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

Protocol Amendment No. 4: Final 5.0, 25 Oct 2023

Clinical Study Protocol	
Study Intervention	AZD7442
Study Code	D8850C00006
Version	5.0
Date	25 October 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 Name:	**AstraZeneca AB**
Legal Registered Address	151 85 Södertälje, Sweden.
Regulatory Agency Identifier Number(s):	**IND number: 150712** **EudraCT Number: 2021-006056-13**

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures. The Clinical Study Protocol is publicly registered, and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: D8850C00006

Amendment Number: 4

Study Intervention: AZD7442

Study Phase: I

Short Title: AZD7442 PK, PD, and safety evaluation in children aged ≥ 29 weeks gestational age to < 18 years

Study Physician Name and Contact Information will be provided separately

International Coordinating Investigator: PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document		**Date**
Amendment 4	Version 5.0	25 October 2023
Amendment 3	Version 4.0	22 September 2022
Amendment 2	Version 3.0	03 March 2022
Amendment 1	Version 2.0	16 December 2021

Amendment 4 [25 October 2023]

Overall Rationale for the Amendment:

The CSP was amended with the following substantial changes: last study visit changed from Day 457 to Day 366. Currently the totality of the available data in adults (15 months for AZD7442 in the PROVENT and TACKLE studies and interim analysis data from this TRUST study) suggest that it is possible to extrapolate or infer the safety of AZD7442 in pediatrics from the existing data up to 15 months, which represents 5 half-lives of AZD7442. Reducing the follow-up period in the TRUST study to 12 months (Day 366) would also alleviate further burden of being in the clinical trial.

Section No and Name	Description of Change	Brief Rationale
Global changes to protocol	Updated last study visit from Day 457 to Day 366, removing the safety follow-up at Day 457.	• Feasible to extrapolate or infer the safety of AZD7442 in pediatrics from the existing data up to 15 months. • Lessen the overall burden on participants in the clinical trial by shortening the duration of the final study visit from Day 457 to Day 366.
1.1 Synopsis; Overall Design	Changed inclusion of participants in the study from 15 to 12 months following administration of IMP.	To be consistent with the change in the last study visit from Day 457 to Day 366.
1.1 Synopsis; Intervention Groups and Duration	Changed monitoring of participants from 15 to 12 months after AZD7442 administration	To be consistent with the change in the last study visit from Day 457 to Day 366.
1.2 Schematic; Figures 1 and 2	Changed Day 457 to Day 366 in Figure 1. Changed Week 65 to Week 52 in Figure 2.	To be consistent with the change in the last study visit from Day 457 to Day 366.

Section No and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities; Tables 2 and 3	Deleted the column related to Day 457 safety follow-up assessment in both tables. Deleted the footnote related to Day 457 safety follow-up assessment under both tables.	To be consistent with the change in the last study visit from Day 457 to Day 366.
4.1 Overall Design	Deleted "Follow-up will continue through Day 457 (± 15 days) when participants will receive a telephone call to assess safety." Changed the maximum duration of the study for each participant, including screening, from 479 to 388 days.	To be consistent with the change in the last study visit from Day 457 to Day 366.
4.2.1 Rationale for Choice of Endpoints	Changed the following (old information as strikethrough, new information in bold) "The revised study duration of 366 days ~~456-day Follow-up Period~~ will allow follow-up of dosed participants through approximately ~~5~~ **4** AZD7442 half-lives,"	To be consistent with the change in the last study visit from Day 457 to Day 366.
6.1.1 Investigational Product	Changed the following (old information as strikethrough, new information in bold) All eligible participants will receive a single dose of AZD7442 on Day 1, either IM (AZD8895 followed by AZD1061 administered separately) or a single IV infusion (AZD8895 and AZD1061 co-administered), and participants will be monitored for ~~456~~ **365** days after IMP administration	To be consistent with the change in the last study visit from Day 457 to Day 366.
7.4.1 Stopping Rules for an Individual Participant, at Any Time in the Study	Changed the following (old information as strikethrough, new information in bold) "Unless consent for follow-up is withdrawn, participants discontinued after receiving a	To be consistent with the change in the last study visit from Day 457 to Day 366.

Section No and Name	Description of Change	Brief Rationale
	partial dose of IMP will be followed for the full study period (up to and including Day ~~457~~ **366**, ~~65~~ **52** weeks after IMP dosing)"	

CSP, Clinical Study Protocol; DSMB, Data Safety Monitoring Board; EUA, emergency use authorization; GA, gestational age; mo, month; IB, Investigator's Brochure; IM, intramuscular(ly); IV, intravenous(ly); mAb, monoclonal antibody; PK, pharmacokinetics; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; wk, week.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol 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.

Short Title: AZD7442 PK, PD, and safety evaluation in pediatric participants aged ≥ 29 weeks GA to < 18 years.

Rationale: 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 the generation of anti-drug antibodies to AZD7442, following a single IM or IV AZD7442 dose administration in different pediatric age groups.

Objectives and Endpoints

Objectives	Endpoints
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 study period when administered as a single IM or IV dose • Serum PK parameters (if data permits): C_{max}, t_{max}, $t_{1/2}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, t_{last}, $\%AUC_{ex}$, and: ° for IM: CL/F, and V_z/F ° for IV: CL, and V_{ss} • 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 • 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
Secondary – All Cohorts	
• To evaluate the PD of AZD7442 after a single IM or IV dose in pediatric participants	• Titer of SARS-CoV-2 neutralizing antibodies
• To evaluate the immunogenicity profile of AZD7442 after a single IM or IV dose in pediatric participants	• Incidence of ADA and nAb to AZD7442 in serum

Objectives	Endpoints
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)	
• 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
• 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
• To evaluate COVID-19-related death after a single IM or IV dose of AZD7442 in pediatric participants	• The incidence of COVID-19-related death occurring after dosing with IMP through 90 days
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)

$\%AUC_{ex}$, percentage of $AUC_{0\text{-}inf}$ extrapolated to infinity; ADA, anti-drug antibodies; AESI, adverse event of special interest; $AUC_{0\text{-}inf}$, area under the serum concentration versus time curve extrapolated to infinity; $AUC_{0\text{-}last}$, area under the serum concentration versus time curve from time zero to time of last measurable concentration; BP, blood pressure; CL, systemic clearance; CL/F, apparent total clearance; C_{max}, maximum serum concentration; COVID-19, Coronavirus disease-2019; ECG, electrocardiogram; IM, intramuscular; IMP, investigational medicinal product; IV, intravenous; nAb, neutralizing antibodies; MIS-C, multisystem inflammatory syndrome – children; PD, pharmacodynamics; PK, pharmacokinetics; qRT-PCR, quantitative real-time polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; $t_{1/2}$, terminal half-life; t_{last}, time to last measurable concentration; t_{max}, time to reach maximum serum concentration; TEAE, treatment emergent adverse event; V_{ss}, volume of distribution at steady state; V_z/F, apparent volume of distribution based on terminal phase.

For the exploratory objective and endpoint, see Section 3 of the protocol.

