 Presentation

IPDs will be listed including the deviation type. The number of participants with IPDs will be summarized qualitatively by deviation type. The denominator for percentages will be the number of participants in the FAS.

### 4.1.4 Demographics

#### 4.1.4.1 Definitions and Derivations

Demographics (age, age categories, estimated gestational age for prematurely born infants at birth, sex, race and ethnicity) will be listed and summarized for the SAF.

**Age**

A participant's age is captured during randomization in categories "≥ 29 week gestational age to < 1 month", "≥ 1 month to < 1 year", "1 year", "2 years", etc. to "17 years". These categories will be integrated from the IRT into the study EDC system.

Additionally, for participants younger than 1 year, age in weeks (for age from 1 week to 3 months) or age in months (for age from four months to less than 1 year) will be captured. If the participant is prematurely born, the gestational age at birth in weeks is captured.

Age categories (1, 2, 3, 4, 4a and 4b) defined in Section 3.2 will be summarized by count and percent (relative to the number of participants in the analysis set) and age in years continuously for participants aged 0 to less than 12 years and 12 years or older separately.

In case transformations of units will need to be done, 4.3 weeks will amount to 1 month.

#### 4.1.4.2 Presentation

The denominator for percentages will be the number of participants in the SAF. Summaries and listings will be done by cohort for the SAF.

Quantitative summary of age will be computed for each weight category separately.

A summary of demographics for those participants with a positively adjudicated Cardiovascular (CV) event will be presented.

### 4.1.5 Baseline Characteristics

#### 4.1.5.1 Definitions and Derivations

Participant characteristics at baseline height [cm], weight [kg] and weight category and COVID-19 vaccination status at baseline will be listed and summarized.

Quantitative summary of height and weight will be computed by cohort and weight category.

#### 4.1.5.2 Presentation

Both listings and summaries will be presented for the SAF.

A summary of demographics for those participants with a positively adjudicated Cardiovascular (CV) event will be presented.

### 4.1.6 Disease Characteristics

#### 4.1.6.1 Definitions and Derivations

COVID-19 status (Negative/Positive) will be determined at screening for all participants and severity for those assigned to Cohorts 2 and 3. A COVID-19 symptom screen is performed for occurrence and severity of COVID-19 symptoms (none, mild, moderate, severe, unknown). The symptom screen is also performed when Cohort 1 participants develop at least one of the below symptoms post Day 1.

- Symptoms of any duration
    - Fever
    - Shortness of breath
    - Difficulty breathing
- Symptoms present for 2 or more days
    - Chills
    - Cough
    - Fatigue
    - Muscle aches
    - Body aches
    - Headache
    - New loss of taste
    - New loss of smell
    - Sore throat

#### 4.1.6.2 Presentation

Each symptom will be summarized qualitatively by category (none, mild, moderate, severe, unknown). For Cohorts 2 and 3, the summary will include only the screening visit. For subjects of Cohort 1, the summary will be calculated for occurrence at any time after Day 1.

### 4.1.7 Medical History and Concomitant Disease

#### 4.1.7.1 Definitions and Derivations

Disease related medical history (past, ie, started and stopped before treatment and current, ie, started before study and ongoing at treatment visit) will be coded using MedDRA version 24.1 or higher.

#### 4.1.7.2 Presentation

All related medical history will be listed including visit, description of the disease/procedure, MedDRA SOC, PT, start date and stop date (or ongoing, if applicable). Number of subjects with a history or concomitant condition will be counted by SOC and PT and by cohort.

A summary of medical history for those participants with a positively adjudicated Cardiovascular (CV) event will be presented.

### 4.1.8 Prior and Concomitant Medications

#### 4.1.8.1 Definitions and Derivations

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study will be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Prior medications are those with start and stop date before the day of treatment.

Concomitant medications are any medications taken at least once between day of treatment (inclusively) and end of the follow-up period. Ie, medications with start date prior to Day 1 and ongoing, medications with start date between Day 1 and day of Visit 6 (or early discontinuation).

The duration of the medication will be calculated as:

Duration = (end date/time) – (start date/time) +1

The duration may be presented in hours or days in the listing depending on the applicability to the emerging data. For medications with partial or completely missing start date/times and/or end date/times, the duration will not be calculated.

Prior and concomitant medications will be coded using the AstraZeneca dictionary.

#### 4.1.8.2 Presentation

Prior and concomitant medications will be listed by participant and will include the following information: reported name, preferred term, the route of administration, dose, frequency, start date/time, duration, and indication.

The number of participants exposed to a medication will be presented for each occurring coded term of prior/concomitant medications. The percentage will be based on the number of subjects in each cohort in the SAF.

### 4.1.9 Study Drug Compliance

#### 4.1.9.1 Definitions and Derivations

No analysis for study drug compliance is planned as the drug is only administered once.

#### 4.1.9.2 Presentation

Not applicable.

## 4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary, secondary, other endpoints. Sensitivity analyses are done by repeating the endpoint analyses using a sensitivity analysis set if indicated in Table 2. The analysis sets shown are applicable to the tables of the endpoints. Listings may utilize other sets. All endpoint analyses will be descriptive qualitative or quantitative summaries.