Overall Design

This is a Phase I, open-label, uncontrolled, multicenter, single dose study to evaluate the PK, PD, safety, and tolerability of AZD7442 administered IM or IV in pediatric participants aged ≥ 29 weeks GA (infants born between gestational age of 29 weeks to full term) to < 18 years. Up to 3 cohorts of participants will be enrolled based on the adult indication and dose: 1) participants who are SARS-CoV-2 negative at screening and have not knowingly been exposed to a SARS-CoV-2 positive individual (pre-exposure prophylaxis); 2) participants who are SARS-CoV-2 positive at screening and have mild to moderate coronavirus disease 2019 (COVID-19) symptoms; and 3) participants who are SARS-CoV-2 positive at screening and

have severe COVID-19. Both Cohorts 1 and Cohort 2 are required to be at increased risk of developing severe COVID-19. Recruitment will start with Cohort 1; Cohorts 2 and 3 will be added if the indications are progressed in adults. If a cohort is not opened, that cohort's minimum number of participants will be re-allocated to available open cohorts in order for there to be a minimum of 6 participants receiving IV administration and a minimum of 6 participants receiving IM administration of the IMP in each of the four main age categories. All participants will be included in the study for 12 months following administration of IMP.

Disclosure Statement: This is a sequential basic science study with one arm that is participant and treatment unblinded.

Number of Participants:

Approximately 120 participants will be enrolled such that a minimum of 100 evaluable participants are assigned to study intervention. Recruitment will be stratified to ensure that all pediatric age groups are represented.

Note: "Enrolled" means a participant's or their parent or legally acceptable representative's agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not assigned in the study, are considered "screen failures", unless otherwise specified by the protocol.

Intervention Groups and Duration:

Eligible participants will receive a single dose of AZD7442 given via IM (AZD8895 followed by AZD1061 administered separately) or a single IV infusion (AZD8895 and AZD1061 co-administered) based on the participant's body weight (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). Investigational medicinal product will be administered on Day 1, and participants will be monitored for up to 12 months after AZD7442 administration.

Data Safety Monitoring Board:

Yes

Statistical Methods:

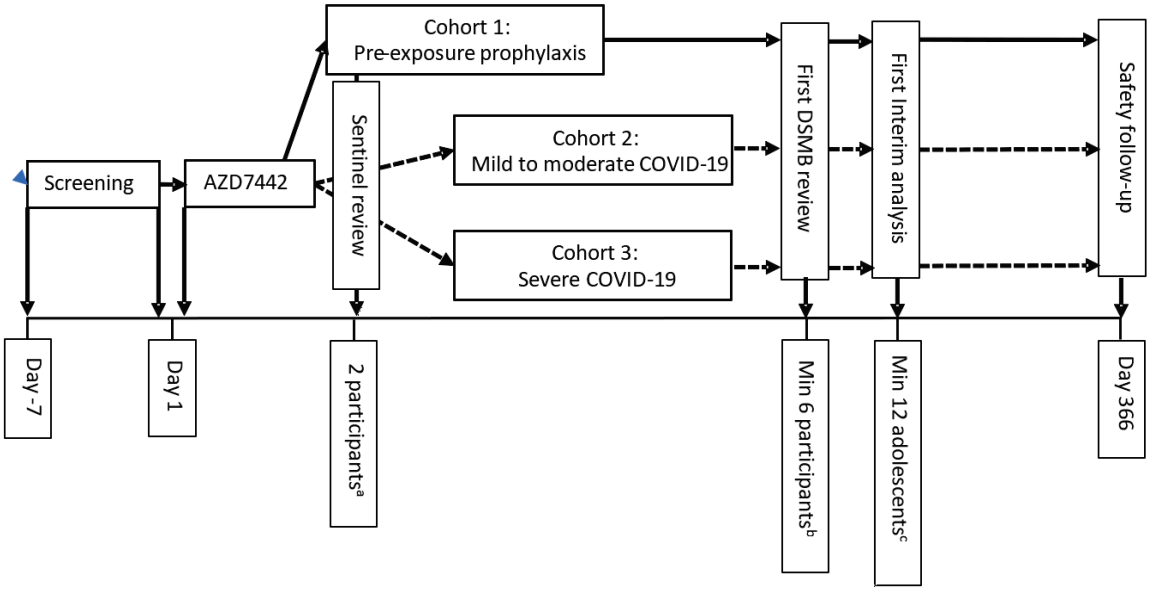
All original and derived parameters as well as demographic and disposition data will be listed and described using summary statistics. All safety data (scheduled and unscheduled) will be presented in the data listings. Frequency counts (number of participants [n] and percentages) will be provided for each qualitative variable. Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be calculated for each quantitative variable. At least one interim analysis is planned 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 or at the discretion of the Sponsor. No hypotheses are planned in this PK, PD, safety study so multiplicity is not a concern. All statistical analyses and production of tables, figures and listings will be performed using SAS® version 9.4 or higher.

AZD7442 serum concentrations will be analyzed by non-compartmental analysis and PK parameters summarized descriptively. AZD7442 serum concentrations will also be analyzed by population methods and population PK parameter estimates presented.

1.2 Schematic

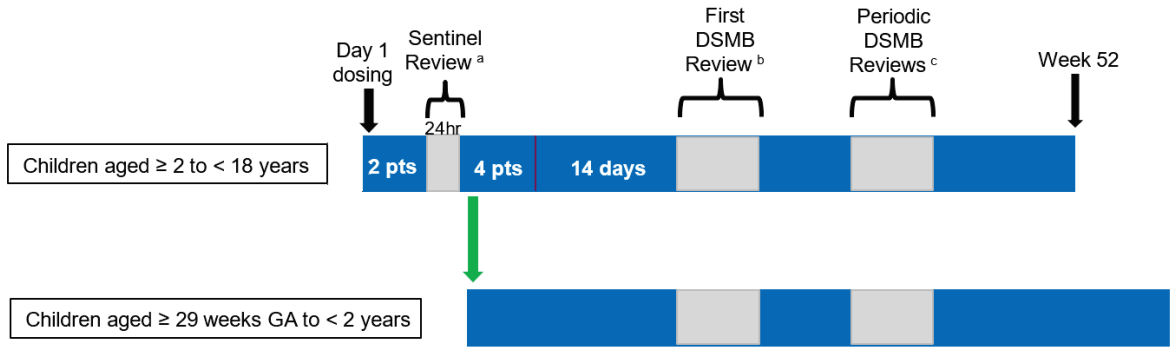
Figure 1 Study Design



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

Cohort 1: Participants who are SARS-CoV-2 RT-PCR negative at screening and have not knowingly been exposed to a SARS-CoV-2 positive individual and who are at increased risk of developing severe COVID-19.
Cohort 2: Participants who are SARS-CoV-2 RT-PCR positive at screening and have mild to moderate COVID-19 and who are at increased risk of developing severe COVID-19. Cohort 2 will only start recruiting if this indication is progressed in adults.
Cohort 3: Participants who are SARS-CoV-2 RT-PCR positive at screening and have severe COVID-19. Cohort 3 will only start recruiting if this indication is progressed in adults.
Recruitment will be paused during the sentinel review but not during the DSMB reviews.
COVID-19, coronavirus disease 2019; DSMB, Data Safety Monitoring Board; Min, minimum; PK, pharmacokinetic; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Figure 2 Recruitment and Safety Review During the Study



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

[b] First DSMB Review: The review will be conducted when at least 6 participants from any age group (including the 2 sentinel participants) have at least 14 days of safety data (all available safety data from all participants will be included in the DSMB review). Recruitment will continue during the DSMB review.