**Table 2: Analysis Endpoints**

| Objectives | Endpoints | Analysis Set |
|---|---|---|
| **Primary** | | |
| 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 one-year study period when administered as a single IM or IV dose | PKS |
| | Serum PK parameters (if data permits): Cmax, tmax, t1/2, AUC0-last , AUC0-inf , tlast, %AUCext, and:<br>• for IM: CL/F, and Vz/F<br>• for IV: CL, and Vss | PKS |
| | Model-derived predicted serum AZD7442 concentrations, Cmax and AUC0-inf | PKS |
| To evaluate the safety and tolerability of AZD7442 after a single IM or IV dose in pediatric participants | TEAEs, SAEs, and AESIs (including anaphylaxis, injection/infusion site reactions, MIS-C). | SAF |
| | 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. | SAF |
| **Secondary – All Cohorts** | | |

| Objectives | Endpoints | Analysis Set |
|---|---|---|
| To evaluate the PD of AZD7442 after a single IM or IV dose | Titer of SARS-CoV-2 neutralizing antibodies | SES |
| To evaluate the immunogenicity profile of AZD7442 | Incidence of ADA and nAb to AZD7442 in serum | ADS1/2/3 |
| **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 | SAF, mFAS |
| **Secondary – Cohort 2 and Cohort 3 (Treatment)** | | |
| To quantify SARS-CoV-2 viral loads after a single IM or IV dose of AZD7442 in pediatric participants | Change from baseline to Day 8 in viral load as measured by qRT-PCR. | SAF |
| To evaluate the proportion of participants with progression of COVID-19 after a single IM or IV dose of AZD7442 in pediatric participants | Proportion of participants with progression of COVID-19 through Day 29 | SAF |
| 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 | SAF |
| **Secondary – 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 | Time to sustained recovery (defined as being discharged from the index hospitalization, followed by being alive and home for 14 consecutive days) | SAF |
| **Exploratory** | | |
| To evaluate the concentrations of AZD7442 in nasal fluid after a single IM or IV | Nasal concentrations of AZD7442 at specified time points during the one-year study period when administered as a single IM or IV dose | SAF |

| Objectives | Endpoints | Analysis Set |
|---|---|---|
| dose in pediatric participants | | |

### 4.2.1 Primary PK Endpoints

To evaluate the serum concentrations of AZD7442 after a single IM or IV dose in pediatric participants, the primary PK endpoints serum AZD7442 concentrations and PK parameters derived from these by non-compartmental analysis in accordance with AstraZeneca Pharmacokinetic Evaluations in Clinical Trials guideline will be listed and presented separately in tabular and graphical form.

Any serum concentrations for AZD7442 will be reported as the individual component concentrations AZD8895 and AZD1061 as well as the sum of the two individual component concentrations labelled as AZD7442.

The analysis of these endpoints will comprise of descriptive summary statistics stratified by cohort, route of administration (IM or IV) and weight categories (1, 2, 3, 4 and all).

For PK parameters other than tmax and tlast, the following descriptive statistics will be presented: n, gmean, gSD, 95% CI for the gmean, gCV, arithmetic mean, arithmetic SD, median, minimum, and maximum. For tmax and tlast, only n, median, minimum, and maximum will be presented.

#### 4.2.1.1 Serum Concentration Data

For AZD7442 mAbs, the serum concentrations for each scheduled time point will be summarized based on the PKS.

A listing of all serum concentration-time data, ie, PK scheduled times, actual sample collection times, sample actual relative times (ie, relative to time of administration of the IMP), as well as derived sampling time deviations (ie, difference between actual and scheduled time) will be presented for all participants in the SAF.

#### 4.2.1.2 Figures for Serum Concentration Data

Individual serum concentration-time data (AZD7442, AZD8895 and AZD1061) will be graphically presented on linear and semi-logarithmic scales, for all participants in the PKS . Combined individual serum concentration versus actual times will be plotted on both the linear and semi-logarithmic scales for all participants in the PKS. Plots will be grouped by cohort, route of administration and weight categories. Figures for the gmean (±gSD) serum concentration-time data will be presented by cohort, route of administration and weight categories (1, 2, 3, 4 and all) on both a linear and semi-logarithmic scale (no gSD presented for the semi-logarithmic scale), for all participants in the PKS.

#### 4.2.1.3 Serum Pharmacokinetic Parameters

All reportable AZD7442, AZD8895 and AZD1061 PK parameters, obtained by non-compartmental analysis method, including individual diagnostic and λz-related parameters, will be listed for each participant by cohort, route of administration and weight categories, based on the PKS. All PK parameters will be summarized based on the PKS.

**Table 3: PK Parameters**

| Parameter | Definition | Calculation |
|---|---|---|
| Cmax | Maximum observed serum (peak) drug concentration | |
| Clast | Last observed (quantifiable) concentration | |
| Ctrough | Observed drug concentration at the end of a specified time interval that is indication specific | For cohort 2 and 3 (treatment): concentration 28 days post-dose<br>For cohort 1 (prophylaxis): concentration 182 days post-dose |
| tmax | Time [days] to reach peak or maximum observed concentration following drug administration | |
| AUC(0-92d) | area under the serum concentration-time curve from time zero to day 92 | Using the linear up/log down trapezoidal rule |
| AUC0-last | Area under the serum concentration-time curve from time zero to time of last quantifiable concentration | Using the linear up/log down trapezoidal rule |
| AUC0-inf | Area under serum concentration-time curve from time zero to infinity | Calculated by AUC(0-t) and then extrapolated by Clast/λz to infinity |
| tlast | Time of last quantifiable serum concentration [days] | |
| %AUCext | percentage of AUC extrapolated | |
| λz | Terminal elimination rate constant | Estimated from linear regression of the terminal part of the log concentration versus time curve |
| t½ λz | Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve (final analysis only) [days] | ln 2/λz |
| MRT | Mean residence time | |
| CL/F (for IM) | Apparent total body clearance of drug from serum after extravascular administration | Dose/AUC0-inf |

| Parameter | Definition | Calculation |
|---|---|---|
| Vz/F (for IM) | Volume of distribution (apparent) following extravascular administration (based on terminal phase) | Dose/(λz * AUC0-inf) |
| CL (for IV) | Total body clearance of drug from serum after intravenous administration | DoseIV / AUC0-inf |
| Vss (for IV) | Volume of distribution at steady state after intravenous administration | MRT * CL |

#### 4.2.1.4 Final Population PK Model

At the end of covariate testing, alternative variance-covariance structures for Ω will be evaluated including partial and full block structures. Such a structure is deemed suitable if it provides a statistically significant ($p < 0.001$) improvement in the model OFV and if it improves model stability as measured by the condition number and/or a successful covariance step. The model that results from this step of the model building process is considered the final model.