[c] Periodic DSMB Reviews: Cumulative safety data will be reviewed after the following number of participants have been recruited: 21, 36, 51, 66, 81, and 96. Recruitment will continue during the DSMB reviews.

DSMB, Data Safety Monitoring Board; GA, gestational age; pts, participants; h, hour.

1.3 Schedule of Activities

Table 1 summarizes the SoA at screening for all participants. Table 2 and Table 3 summarize the SoA during the main study for neonates (modified sample collection) and non-neonates, respectively.

Table 1 Schedule of Activities: Screening Period (All Participants)

Procedure/study day	Day -7 to Day 1 [a]	For details, see section:
Informed consent/assent	X	5.1
Assignment SID number [b]	X	6.3
Demographics and risk categorization	X	5.1
Medical history	X	NA
Complete physical examination, including height and weight	X	8.2.1
Vital signs (including pulse oximetry)	X	8.2.2
Triplicate 12-lead ECG	X	8.2.3
Serum chemistry, hematology, urinalysis [c]	X	8.2.4

Table 1 Schedule of Activities: Screening Period (All Participants)

Procedure/study day	**Day -7 to Day 1 [a]**		**For details, see section:**
Coagulation	X		8.2.4
Urine pregnancy test (post-pubertal females only) [d]	X		8.2.4.5
Assessment of SAEs	X		8.3
Concomitant medications	X		6.5
Serum sample for SARS-CoV-2 serology (anti-nucleocapsid) testing (all participants other than neonates)	X		8.5.3.2
Verify eligibility criteria	X		5.1, 5.2
Screening criteria specific to each cohort	**Cohort 1 Pre-exposure prophylaxis**	**Cohorts 2 and 3 Treatment of COVID-19**	**For details, see section:**
Documented SARS-CoV-2 RT-PCR test taken ≤ 3 days before Day 1 [e] OR Rapid SARS-CoV-2 antigen test (for assignment to study cohorts) per local standard of care authorized for screening or diagnosis	X (negative)	X (positive)	8.6.1
COVID-19 Symptom screen	NA	X (Yes)	5.1

[a] Screening activities may be collected over more than one visit during the 7-day screening window if necessary; if screening and dosing occur at the same visit, only one evaluation is required, unless otherwise specified. The sample taken closest to dosing and prior to dosing is considered the baseline sample.
[b] Assigned by the IRT system. See Section 6.3 for further information.
[c] Collection of urine samples for urinalysis from participants who are unable to provide urine samples is not mandatory provided that a reasonable attempt has been made to collect the samples.
[d] If urine tests positive or is indeterminate, a quantitative serum β-hCG will be performed for confirmation before the participant is enrolled in the study. Pregnancy testing is for baseline purposes only, and a participant with a positive urine pregnancy test can still participate in the study.
[e] This test is not performed as part of the clinical study but may be available prior to enrollment. If a documented SARS-CoV-2 RT-PCR test is not available at screening, a rapid SARS-CoV-2 antigen test will be performed (to be sourced by the investigational site).

β-hCG, beta-human chorionic gonadotropin; COVID-19, coronavirus disease 2019; ECG, electrocardiogram; IRT, Interactive Response Technology; NA, not applicable; RT-PCR, reverse transcriptase polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2; SID, subject identification.

Table 2 Schedule of Activities: Treatment and Follow-up Period for Neonates – Main Study

Procedure	Treatment and follow-up period							Early discontinuation visit	For details, see section:
	Visit 1	Visit 2	Visit 2A	Visit 3[a]	Visit 4[a]	Visit 5[a]	Visit 6[a]		
Day	1	4, 8, 11 or 15[b]	8	31	92	183	366		
Window (days)	NA	± 2	± 3	+ 5	± 5	± 10	± 15		
Targeted physical examination		X		X	X	X	X	X	8.2.1
Vital signs (including pulse oximetry)	X[c] (post dose)	X		X	X	X	X	X	8.2.2
Triplicate 12-lead ECG							X	X	8.2.3
Serum chemistry, hematology				X		X	X	X	8.2.4
Coagulation tests				X	X		X	X	8.2.4
Urinalysis[d]				X	X	X	X	X	8.2.4
Concomitant medications	X	X		X	X	X	X	X	6.5
Verify eligibility criteria	X								5.1, 5.2
IMP administration	X								
Sample for SARS-CoV-2 RT-PCR (central laboratory)	X[e,f] (pre-dose)		X[f]						8.6.1
Pharmacokinetics, pharmacodynamics, and ADA assessments									
Serum sample for AZD7442 PK assessment	Only participants receiving AZD7442 IV (post dose[g])	X		X	X	X	X	X	8.5.2

Table 2 Schedule of Activities: Treatment and Follow-up Period for Neonates – Main Study

Procedure	Treatment and follow-up period							Early discontinuation visit	For details, see section:
	Visit 1	Visit 2	Visit 2A	Visit 3[a]	Visit 4[a]	Visit 5[a]	Visit 6[a]		
Day	1	4, 8, 11 or 15[b]	8	31	92	183	366		
Window (days)	NA	± 2	± 3	+ 5	± 5	± 10	± 15		
Safety assessments									
Post dose observation – 1 hour[h]	X								8.3.1
AEs[i]	←	—	—	—	—	—	→	X	8.3
SAEs, MAAEs, and AESIs[i]	←	—	—	—	—	—	→	X	8.3

[a] Blood samples for safety (serum chemistry, hematology, coagulation) and PK should be taken over 2 days within the visit window (see Table 16 in Section 8.5.1 for further information).

[b] Participants will be randomly assigned to have a PK sample taken on one of the following days: Day 4, 8, 11, or 15 (ie, one sample per participant). See Section 6.3 for information.

[c] Perform 15 minutes (± 5 minutes) after the IMP injection is complete.

[d] Collection of urine samples from participants who are unable to provide urine samples is not mandatory provided that a reasonable attempt has been made to collect the samples.

[e] Baseline sample, not a screening sample; results not needed prior to dosing.

[f] All participants will have sample collected for SARS-CoV-2 RT-PCR on Day 1. Only Cohorts 2 and 3 (treatment arms) will have a sample collected for quantitative RT-PCR on Day 1 and Day 8. For RT-PCR, the central laboratory should be used. For participants in Cohort 1 that have COVID-19 qualifying symptoms (Table 13) at any time during the study, an unscheduled sample will be collected for SARS-CoV-2 RT-PCR to confirm the participant is SARS-CoV-2 positive (Section 8.1.1).

[g] For participants who receive AZD7442 via an IV infusion, a serum sample should be taken at the end of the infusion (and from the opposite side to the one used for the infusion).

[h] All participants will be monitored on site for general safety, including injection/infusion site reactions and other hypersensitivity reactions, for at least one hour after IMP administration (Section 8.3.1).

[i] All participants will be contacted weekly starting from the time of IMP administration. During weekly contacts the Investigator will enquire about AEs, SAEs, MAAEs, and AESIs as well as any COVID-19 symptoms from the past 7 days.

Where necessary, the visit windows in the SoA can be used to collect samples across a number of days. When sample collection occurs over ≥ 2 days for a given study visit, participants are required to visit the site at least once per study visit. If practical, additional sample collection can take place at home visits as long as the samples are obtained per protocol by qualified personnel.

ADA, anti-drug antibody; AE, adverse event; AESI, adverse event of special interest; COVID-19, Coronavirus disease-2019; ECG, electrocardiogram; FU, follow-up; IMP, investigational medicinal product; IV, intravenous; MAAE, medically attended adverse event; NA, not applicable; PK, pharmacokinetic; RT-PCR, reverse transcriptase polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SoA, schedule of activities.

Table 3 Schedule of Activities: Treatment and Follow-up Period for Participants Other Than Neonates – Main Study

Procedure	Treatment and follow-up period							Early discontinuation visit	For details, see section:
	Visit 1	Visit 2	Visit 2A	Visit 3	Visit 4	Visit 5	Visit 6		
Day	**1**	**4, 8, 11 or 15[a]**	**8**	**31**	**92**	**183**	**366**		
Window (days)	**NA**	**± 2**	**± 3**	**+ 5**	**± 5**	**± 10**	**± 15**		
Targeted physical examination		X		X	X	X	X	X	8.2.1
Vital signs (including pulse oximetry)	X[b] (post dose)	X		X	X	X	X	X	8.2.2
Triplicate 12-lead ECG							X	X	8.2.3
Serum chemistry, hematology				X		X	X	X	8.2.4
Coagulation tests				X	X		X	X	8.2.4
Urinalysis[c]				X	X	X	X	X	8.2.4
Pregnancy test – urine (females of childbearing potential only)[d]	X (pre-dose)								8.2.4
Concomitant medications	X	X		X	X	X	X	X	6.5
Verify eligibility criteria	X								5.1, 5.2
IMP administration	X								
Sample for SARS-CoV-2 RT-PCR (central laboratory)[e]	X[f, g] (pre-dose)		X[g]						8.6.1
Serum sample for SARS-CoV-2 serology (anti-nucleocapsid) (Cohort 1 only)				X	X	X	X	X	8.5.3.2

Table 3 Schedule of Activities: Treatment and Follow-up Period for Participants Other Than Neonates – Main Study

Procedure	Treatment and follow-up period							Early discontinuation visit	For details, see section:
	Visit 1	Visit 2	Visit 2A	Visit 3	Visit 4	Visit 5	Visit 6		
Day	1	4, 8, 11 or 15[a]	8	31	92	183	366		
Window (days)	NA	± 2	± 3	+ 5	± 5	± 10	± 15		
Pharmacokinetics, pharmacodynamics, and ADA assessments									
Serum sample for AZD7442 PK assessment	Only participants receiving AZD7442 IV (post dose[h])	X		X	X	X	X	X	8.5.2
Serum sample for AZD7442 ADA assessment	X (pre-dose)			X	X	X	X	X	8.5.3.1
Serum sample for SARS-CoV-2 nAbs assessment	X (pre-dose)			X	X	X	X	X	8.5.4.1
Nasal sample for exploratory PK assessment		X		X	X	X	X	X	8.5.2.2
Safety assessments									
Post dose observation – 1 hour[i]	X								8.3.1
AEs[j]	←	—	—	—	—	—	→	X	8.3
SAEs, MAAEs, and AESIs[j]	←	—	—	—	—	—	→	X	8.3

[a] Participants will be randomly assigned to have a PK sample taken on one of the following days: Day 4, 8, 11, or 15 (ie, one sample per participant). See Section 6.3 for information.

[b] Perform 15 minutes (± 5 minutes) after the IMP injection is complete.

[c] Collection of urine samples from participants who are unable to provide urine samples is not mandatory provided that a reasonable attempt has been made to collect the samples.

[d] A pregnancy test at Day 1 is not required if already done and results received during the Screening Period (Day -7 to Day 1). If urine tests positive or indeterminate, a quantitative serum β-hCG will be performed for confirmation before the participant receives IMP. Pregnancy testing is for baseline purposes only, and a participant with a positive urine pregnancy test can still participate in the study.

[e] The type of sample (eg, saliva, blood, nasopharyngeal) should be consistent between all study visits for each participant, but particularly for the samples collected on Day 1 and Day 8 which will be used to estimate the change in viral load. For participants in cohort 1 that have COVID-19 qualifying symptoms (Table 13) at any time during the study, an unscheduled sample will be collected for SARS-CoV-2 RT-PCR to confirm the participant is SARS-CoV-2 positive (Section 8.1.1).

[f] Baseline sample, not a screening sample; results not needed prior to dosing.

[g] All participants will have a sample collected for SARS-CoV-2 RT-PCR on Day 1. Only Cohorts 2 and 3 (treatment arms) will have a sample collected for quantitative RT-PCR on Day 1 and Day 8. For RT-PCR, the central laboratory should be used.

[h] For participants who receive AZD7442 via an IV infusion, a serum sample should be taken at the end of the infusion (and from the opposite side to the one used for the infusion).

[i] The first 2 participants aged ≥ 2 years to < 18 years in Cohort 1 (Sentinel Cohort) will undergo internal safety monitoring for 24 hours post IMP administration (including injection/infusion site reactions and other hypersensitivity or adverse reactions). Once the 24 h safety data review of the Sentinel Cohort is complete, recruitment can start in the remaining pediatric participants. All other participants will be monitored on site for general safety, including injection/infusion site reactions and other hypersensitivity reactions, for at least one hour after IMP administration (Section 8.3.1).

[j] For the first 4 days after IMP administration, the sentinel participants (2 participants aged ≥ 2 to < 18 years) will be contacted daily for safety monitoring followed by weekly contact. All other participants will be contacted weekly starting from the time of IMP administration. During weekly contact the Investigator will enquire about any AEs, SAEs, MAAEs, and AESIs as well as any COVID-19 symptoms from the past 7 days.

If necessary, the visit windows in the SoA can be used to collect samples across a number of days. If it is not possible to obtain sufficient blood from a participant at a study visit, the order of the samples will be prioritized according to the key requirements of the study. The following hierarchy will be applied: safety (serum chemistry, hematology, and coagulation), PK, SARS-CoV-2 nAbs, and ADA (see Laboratory Manual).

ADA, anti-drug antibody; AE, adverse event; AESI, adverse event of special interest; β-hCG, beta-human chorionic gonadotropin; COVID-19, Coronavirus disease 2019; ECG, electrocardiogram; FU, follow-up; h, hour; IMP, investigational medicinal product; IV, intravenous; MAAE, medically attended adverse event; NA, not applicable; nAb, neutralizing antibody; PK, pharmacokinetic; RT-PCR, reverse transcriptase polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SoA, schedule of activities.