Further criteria for accepting a model as the final run includes the following:

- The minimization (for gradient methods) is successful.
- There are no estimates close to a boundary.
- Relative standard errors (RSE) of the estimates should be < 30% for fixed-effect parameters and < 50% for random-effect parameters.
- There are no unacceptable trends in goodness-of-fit plots.
- The model allows for the goal of the analysis to be met.
- The parameter shrinkage is acceptable.

- Population PK parameter estimates from the final model will be presented, including bodyweight-adjusted clearance for each bodyweight category (adjusted to the mean bodyweight of each weight category). Additionally, the post-hoc individual PK parameter estimates (including AUC0-inf) will be summarized.

#### 4.2.1.5 Evaluation of the Final Population PK Model

Model qualification will be based on criteria including successful numerical convergence, acceptable goodness of fit plots with no indication of bias, adequate precision in parameter estimates evaluating shrinkage in important parameters (CL, V and Ka parameters). In addition, Visual Predictive Checks (VPCs) will be used to evaluate the predictive ability of the final model. Where applicable, VPCs will be performed with prediction correction. Plots of observed data distributions will be compared with simulated distributions to demonstrate the model's ability to adequately predict the data on which the model was based. VPCs will be based on at least 500 simulations and will be stratified by covariates of

potential interest. Specifically, VPCs will be stratified by cohort, route of administration and weight category.

#### 4.2.1.6 Handling of Missing Data and LLOQ

Individual concentrations below the Lower Limit of Quantification (LLOQ) of the bioanalytical assay will be reported as NQ (Not Quantifiable) in the listings with the LLOQ defined in the footnotes of the relevant tables, listings and figures. Individual serum concentrations that are Not Reportable will be reported as NR and those that are missing will be reported as NS (No Sample) in the listings. Serum concentrations that are NQ, NR or NS will be handled as follows for the provision of descriptive statistics:

- Any values reported as NR or NS will be excluded from the summary tables and corresponding figures.
- At a time point where less than or equal to 50% of the concentration values are NQ, all NQ values will be set to the LLOQ, and all descriptive statistics will be calculated accordingly.
- At a time point where more than 50% (but not all) of the values are NQ, the gmean, gmean ± gSD and geometric coefficient of variation (gCV) will be set to NC. The maximum value will be reported from the individual data, and the minimum and median will be set to NQ.
- If all concentrations are NQ at a time point, no descriptive statistics will be calculated for that time point. The gmean, minimum, median and maximum will be reported as NQ and the gCV and gmean ± gSD as NC.
- The number of values below LLOQ (n < LLOQ) will be reported for each time point together with the total number of collected values (n).

Three observations > LLOQ are required as a minimum for a serum concentration or PK parameter (eg, Cmax, Clast) to be summarized. Two observations > LLOQ are presented as minimum and maximum with the other summary statistics as NC.

For AZD7442 concentration derived as the sum of AZD1061 and AZD8895 concentrations, the following cases of < LLOQ or missing hold:

| AZD1061 concentration | AZD8895 concentration | Result of AZD7442 concentration |
|---|---|---|
| < LLOQ | < LLOQ | < LLOQ |
| < LLOQ | XX | XX |
| YY | < LLOQ | YY |
| YY | XX | YY + XX |
| Missing | XX | Missing |
| YY | Missing | Missing |
| Missing | Missing | Missing |

#### 4.2.1.7 Population PK Analysis

Pharmacokinetic data from all cohorts, routes of administration and age group/weight categories will be analysed simultaneously by population PK approaches.

##### 4.2.1.7.1 Dataset to Develop the Population PK Model

A population model based on adult studies are under development. The AZD7442 population PK structural model will be developed based on serum concentration time- profile from the Phase I study (D8850C00001) conducted in healthy adult subjects, Phase III studies conducted in adult patients that will include at least studies D8850C00002, D8850C00003, D8851C00001 and ACTIV-3 and paediatric PK/PD/safety study D8850C00006, when data are available. Individuals will be defined as evaluable for the population PK analysis if they have at least one AZD7442 post-dose serum sample that are above the lower limit of quantification (LLOQ). Missing data will not be imputed. Concentrations below the LLOQ will be handled with the M3 method. Population PK data from this study as defined in section 4.2.1.7 will be added to the adult population PK dataset. A brief description of the minimum studies to be included in the dataset is provided in Table 5 Description of the studies to be included in the population PK analysis. in the appendix.

##### 4.2.1.7.2 Data analysis methods

The analysis will be carried out according to the FDA and EMA guidances “Guidance for Industry: Population Pharmacokinetics” and “Guidance on Reporting the Results of Population Pharmacokinetic Analyses”, respectively.

##### 4.2.1.7.3 Covariates to be used in the analysis

This updated Population PK model will account for clinically relevant covariates and will include a weight-based allometric scaling of clearance and volume, with fix allometric exponents along with an age-based maturation function for clearance. Covariates in the

latest adult population PK model will be included such as age, body weight, sex, race and eGFR co-morbidity etc. Additional covariates such as body surface area (BSA), body mass index (BMI), albumin, anti-drug antibodies, hepatic function, renal function, SARS-CoV-2 infected or not, viral load, severity of disease, asymptomatic or not, and different co-morbidities may be evaluated as well if deemed appropriate. Co-linearity among covariates will be examined. For pairs with correlation > 80%, a determination will be made as to which variable to retain based on factors such as clinical relevance consistency of variable. The covariates, whenever available, for the population PK analysis will be collected for all subjects who have received AZD7442 and had at least 1 valid serum concentrations. The assessment of each categorical covariate will be done if enough data are available to perform the test, ie if more than 20 subjects or more than 10% of subjects represent this subgroup of covariate. Race will be tested and potentially combined if deemed appropriate, such as combining all Asian populations.