2 INTRODUCTION

Severe acute respiratory coronavirus 2, is a novel coronavirus that appears to have first emerged in China in late 2019 (Zhou et al 2020b) causing cases of atypical pneumonia, later named COVID-19 and being declared a pandemic by the WHO on 11 March 2020 (WHO 2020). Since then, the COVID-19 pandemic has caused major disruption to healthcare systems with significant socioeconomic impacts. As of 5 August 2021, there have been over 200 million confirmed cases of COVID-19, including 4.2 million deaths, reported to WHO (WHO 2021). With a basic reproduction number R_0 value estimated between 2.43 to 3.10 without intervention, SARS-CoV-2 is highly transmissible from person to person, which has contributed to its rapid dissemination worldwide (D'Arienzo and Coniglio 2020). The pandemic continues to evolve via the emergence of variants and their ability to increase the R_0 value and potentially evade a vaccine only approach.

Relative to the total number of confirmed COVID-19 cases, the proportion of pediatric cases is estimated to be < 13% in Europe/United Kingdom (ECDC 2021) and < 12% in the USA (CDC 2021a), and the proportion of COVID-19-associated pediatric deaths is less than ≤ 1% of the total (ECDC 2021; CDC 2021a). COVID-19 in children is generally mild or asymptomatic and the prognosis is good, even inpatients who develop severe disease (including MIS-C) (CDC 2021d; Götzinger et al 2020; Swann et al 2020). Children with the greatest risk of poor outcomes with COVID-19 are those < 1 month of age, children of any age having, an underlying condition (including cardiovascular disease, malignancy, immunosuppression, chronic kidney disease, heart disease since birth, genetic, neurologic, or metabolic conditions), or being of black or Hispanic race (CDC 2021b; Götzinger et al 2020; Ludvigsson 2020; Swann et al 2020).

As a response to the ongoing pandemic, AstraZeneca has developed mAbs targeting the SARS-CoV-2 spike protein. The SARS-CoV-2 spike protein contains the RBD, which enables the virus to bind to ACE2 receptors on human cells. By targeting this region of the spike protein on the virus, antibodies can block the virus's attachment to ACE2 receptors and, therefore, are expected to block infection. AZD7442 consists of 2 separate mAbs which bind to distinct, non-overlapping sites on the SARS-CoV-2 spike protein RBD. Binding to either of these sites blocks the virus's ability to bind to ACE2 resulting in a blockade of virus entry, effectively neutralizing the SARS-CoV-2 virus. By blocking virus entry into human cells, AZD7442 stops virus replication, which stops infection, and is, therefore, being developed for the prophylaxis of COVID-19 and treatment of COVID-19.

AZD7442 retains full to nearly full neutralization activity against pseudoviruses and/or authentic SARS-CoV-2 variant strains harboring all spike substitutions identified in circulating variants of concern (including the Omicron BA.2 variant), variants of interest, variants alerts for further monitoring, and variants de-escalated from further monitoring. For

the Omicron BA.1 variant, independent laboratories have generated in vitro potency data showing that AZD7442 maintains neutralizing activity, although increases in IC_{50} compared to the original SARS-CoV-2 strain were observed (Dejnirattisai et al 2021; FNIH 2022; VanBlargan et al 2022; Zhou et al 2021). Virological surveillance is ongoing in the clinical studies to characterize how changes in potency observed in authentic SARS-CoV-2 or pseudotyped virus-like particle neutralization assays correlate with clinical outcomes.

On 08 December 2021, the FDA authorized AZD7442 as EVUSHELD™ (tixagevimab and cilgavimab administered together) for emergency use under an EUA for the pre-exposure prophylaxis of COVID-19 in adults and children (≥ 12 years weighing at least 40 kg) who are moderately to severely immunocompromised (Section 2.3.2).

A detailed and current description of the chemistry, pharmacology, efficacy, safety and marketing experiences of AZD7442 is provided in the latest version of the AZD7442 IB.

2.1 Study Rationale

This Phase I pediatric study will provide information on the AZD7442 PK profile, SARS-CoV-2-neutralizing antibody titers, effect on viral load, as well as 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.

2.2 Background

Coronaviruses are spherical, enveloped viruses with positive-sense, single-stranded RNA genomes. One fourth of their genome is responsible for coding structural proteins, such as the spike glycoprotein, envelope, membrane, and nucleocapsid proteins. Envelope, membrane, and nucleocapsid proteins are mainly responsible for virion assembly, while the spike protein is involved in receptor binding, mediating virus entry into host cells during coronavirus infection via different receptors (Li 2016). The SARS-CoV-2 belongs to the phylogenetic lineage B of the genus *Beta-coronavirus*, and it recognizes the ACE2 as the entry receptor (Zhou et al 2020a). It is the seventh coronavirus known to cause human infections and the third known to cause severe disease after SARS-CoV-1 and MERS-CoV.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD7442 is provided in the IB.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of AZD7442 may be found in the IB and Participant/Parent Information Leaflet.

2.3.1 Risk Assessment

There are no identified risks associated with AZD7442. To date, no observations are considered to represent expected adverse reactions that would form part of an emerging safety profile. In the FTIH Phase I dose escalation study (D8850C00001) in healthy adult volunteers, 60 participants had received IMP by the data cut-off date for the interim analysis of 06 June 2021. The results demonstrated an acceptable safety profile for AZD7442, including no observed infusion-related reactions (for IV administration), injection site reactions (for IM administration), or hypersensitivity reactions. No risks to date have been identified in the Phase III studies.

Due to observations in the adult population in the Phase III pre-exposure prophylaxis study PROVENT (n = 5197), cardiac ischemia, cardiac failure, and thrombotic events have been included as AESIs in this study. In PROVENT, a small numerical imbalance in SAEs in the Cardiac Disorders SOC was observed between the treatment groups. The number of participants with Cardiac Disorder SAEs adjusted by exposure (in patient-years) were 23 (1.2%) in the AZD7442 group and 5 (0.5%) in the placebo group. There were no reports of severe COVID-19 or COVID-19-related deaths in those treated with AZD7442. In the placebo arm, there were 3 cases of severe COVID-19, which included 2 deaths. In STORM CHASER, a separate Phase III post-exposure prophylaxis study of AZD7442 in adults (n = 1121), which enrolled a younger population with fewer baseline cardiac risk factors than PROVENT, no Cardiac disorder SAEs were reported. In TACKLE, a Phase III treatment study of AZD7442 in adults (n = 903), there were 2 (0.4%) SAEs in the Cardiac disorders SOC in the AZD7442 group and 1 (0.2%) in the placebo group. None of the Cardiac disorder SAEs in the AZD7442 group were considered related to the investigational product by the investigator. All participants in the Phase III studies who experienced cardiac disorder SAEs had numerous cardiac related risk factors and/or a prior history of CV disease at baseline. There was no clear temporal pattern, and a causal relationship between AZD7442 and these events has not been established. There was no signal for cardiac toxicity or thrombotic events identified in nonclinical studies.

AZD7442 is a combination of 2 human mAbs, with non-overlapping epitopes directed against RBD of the SARS-CoV-2 spike protein for neutralization of the virus. Neither mAb has any human target. There are no potential risks based on mechanism of action.

There are potential risks associated with the administration of any immunoglobulin, including polyclonal immunoglobulin preparations and mAbs. The potential risks include, but are not limited to injection site reactions, infusion-related reactions, and antibody-dependent enhancement of disease.

Injection site reactions may be observed and may manifest as local inflammation, redness, itching, pain, bruising, infection, or excessive bleeding at the site of injection. Clinical studies

with AZD7442 will closely monitor participants during and after IMP administration. These reactions should be managed according to standard clinical practice.

An infusion-related reaction is defined as any other reaction (other than hypersensitivity and anaphylaxis) occurring during infusion of IMP or felt to be temporally related to the infusion and occurring within 30 minutes to 2 hours after the initiation of first IMP infusion. However, though less frequent, infusion-related reactions can also occur later on within the first 24 hours from the start of infusion and are less common following subsequent exposures. Infusion-related reactions may manifest with single or multiple signs and symptoms. Most are mild in intensity, but severe and even fatal reactions have been reported. Unlike infusion-related reaction, anaphylaxis is a rare event, usually occurring after subsequent exposure to an antigen, and is most commonly accompanied by severe systemic skin and/or mucosal reactions.

Antibody-dependent enhancement of disease is a theoretical risk. Two different syndromes exist:

1. Antibody-dependent enhancement of disease, which involves increased binding efficiency of virus-antibody complexes to Fc receptor bearing cells and which triggers virus entry. The mAbs in AZD7442 have been designed with a modification to prevent binding to cellular Fc receptors, so the risk of antibody-dependent enhancement of disease occurring via this mechanism should be very low to none.
2. Vaccine-associated enhanced respiratory disease: a distinct clinical syndrome that occurred in young children in the 1960s when whole inactivated virus vaccines for measles and RSV were tested. Immunizing with limiting doses of RSV antigen, especially with conformationally incorrect antigens, can result in 2 major types of immunological phenomena:
    a) A relatively high ratio of antibody that binds, but does not neutralize, virus could potentially result in immunogenic cell death and complement activation (leading to inflammation and airway obstruction).
    b) Immunization with whole inactivated virus vaccines can result in allergic inflammation characterized by, eg, increased mucus production, airway hyper-responsiveness, and attenuated cytolytic T cell activity (T helper 2 cell immune response). This mechanism, induced by vaccines, should not be provoked by mAbs.

The potential risks in this study will be addressed by the following mitigation strategies:

- Safety data from a Sentinel Cohort (of 2 participants aged ≥ 2 to < 18 years from Cohort 1) for at least 24 hours will be reviewed by the International Co-ordinating Investigator, the AstraZeneca Global Safety Physician, and the AstraZeneca Global

Clinical Head before the remaining participants in the study are dosed (Section 4.1). Recruitment will be paused during this review.

- A DSMB will conduct a safety review of a minimum of 14 days of safety data from at least the first 6 participants enrolled in the study (Section 4.1). Subsequent DSMB meetings will review cumulative safety data after 21, 36, 51, 66, 81, and 96 participants have been dosed with AZD7442.
- Participants will be monitored on site for adverse reactions for a minimum of one hour after IMP administration (Section 8.3.1).
- Stopping rules (Section 7.4).

2.3.2 Benefit Assessment

This is the first study in pediatric participants so the benefits of AZD7442 in prophylaxis and treatment of COVID-19 in pediatrics is unknown. In both the PROVENT and STORM CHASER trials in adults, AZD7442 reduced the risk of developing symptomatic COVID-19 by more than 70% compared with placebo in participants who were SARS-CoV-2 negative at baseline (see Section 2). In the TACKLE study (NCT04723394), AZD7442 reduced the risk of developing severe COVID-19 or death by 50% compared to placebo in non-hospitalized adults who had been symptomatic for 7 days or less, and the risk was reduced by 67% if participants were treated within 5 days of symptom onset. Importantly, 90% of trial participants were from populations at high risk for progressing to severe COVID-19. Additional adult studies for the treatment of mild to moderate COVID-19 and severe COVID-19 with AZD7442 are ongoing.

The FDA has authorized for emergency use under an EUA, AZD7442 as EVUSHELD (tixagevimab and cilgavimab administered together) for the pre-exposure prophylaxis of COVID-19 in adults and children (≥ 12 years weighing at least 40 kg) who are moderately to severely immunocompromised due to an underlying immune disease or are taking immunosuppressive medications and therefore unable to mount an adequate immune response to COVID-19 vaccine. In addition, use is authorized in those with a history of severe adverse reaction to a COVID-19 vaccine, in whom COVID-19 vaccine is not recommended.

Despite the rollout of effective SARS-CoV-2 vaccines, a sizeable proportion of the general population remain unprotected and many young children are ineligible to receive a vaccine. There remains a clear unmet medical need to neutralize SARS-CoV-2 and ensure protection against emerging variants, particularly in those individuals not expected to mount an adequate response to complete active immunization (CDC 2021c), and those for whom vaccination is not suitable. AZD7442 remains the only prophylactic mAb to successfully neutralize the Omicron variant authentic virus (BA.1) in vitro (VanBlargan et al 2022).

Recruitment will target pediatric participants aged ≥ 29 weeks GA to < 18 years who are likely to benefit from prophylaxis or treatment with AZD7442 because they either have severe COVID-19 or an underlying condition that increases their risk of developing severe COVID-19.

2.3.3 Overall Benefit:Risk Conclusion

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with AZD7442 are justified by the anticipated benefits that may be afforded to pediatric participants who have severe COVID-19 or who are at risk of developing severe COVID-19 if they contract SARS-CoV-2.

3 OBJECTIVES AND ENDPOINTS

Table 4 lists the objectives and endpoints for the study. The co-primary objectives are to evaluate the PK of AZD7442 and the safety and tolerability of AZD7442 administered as a single IM or IV dose to pediatric participants ≥ 29 weeks GA to < 18 years of age who either have severe COVID-19 or an underlying co-morbidity that increases their risk of developing severe COVID-19 (eg, immunosuppression).