**Demographics and baseline clinical chemistry covariates in consideration for investigation**

- Route of Administration (1 = IV Intra Venous; 2 = IM Intra Muscularly)
- Sex (SEX), 1 = males and 0 = females
- Race (RACE), 1 = White; 2 = Black; 3 = Asian; 4 = Other
- Age (AGE), year, weeks
- Body weight (WT), kg
- BMI (kg/m2)
- Alanine Aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Estimated Glomerular Filtration Rate (eGFR)
- Serum Creatinine (SCR)
- Total Bilirubin (BIL)
- Serum Albumin
- Co-morbidity information
- Viral Load

Covariates that change over time will be considered in order to obtain values that match the observation time of the dependent variable, such as age and body weight especially in the paediatric patients.

**Derived covariates**

- Creatinine clearance (CrCL) (mL/min) is estimated depending on age using the following methods:
    1. Original or Bedside Schwartz Equations for pediatric patients:

$$eGFR = k * \frac{height\ in\ cm}{SCR}$$

(a) Original Schwartz Equation for participants < 1 year of age:
- k = 0.33 in preemie infants
- k = 0.45 in term infants to 1 year of age

(b) Bedside Schwartz Equation for participants ≥ 1 to < 12 years of age:
- k = 0.413

2. Cockcroft and Gault method for adolescent subjects ≥ 12 years of age:

$$CRCL(mL/\min) = \frac{[140 - age(yr)] \cdot Weight(kg)}{72 \cdot SCR(mg/dL)}$$ in males

$$CRCL(mL/\min) = \frac{0.85 \cdot [140 - age(yr)] \cdot Weight(kg)}{72 \cdot SCR(mg/dL)}$$ in females

Where SCR = serum creatinine concentration.

- Baseline Body Mass Index (kg/m²)
  BMI = $W/H^2$

**Subject population**

- Healthy volunteers
- Subjects who do not have COVID-19
- Subjects with mild/moderate COVID-19
- Subjects with severe COVID-19

#### 4.2.1.7.4 Structural Population PK Model and Covariate Model Development

Based on prior experience, a 2-compartment model with fixed standard allometric exponents (0.75 for clearances and 1 for volumes) will be evaluated with the inclusion of an age-based maturation function for clearance to represent the paediatric population.

Random Effects in the Population PK Model

Inter-individual random effects on the parameters will be introduced and retained if their inclusion do not cause model instability and if their estimates are not close to zero. These will be modeled assuming a log-normal distribution as given by the following expression:

$$\theta_{ki} = \theta_k * e^{\eta_{ki}}$$

where $\theta_{ki}$ denotes the parameter value for the $i^{th}$ subject, $\theta_k$ denotes the typical parameter value, and $\eta_{ki}$ denotes the inter-individual random effect for the $i^{th}$ subject – assumed to have mean of 0 (zero) and variance $\omega_k^2$.

Collectively, the vector of random effects (across the parameters indexed by k) has the covariance matrix Ω. Covariance matrix structures including diagonal and blocked diagonal structures will be evaluated after the completion of covariate model building.

The residual error structure will be assumed to follow an proportional error model described by the following:

$$Y_{ij} = C_{ij} * (1 + \varepsilon 1_{ij})$$

where $Y_{ij}$ is the $j^{th}$ observed concentration for the $i^{th}$ subject, $C_{ij}$ is the corresponding predicted concentration, and $\varepsilon 1_{ij}$ (proportional) is the residual error under the assumption that $\varepsilon \sim N(0, \sigma^2)$.

The residual error model will be optimized until no trends are visible in residual plots (in particular, absolute values of IWRES versus IPRED.

Covariates in the latest adult population PK model will be included

The latest adult population PK model including covariates will serve as the base model. For additional covariate investigation, the covariate selection will be performed using a forward addition process followed by backward elimination process. The likelihood ratio test will be used to evaluate the significance of incorporating or removing fixed effects into the population model based on significance levels set a priori. For forward addition and backward elimination, significance levels of 0.01 and 0.001 are utilized, respectively. The improvement of the model relative to the base model is compared when each of the covariates is added univariately, and the model with the largest improvement is kept for the next evaluation step, given that there is an overall statistical significance supporting the inclusion of the respective covariate. During the backward elimination process, covariates are removed from the model one at a time if their deletion leads to insignificant model deterioration. The most insignificant covariate is removed first, and the procedure is repeated until no further insignificant covariate relationship is detected.

All continuous covariates are incorporated into the population model using a scaled structure based on either the median value of the covariate in the population or a reference value for the covariate (eg 70 kg for body weight, as was the case in the previous popPK model). This approach ensures that covariate effects are relative to an individual in the middle of the population distribution for that covariate. All categorical covariates are incorporated into the population model using a proportional structure with either the most common level of the covariate being the reference or a level specific to the analysis (eg healthy volunteer versus patient). This approach ensures that categorical covariate effects are relative to a reference group or category. The mathematical structures of the covariate models are shown below:

| **Continuous** | **Categorical** |
|---|---|
| $P_{ki} = \theta_k * \left(\frac{X_{ij}}{M(X_j)}\right)^{\theta_j}$ | $P_{ki} = \theta_k * (1 + \theta_j)^{X_{ij}}$ |

where $P_{ki}$ is the population estimate of the parameter $P_k$ for subject i, $X_{ij}$ is the value of continuous covariate $X_j$ for subject i, or an indicator variable for subject i for categorical covariate $X_j$ with value 1 for the nonreference category and 0 for the reference category, $M(X_j)$ is the median of covariate $X_j$ in the analysis dataset, $\theta_k$ is the typical value of the parameter $P_k$, and $\theta_j$ is a coefficient that reflects the effect of covariate $X_j$ on the parameter.