Table 4 Objectives and Endpoints

Objectives	Endpoints
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 study period when administered as a single IM or IV dose • Serum PK parameters (if data permits): C_{max}, t_{max}, $t_{1/2}$, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, t_{last}, $\%AUC_{ex}$, and: ° for IM: CL/F, and V_z/F ° for IV: CL, and V_{ss} • 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 • 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
Secondary – All Cohorts	
• To evaluate the PD of AZD7442 after a single IM or IV dose in pediatric participants	• Titer of SARS-CoV-2 neutralizing antibodies
• To evaluate the immunogenicity profile of AZD7442 after a single IM or IV dose in pediatric participants	• Incidence of ADA and nAb to AZD7442 in serum

Table 4 Objectives and Endpoints

Objectives	Endpoints
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)	
• 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.
• 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
• To evaluate COVID-19-related death after a single IM or IV dose of AZD7442 in pediatric participants	• The incidence of COVID-19-related death occurring after dosing with IMP through 90 days
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)
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

$\%AUC_{ex}$, percentage of $AUC_{0\text{-}inf}$ extrapolated to infinity; ADA, anti-drug antibodies; AESI, adverse event of special interest; $AUC_{0\text{-}inf}$, area under the serum concentration versus time curve extrapolated to infinity; $AUC_{0\text{-}last}$, area under the serum concentration versus time curve from time zero to time of last measurable concentration; BP, blood pressure; CL, systemic clearance; CL/F, apparent total clearance; C_{max}, maximum serum concentration; COVID-19, coronavirus disease 2019; ECG, electrocardiogram; IM, intramuscular; IMP, investigational medicinal product; IV, intravenous; nAb, neutralizing antibodies; MIS-C, multisystem inflammatory syndrome – children; PD, pharmacodynamics; PK, pharmacokinetics; qRT-PCR, quantitative real-time polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; t_{max}, time to reach maximum serum concentration; $t_{1/2}$, terminal half-life; TEAE, treatment emergent adverse event; V_{ss}, volume of distribution at steady state; V_z/F, apparent volume of distribution based on terminal phase.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase I, open-label, uncontrolled, multicountry, multicenter, single dose study to evaluate the PK, PD, safety, and tolerability of AZD7442 administered IM or IV in pediatric participants aged ≥ 29 weeks GA (infants born between gestational age of 29 weeks to full

term) to < 18 years. Up to 3 cohorts of participants will be enrolled based on the adult indication and dose: 1) participants who are SARS-CoV-2 negative at screening and have not knowingly been exposed to a SARS-CoV-2 positive individual (pre-exposure prophylaxis); 2) participants who are SARS-CoV-2 RT-PCR positive at screening and have mild to moderate COVID-19; and 3) participants who are SARS-CoV-2 positive at screening and have severe COVID-19. Both Cohort 1 and Cohort 2 are required to be at increased risk of developing severe COVID-19. Recruitment will start with Cohort 1; Cohorts 2 and 3 will be added if the indications are progressed in adults. If recruitment in a cohort is not initiated, the minimum number of participants in the other cohort(s) will be increased such that there is a minimum of 6 participants receiving IV administration and a minimum of 6 participants receiving IM administration of the IMP in each of the four main age categories. Approximately 33 sites will participate in this study.

To facilitate recruitment, participants will be assigned to a cohort and receive treatment based on the results of a documented RT-PCR test taken ≤ 3 days before Day 1 (if available) or a SARS-CoV-2 rapid antigen test at screening. A sample will also be taken on Day 1 for a pre-dose SARS-CoV-2 RT-PCR test to be conducted at the central laboratory (baseline). Participants will continue in their assigned cohort even if the Day 1 pre-dose SARS-CoV-2 RT-PCR test does not confirm the initial screening test results. Approximately 120 participants will be enrolled to ensure a minimum of 100 evaluable participants. If necessary, recruitment will be increased to replace participants who withdraw from the study.

Measures will be undertaken to ensure minimal SARS-CoV-2 exposure for site staff as well as study participants according to local requirements. Exclusion and withdrawal criteria are in place to ensure site staff and study participant safety. In Cohort 1 (prophylaxis), a post-baseline SARS-CoV-2 positive result in participants who were SARS-CoV-2 negative at baseline and developed COVID-19 symptoms during the study will be reported as an AE. Measures will be applied at the discretion of the Investigator to minimize further SARS-CoV-2 exposure as much as possible. Guidance for management of participants who wish to receive or parents who wish for their child to receive an authorized vaccine for protection against SARS-CoV-2 during the study is provided.

The study flow chart is presented in Figure 1 and a graphical representation of the recruitment and safety reviews is presented in Figure 2. The SoA displaying assessments/tasks and time points is presented in Section 1.3. Following a screening evaluation, which can be conducted over one or more visits between Day -7 to Day 1, participants will receive a single dose of IMP. After administration of the dose of IMP on Day 1, participants will be monitored on site for at least one hour for general safety, including injection/infusion site reactions and hypersensitivity reactions (including anaphylaxis). Participants will undergo a follow-up until Study Day 366 for safety, including recording of AEs and SAEs, and collection of blood samples for PK, PD, and ADAs, and exploratory efficacy endpoints. The maximum duration

of the study for each participant, including screening, will be 388 days.

Participants will be stratified by age with a minimum number of participants to be assigned to each cohort and route of administration as shown in Table 5. These minimum numbers consider both FDA and European Medicines Agency Paediatric Committee (PDCO) feedback. In Cohorts 1 and 2, participants will receive IM AZD7442 (AZD8895 followed by AZD1061) unless they meet the inclusion criteria specified for IV administration (Section 5.1). Participants with severe COVID-19 in Cohort 3 will receive AZD7442 by IV infusion (AZD8895 and AZD1061 co-infusion). Proposed IM and IV AZD7442 doses for investigation by weight range for pediatric participants in Cohort 1 (prophylaxis) and Cohorts 2 and 3 (treatment) are provided in Table 6. Interactive Response Technology will be used to ensure that all minimum targets are met and that each cohort and age group does not over-enroll by more than 20%.

Sentinel dosing will be applied to ensure participant safety. The first 2 participants aged ≥ 2 to < 18 years in Cohort 1 will undergo internal safety monitoring for at least 24 hours during which recruitment will be paused. After review of the Sentinel Cohort, the International Co-ordinating Investigator, the AstraZeneca Global Safety Physician, and the AstraZeneca Global Clinical Head will decide whether recruitment can proceed for the rest of the study participants, including those aged ≥ 29 weeks GA to < 2 years (Figure 2).

The DSMB will conduct a review once at least 14 days of safety data are available from the first 6 participants recruited into the study (derived from any of the pediatric age groups). Recruitment will continue during the DSMB safety review. The DSMB may request recruitment to be stopped after that review. The minimum 14-day Follow-up Period for the DSMB safety review should provide adequate safety information for the review because 1) no binding to any tissues was observed in tissue cross-reactivity studies, confirming the absence of target and off-target binding in humans and cynomolgus monkey adult tissues and human fetal tissues, and 2) no safety concerns have been observed in adult studies to date. The DSMB will continue to meet to review cumulative safety data after 21, 36, 51, 66, 81, and 96 participants have been recruited into the study.