To ensure that the model emerging from the covariate testing process did not neglect any important covariate effects, random effects from the final model are plotted versus potential covariates and evaluated for residual trends in parameter covariate relationships.

#### 4.2.1.8 Final Population PK Model

At the end of covariate testing, alternative variance-covariance structures for Ω will be evaluated including partial and full block structures. Such a structure is deemed suitable if it provides a statistically significant ($p < 0.001$) improvement in the model OFV and if it improves model stability as measured by the condition number and/or a successful covariance step. The model that results from this step of the model building process is considered the final model.

Further criteria for accepting a model as the final run includes the following:

- The minimization (for gradient methods) is successful.
- There are no estimates close to a boundary.
- Relative standard errors (RSE) of the estimates should be < 30% for fixed-effect parameters and < 50% for random-effect parameters.
- There are no unacceptable trends in goodness-of-fit plots
- The model allows for the goal of the analysis to be met.
- The parameter shrinkage is acceptable.

Population PK parameter estimates from the final model will be presented, including bodyweight-adjusted clearance for each bodyweight category (adjusted to the mean bodyweight of each weight category). Additionally, the post-hoc individual PK parameter estimates (including AUC0-inf) will be summarized.

#### 4.2.1.9 Evaluation of the Final Population PK Model

Model qualification will be based on criteria including successful numerical convergence, acceptable goodness of fit plots with no indication of bias, adequate precision in parameter estimates evaluating shrinkage in important parameters (CL, V and Ka parameters). In addition, Visual Predictive Checks (VPCs) will be used to evaluate the predictive ability of the final model. Where applicable, VPCs will be performed with prediction correction. Plots of observed data distributions will be compared with simulated distributions to demonstrate the model's ability to adequately predict the data on which the model was based. VPCs will be based on at least 500 simulations and will be stratified by covariates of potential interest. Specifically, VPCs will be stratified by cohort, route of administration and weight category.

#### 4.2.1.10 Subgroup Analyses

No analyses for a specific subgroup are planned.

### 4.2.2 Primary Safety Endpoints

To evaluate the safety and tolerability of AZD7442 after a single IM or IV dose in pediatric participants, the primary safety endpoints will be used: TEAE, SAE, AESI, safety laboratory parameters, electrocardiogram (ECG), vital signs and physical examinations. The analysis of these endpoints will comprise of qualitative or quantitative summary statistics.

All summaries of primary safety endpoints will be based on the SES, listings will be created for the SAF.

#### 4.2.2.1 Adverse Events

Adverse Events will be collected throughout the study from date of informed consent until the end of the follow-up. The MedDRA will be used to code the AEs using the latest available version.

Treatment-emergent AEs are those AEs with onset date/time at or after dosing.

A listing will cover details for each individual AE including MedDRA SOC, PT, reported term, seriousness, start and stop date/time, relatedness to IMP, intensity (mild, moderate, severe and CTCAE grade 1-5), actions taken, time from last dose, whether or not leading to withdrawal from the study, AESI identification and outcome.

**Serious Adverse Events**

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, followup), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above

Serious Adverse Events are identified as serious via the eCRF.

**Adverse Event of Special Interest**

An AESI includes any of the following TEAEs (categorized in the eCRF):

- Anaphylaxis
- Hypersensitivity
- Serious Hypersensitivity Reaction including immune complex disease
- Injection Site and Infusion Site Reactions (as identified by the investigator in the Adverse Event eCRF form. For the summary of injection/infusion site inspection, please see Section 4.2.8.2)
- MIS-C

- Thrombotic events, heart failure and cardiac ischemia

**Cardiovascular Events**
Cardiovascular (CV) AEs are be referred to a CV Event Adjudication Committee. Only adjudicated events will be included as AESIs.

CV events (cardiac ischemia, CV death, heart failure, stroke, thrombotic event) with their adjudication results will be listed and summarized:

- Summary of CV adjudication results
- time to onset of the event
- number of participants/events with positive adjudication

Demographics, baseline characteristics and medical history summaries will be repeated for those participants who experienced a positively adjudicated CV event.

**Analysis of Adverse Events**
The safety of AZD7442 will primarily be assessed by:

- Incidence of TEAEs through end of study
- Incidence of SAEs through end of study
- Incidence of AESIs through end of study

Summaries of these incidences will include the number and percentage of participants reporting at least one event with the 95% exact Clopper-Pearson confidence interval for the percentage, number of events, exposure adjusted rates and presented by cohort and route of administration.

An overview of AEs will be presented for each cohort and route of administration, including the number and percentage of participants with any AE and SAEs. Summaries will present the relationship to IMP as assessed by the Investigator, seriousness, and deaths.

#### 4.2.2.2 Laboratory parameters
Hematology, clinical chemistry, coagulation, and urinalysis parameters will be summarized quantitatively by count, mean, SD and median, and listed by visit and cohort together with their changes from baseline.

The listings will include the following information: test name, date of measurement, reference range, result and flags for any measurements that are outside the reference range (eg, AstraZeneca, program, or laboratory ranges) and include repeat or unscheduled measurements. Clinical laboratory data will be reported in System International units.

**Table 4: Laboratory parameters**

| | |
|---|---|
| **Hematology** | |
| White blood cell (WBC) count | Neutrophils absolute count |
| Red blood cell (RBC) count | Lymphocytes absolute count |
| Hemoglobin (Hb) | Monocytes absolute count |
| Hematocrit (HCT) | Eosinophils absolute count |
| Mean corpuscular volume (MCV) | Basophils absolute count |
| Mean corpuscular hemoglobin (MCH) | Platelets |
| Mean corpuscular hemoglobin concentration (MCHC) | |
| **Serum Clinical Chemistry** | |
| Sodium | Alkaline phosphatase (ALP) |
| Potassium | Alanine aminotransferase (ALT) |
| Urea | Aspartate aminotransferase (AST) |
| Creatinine | Gamma glutamyl transpeptidase (GGT) |
| Albumin | Total Bilirubin |
| Calcium | Unconjugated bilirubin |
| Phosphate | Conjugated bilirubin |
| Glucose | Creatine Kinase |
| **Urinalysis** | |
| Glucose | |
| Protein | |
| Blood | |
| Microscopy (if positive for protein or blood): RBC, WBC, Casts (Cellular, Granular, Hyaline) | |
| **Coagulation** | |
| International normalized ratio | Prothrombin Time |
| Activated partial thrombin time | |

#### 4.2.2.3 Vital Signs

The results of heart rate, respiration rate, pulse rate, pulse oximetry, BP, and body temperature measurements will be listed by participant and time point including the date/time of the assessment, changes from baseline and repeat/unscheduled measurements.

Descriptive statistics (count, mean, SD and median) will be presented by time point for both observed values and changes from baseline.

#### 4.2.2.4 Physical Examination

A Complete Physical Examination will include, but not be limited to, assessment of height, weight, general appearance, head, ears, eyes, nose, throat, neck, skin, as well as cardiovascular, respiratory, abdominal, and nervous systems.

Abnormal baseline/results of the Physical Examination will be documented in medical history.

Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment will be reported as an AE.

#### 4.2.2.5 ECG

12-lead ECG results will be listed for each participant with overall evaluation by the investigator as Normal, Abnormal or Borderline including clinical significance (CS or NCS).

These evaluations will be summarized via a shift table showing the frequencies and percentages of the baseline evaluation versus the worst post-baseline overall evaluation.

#### 4.2.2.6 Subgroup Analyses

No analyses for a specific subgroup are planned.

### 4.2.3 Secondary Endpoint – All Cohorts

#### 4.2.3.1 SARS-CoV-2 neutralizing antibodies

To evaluate the PD of AZD7442 after a single IM or IV dose, titers of SARS-CoV-2 neutralizing antibodies will be listed for the SAF and summarized for the SES at each time point.

Descriptive statistics for gmean titers (GMT) and geometric mean fold rises will include number of participants, gmean, gSD, 95% CI for the gmean, minimum, and maximum.

The GMTs for nAbs will be calculated for all participants in the SES as the antilogarithm of Σ(log2 transformed titer/n), ieas the antilogarithm transformation of the mean of the log-transformed titer with base 2, where n is the number of participants with titer information. The gSD for GMT will be calculated as the antilogarithm transformation of the standard deviation of the log-transformed titer. The 95% CI will be calculated as the antilogarithm transformation of the upper and lower limits for a two-sided CI for the mean of the log-transformed titers.

Summary tables will be generated by cohort and route of IMP administration, and separately by cohort, route of administration and COVID-19 vaccination status at baseline (as captured in the eCRF).

#### 4.2.3.2 ADA and nAb to AZD7442 in serum

To evaluate the immunogenicity profile of AZD7442, the incidence of ADA and nAb to AZD7442 in serum will be assessed and summarized for the ADS (ie, ADS1 for AZD1061, ADS2 for AZD8895 and ADS3 for AZD7442).

The ADA for AZD7442 will be assessed for the individual agents AZD8895 and AZD1061 separately. The respective agent's ADA Evaluable Analysis Set (see Table 1: Analysis sets) is to be used for the individual summary. The ADA titer of AZD7442 will be defined as the maximum of AZD8895 and AZD1061 titers at each time point.

Serum samples for AZD8895 and AZD1061 ADA assessments will be conducted utilizing a tiered approach (screen, confirm, titer), and ADA data will be collected at scheduled visits. The ADA results from each sample will be reported as either positive or negative. If the sample is positive in the confirmatory assay, the ADA titer will be reported as well. In addition, the presence of nAb will be tested for all ADA positive samples in the confirmatory assay. The nAb results will consist of a titer result and a subject status reported as positive or negative. Both of these results will be taken as received from the bioanalytical laboratory. A participant is defined as being ADA-positive if ADA evaluable and a positive ADA result in the confirmatory assay is available at any time, including baseline and all post-baseline measurements; otherwise the participant is defined as ADA negative if ADA evaluable.

Specifically for presentation of AZD7442, ADA-positive to AZD7442 is having a positive ADA result to AZD8895 and/or AZD1061 at any time, including baseline and all post-baseline measurements. ADA-negative is having negative ADA results to all evaluable AZD8895 and AZD1061 results at all time, including baseline and all post-baseline measurements. Summaries will include only ADA evaluable subjects for the respective agent.

In the evaluation of ADA results to AZD7442, if a component mAb (ieAZD8895 or AZD1061) is not ADA evaluable, all results from the component would be treated as missing.

ADA sample pos/neg status:

- For a sample of a particular visit, AZD7442 is + for that visit if either AZD1061 and/or AZD8895 is +

ADA subject pos/neg status:

- For a subject, AZD7442 is + if either AZD1061 and/or AZD8895 is + at any visit and if the subject is ADA evaluable for the mAb having the + result

Treatment-induced ADA+:

- For AZD1061, ADA negative at baseline and ADA positive at ≥ 1 post-baseline assessments with ADA titer ≥ 80
- For AZD8895, ADA negative at baseline and ADA positive at ≥ 1 post-baseline assessments with ADA titer ≥ 160

- AZD7442 is treatment-induced ADA+ if either AZD8895 and/or AZD1061 is treatment-induced ADA+

Treatment-boosted ADA+:

- For AZD1061 or AZD8895, Baseline positive ADA titer that was boosted to ≥ 4 -fold during study period
- AZD7442 is treatment-boosted ADA+ if either AZD8895 and/or AZD1061 is treatment-boosted ADA+

Treatment-emergent ADA+:

- For AZD1061 or AZD8895, either treatment-induced ADA+ or treatment-boosted ADA+
- AZD7442 is treatment- emergent ADA+ if either AZD8895 and/or AZD1061 is treatment- emergent ADA+

Persistently ADA+:

- For AZD1061, participants who are Treatment-emergent ADA positive, and having ADA post-baseline positive with ADA titer ≥ 80 at ≥ 2 post-baseline assessments (with ≥ 16 weeks between first and last positive) or positive with ADA titer ≥ 80 at last post-baseline assessment
- For AZD8895, participants who are Treatment-emergent ADA positive, and having ADA post-baseline positive with ADA titer ≥ 160 at ≥ 2 post-baseline assessments (with ≥ 16 weeks between first and last positive) or positive with ADA titer ≥ 160 at last post-baseline assessment
- AZD7442 is persistently ADA+ if either AZD8895 and/or AZD1061 is persistently ADA+

Transiently ADA+

- For AZD1061, participants who are Treatment-emergent ADA positive, and having at least one post-baseline ADA positive assessment with titer ≥ 80 and not fulfilling the conditions of persistently positive
- For AZD8895, participants who are Treatment-emergent ADA positive, and having at least one post-baseline ADA positive assessment with titer ≥ 160 and not fulfilling the conditions of persistently positive
- For AZD7442, treatment-emergent ADA positive and not fulfilling the conditions of persistently positive.

The number and percentage of AZD7442, AZD8895 and AZD1061 ADA-evaluable positive/negative participants in each cohort will be determined. The number of ADA-

evaluable participants in the cohort will be used as the denominator for percentage calculation.

To evaluate the ADA responses to AZD7442, AZD8895 and AZD1061 in serum the following analyses will be presented:

- The date and time of the blood samples collected for assessment of ADAs (samples to confirm the presence or absence of anti-AZD7442 (AZD8895 and AZD1061) antibodies from pre-dose Day 1 to Day 366, including the titer for samples confirmed positive for ADA) and neutralizing Antibodies (nAbs) will be listed. Tabulations will be provided for each cohort. The listings will be based on the SAF, the tabulations on the ADS1/2/3 respecively.

- The results of the ADA assessments will be listed for each participant and time point. This will include the classification of the response (positive/negative) and the measured titers where appropriate. Summary tables will be presented, by weight categories, dose, and route of administration as well as overall by route of administration, for the number and percentage of participants with positive/negative results at each time point, based on the ADS1/2/3 respecively.

In addition, the ADA titers (n, median, minimum, and maximum) will be summarized by cohort, route of administration (IM or IV) and weight categories (1 to 4 and all) for all participants with a positive confirmatory assay result at each time point; this tabulation will include a summary of the highest titer across all time points for each participant.

The impact of ADA on PK, PD, and association with AEs and SAEs will be assessed using the graphical and/or tabular displays.

For each cohort and by route of administration, spaghetti plots of individual PK concentration versus time profile by ADA subject status (positive or negative differentiated in the figure via color and/or line style) will be produced on semi-logarithmic scale. AZD7442, AZD8895 and AZD1061 concentrations will be presented separately.

For each cohort and by route of administration, spaghetti plots of nAb titer versus time profile by ADA subject status (positive or negative differentiated in the figure via color and/or line style) will be produced on semi-logarithmic scale.

### 4.2.4 Secondary Endpoint – 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 develops at least one of the COVID-19 qualifying symptoms (see Section Disease Characteristics4.1.6), an unscheduled visit is performed and a SARS-CoV-2 RT-PCR test is performed to confirm the participant is positive. Additionally, to identify

symptom-free SARS-CoV-2 infections, serology testing is performed at each visit. Any positive SARS-CoV-2 test result indicating infection as well as any symptoms will be reported as an AE.

Incidence will be determined by AE and summarized via frequency and proportion of participants in the SAF by weight categories and route of administration. SARS-CoV-2 serology test results will be summarized by count and number of obervations for each timepoint and cohort.

This summary will be repeated for participants in the mFAS.

### 4.2.5 Secondary Endpoint – Cohort 2 and Cohort 3 (Treatment)

#### 4.2.5.1 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 will be summarized for the SAF by weight categories, dose, and route of administration.

#### 4.2.5.2 Progression of COVID-19

To evaluate the proportion of participants with progression of COVID-19 after a single IM or IV dose of AZD7442 in pediatric participants, the count and percentage of participants in the SAF with worsening of COVID-19 will be determined by occurrence of an increase in symptom severity (reported through AEs and the weekly contact) one or more new symptoms (reported through AEs and the weekly contact) or hospitalization or death related to COVID-19 up to day 29 (inclusive). The summary will be tabulated by cohort.

The time to (first) progression [date of AE – date of Day 1 +1] will also be listed and summarized via n, median, 1$^{st}$ and 3$^{rd}$ quartile, minimum, and maximum by weight categories, dose, and route of administration for the SAF.

#### 4.2.5.3 COVID-19-related death

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 will be tabulated by cohort, weight categories, dose, and route of administration for the SAF.

All fatal events will be further assessed as part of safety evaluation. Identification of deaths related to COVID-19 will be done based on the investigator's judgement and captured in the death details eCRF.

The time to death [date of death – date of Day 1 +1] will also be listed and summarized via n, median, 1st and 3rd quartile, minimum, and maximum by weight categories, dose, and route of administration for the SAF.

### 4.2.6 Secondary Endpoint – Cohort 3 (Severe COVID-19)

#### 4.2.6.1 Recovery

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, if and only if followed by being alive and home for 14 consecutive days, will be calculated. In case of multiple discharges due to re-hospitalization, only the first sustained recovery will be considered.

The time to sustained recovery will then be calculated as [date of discharge +14 days – date of Day 1 +1].

The time to sustained recovery will be listed and summarized via n, median, 1st and 3rd quartile, minimum, and maximum by weight categories, dose, and route of administration for the SAF.

### 4.2.7 Exploratory Endpoint

To evaluate the concentrations of AZD7442 in nasal fluid after a single IM or IV dose in pediatric participants, nasal concentrations of AZD7442 for each visit will be listed and summarized quantitatively by cohort, route of administration and weight category (1 to 4 and all) for the SAF.

### 4.2.8 Other Endpoints

#### 4.2.8.1 Exposure

The IMP administration dates and times will be listed for each participant together with route of administration (IM or IV), planned dose, administered dose and any medication errors that might occur during administration, such as interruptions.

The listing will be created for the SAF.

#### 4.2.8.2 Injection/Infusion site Inspection

The results of the inspection of the injection/infusions site will be listed for each participant presenting time of inspection, visual inspection of site, palpation of site, experience of discomfort and change in experience of discomfort. The results will be tabulated qualitatively by route of administration for the SAF.

#### 4.2.8.3 Potential Hy's Law

In case of potential Hy's Law, any liver risk factors, liver signs and symptoms and liver diagnostic investigation information will be listed.

# 5 INTERIM ANALYSIS

For interim analysis, a subset of the above analyses will be performed on all available data at time of the data snapshot. A database lock will be performed and all data cleaned for the data cut.

The interim analysis will include lisitings, tables and figures including: an overview over the patient population (disposition, demographics, baseline characteristics, medical history), important protocol deviations, safety information (adverse events, COVID related deaths, safety assessments, vital signs), as well as ADA and serum PK concentrations of AZD7442 combined and its individual components and summaries of COVID-19 symptoms and infections, as data permits. Select data may also be presented by cohort, route of administration, weight categories or age groups.

The exact subset of the result tables, listings and figures generated for the interim analysis will be specified in the mock shells.

# 6 APPENDICES

**Table 5 Description of the studies to be included in the population PK analysis.**

| Study description | Dose & PK sampling | Number of Subjects in PK dataset | Phase of Study and Study Population |
|---|---|---|---|
| **D8850C00001**<br>A Phase I Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability and Pharmacokinetics of AZD7442 in Healthy Adults. | Dose: 300 mg IM, 300 mg IV, 1000 mg IV, 3000 mg IV, 3000 mg IV –co-administration<br>PK timepoints: 0, 8 hr, 24 hr, 3, 5, 7, 14, 30, 60, 90, 150, 210, 270, and 360 days post-dose for IM route for both AZD8895 and AZD1061<br>0, 0.25h, 0.5h, 0.75h, 1h, 8 hr, 24h, 3, 5, 7, 14, 30, 60, 90, 150, 210, 270, and 360 days post-dose for IV route (AZD8895)<br>0, 0.75h, 1.5h, 2.25h, 3h, 8 hr, 24 hr, 3, 5, 7, 14, 30, 60, 90, 150, 210, 270, and 360 days post-dose for IV route (AZD1061) | 50 | Phase I, healthy subjects |
| **D8850C00002**<br>A Phase III Randomized, Double-blind, Placebo-controlled, Multi-centre Study in Adults to Determine the Safety and Efficacy of AZD7442, a Combination Product of Two Monoclonal Antibodies | 300 mg IM: PK samples collected on 0, 7, 28, 57, 91, 182, and 365 days post-dose | ~3333 | Phase III, pre-exposure prophylaxis of COVID-19 in Adults |

| Study description | Dose & PK sampling | Number of Subjects in PK dataset | Phase of Study and Study Population |
|---|---|---|---|
| (AZD8895 and AZD1061), for Pre-exposure Prophylaxis of COVID-19. | | | |
| **D8850C00003**<br>A Phase III Randomized, Double-blind, Placebo-controlled, Multi-centre Study in Adults to Determine the Safety and Efficacy of AZD7442, a Combination Product of Two Monoclonal Antibodies (AZD8895 and AZD1061), for Post-exposure Prophylaxis of COVID-19 | 300 mg IM: PK samples collected on 0, 2,5, , 14,28, 57, 91, 182, and 365 days post-dose | ~750 | Phase III, Potential - exposure (within 8 days) to SARS-COV-2 in Adults |
| **D8851C00001**<br>A Phase III Randomized, Double-blind, Placebo-controlled, Multi-centre Study to Determine the Safety and Efficacy of AZD7442 for the Treatment of COVID-19 in Non-hospitalized Adults | 600 mg IM: PK samples collected on 0, 2, 5, 7, 14, 28, 58, 84, 92, 168, 365 days post-dose | ~850 | Phase III, Treatment of COVID-19 in non-hospitalized Adults |
| **ACTIV-3**<br>A Multicenter, Adaptive, Randomized, Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Hospitalized Patients with COVID-19 (NIH funded) | 600 mg IV: PK samples collected on Days 0, 5, 28, and 90 | | Phase II and III, Treatment of COVID-19 in hospitalized Adults |
| **D8850C00006**<br>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 | IM and IV; dose is dependent on cohort indication and participant's weight.<br>PK samples collected at end of infusion (IV only), on either 3, 7, 10 or 14 days post-dose, and then 28, 91, 182, and 365 days post-dose | ~100[a] | Phase I, pre-exposure prophylaxis, Treatment of COVID-19 in non-hospitalized participants, Treatment of COVID-19 in hospitalized participants |

[a] The enrolment for this study was stopped early due to FDA feedback, therefore the full analysis set will only contain 46 participants.

# SIGNATURE PAGE

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