Table 5 Minimum Number of Participants to be Enrolled for Each Cohort, Age Group, and Route of Administration

Age	Cohort 1: Pre-exposure prophylaxis of COVID-19[a]		Cohort 2: Treatment of mild to moderate COVID-19[b]		Cohort 3: Treatment of severe COVID-19[c]	Any cohort[d]	Total
	IM	IV	IM	IV	IV	IM or IV	IM or IV
≥ 12 y to < 18 y	6	4	6	4	4	22	**46**
≥ 6 y to < 12 y	1[e]	6	1[e]	1	4	5	**18**
≥ 1 y to < 6 y	6[e]	1	1[e]	1	4	5	**18**
≥ 29 wk GA to < 1 y	6	1	6	1	4	0	**18**
• ≥ 1 mo to < 1 y	• n = 2		• n = 2				• **n = 4**
• ≥ 29 wk GA to < 1 mo[f]	• n = 2[g]		• n = 2[g]				• **n = 4**
Total	**19**	**12**	**14**	**7**	**16**	**32**	**100**

[a] Pediatric participants who are SARS-CoV-2 negative at baseline.
[b] Pediatric participants who are SARS-CoV-2 positive at baseline and have mild to moderate COVID-19. Recruitment into this cohort will start if the indication is progressed in adults. If this cohort is not included in the study, the minimum number of participants in the other cohort(s) will be increased.
[c] Pediatric participants who are SARS-CoV-2 positive at baseline and have severe COVID-19. Recruitment into this cohort will start if the indication is progressed in adults. If recruitment in this cohort is not initiated, the minimum number of participants in the other cohort(s) will be increased such that there is a minimum of 6 participants receiving IV administration of the IMP in each of the 4 main age categories.
[d] Once the minimum number of participants has been reached in each cohort, the remaining participants can be derived from any of the applicable open cohorts and routes of administration.
[e] In participants who weigh ≥ 15 to < 40 kg in Cohort 1 and Cohort 2, IM dosing is not feasible for prophylaxis and treatment indication due to the volume required for injection.
[f] Born between gestational age of 29 weeks to full term, from birth up to 28 days of life (1 month).
[g] May be administered by IM or IV route, depending on standard local practice for drug administration in neonates.

COVID-19, coronavirus disease 2019; GA, gestational age; IM, intramuscular; IMP, investigational medicinal product; IV, intravenous; mo, month; n, number of participants; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; wk, week(s); y, year(s).

4.2 Scientific Rationale for Study Design

AZD7442 is being evaluated for prophylaxis of COVID-19 and treatment of COVID-19 in adults. This Phase I study will provide information on the PK profile, SARS-CoV-2-neutralizing antibody titers and effect on viral load, as well as data on the safety and tolerability of AZD7442 and potential generation of ADAs to AZD7442 in pediatrics. This study will support the extrapolation of the efficacy and safety data observed in adults to children and determination of the therapeutic dose in children.

4.2.1 Rationale for Choice of Endpoints

The endpoints chosen for this Phase I PK/PD and safety study are consistent with those in AZD7442 studies in adults.

The primary study PK endpoints are those required to characterize the PK profile of AZD7442 following a single IM or IV dose administered to pediatrics aged ≥ 29 weeks GA to < 18 years (Day 1 through Day 366). Pharmacokinetic sampling will be 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 (ie, the total number of samples per participant is 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). Pharmacokinetic data will be analyzed by population methods and if data permit by non-compartmental analysis approach. This sampling scheme also enables serum AZD7442 concentration data to be obtained at the time points of primary efficacy endpoint evaluation for prophylaxis and treatment in the adult program. Pharmacokinetic profiles of AZD7442 are expected to be similar across the prophylaxis and treatment populations recruited because AZD7442 is cleared via nonspecific intracellular metabolism and will not be affected by binding to the exogenous target SARS-CoV-2. Therefore, PK data will be pooled across the cohorts within each age group.

The PD markers that are measured in this PK/PD and safety study will be used to support the assumption that the exposure-response relationship is similar for adults and children. In SARS-CoV-2 infected and non-infected children, the SARS-CoV-2 neutralizing antibody titer will be measured in a validated live neutralization assay. In addition, the neutralizing antibody titer will be correlated to the serum AZD7442 concentration. The correlation between drug level and neutralizing antibody titer in children will be compared to the correlation derived in adult serum samples.

The measures of viral load, disease progression or recovery, SARS-CoV-2 infections, and COVID-19-related death mirror the endpoints in the adult studies with AZD7442.

Adverse events associated with exogenous immunoglobulins as a class, ie, infusion reactions, hypersensitivity reactions, including anaphylaxis, and injection site reactions, typically manifest within minutes to hours, and rarely after 24 hours. For such events, the 24 hours of monitoring assigned to the sentinel dosing group should be sufficient for detection. The safety endpoints are standard endpoints for safety assessment and include incidence of treatment-emergent AEs, SAEs, and safety clinical laboratory measurements, with the addition of MIS-C as an AESI that is specific for SARS-CoV-2 infection in children. The presence of ADA and the potential impact of ADA on PK, PD, or safety will also be assessed.

The revised study duration of 366 -days will allow follow-up of dosed participants through approximately 4 AZD7442 half-lives, which is expected to provide sufficient safety follow-up and will also maximize the probability of detecting ADA to AZD7442.

4.2.2 Rationale for Study Population

Children of all ages are susceptible to SARS-CoV-2 infection and COVID-19 but many children will not develop severe disease; therefore, Cohorts 1 and 2 (prophylaxis and treatment of mild to moderate disease) will only include participants who have an underlying condition that increases their risk for developing severe COVID-19. Participants in Cohort 3 (treatment of severe disease) require urgent treatment, so they are not required to have any pre-existing health conditions.

Participants will be stratified by age (≥ 29 weeks GA to < 1 year; ≥ 1 year < 6 years; ≥ 6 years to < 12 years; ≥ 12 years to < 18 years) to ensure that data are obtained from all pediatric age groups in the study. In addition, the youngest age category has been further stratified into 2 subgroups (≥ 29 weeks GA to < 1 month and ≥ 1 month to < 1 year), to ensure that neonates are represented as they are particularly susceptible to COVID-19.

4.2.3 Participant Input into Design

Not applicable for a PK study.

4.3 Justification for Dose

The IM and IV doses to be investigated in this study were determined by simulations using the population PK model developed based on available data from the adult studies. The model used for the simulations included a weight-based allometric scaling of CL and volume as well as an age-based maturation function for CL to represent the entire range of the pediatric population. A dosing by body weight bands approach was chosen. Four weight band categories were considered: ≥ 1.5 to < 5 kg; ≥ 5 to < 15 kg; ≥ 15 to < 40 kg and ≥ 40 kg. The IM and IV doses in the respective body weight categories were selected so the predicted exposure in each weight category matches as closely as possible the exposure in adults at the highest authorized or investigated (if indication not yet approved) doses in each indication at the time of recruitment initiation in each cohort. In particular, pediatric prophylaxis doses

were selected such that the AZD7442 predicted serum concentrations were within the same range as adults at 6 months. The doses to be investigated in each weight category in the different indications are presented in Table 6. AZD7442 was investigated at doses up to 3000 mg administered IV in adults in the Phase I FTIH study (D8850C00001), which is 5-fold higher than the maximum adult dose investigated in the Phase III adult studies.

Intramuscular injection is the preferred route of administration for outpatients (prophylaxis or treatment of mild to moderate disease) but for some participants, the IV route of administration will be more appropriate (see criteria for IV administration specified in the inclusion criteria in Section 5.1). Therefore, the IV route of administration has also been included for eligible participants in Cohorts 1 and 2. For patients who are hospitalized with severe COVID-19 in Cohort 3, IV administration is the route investigated in the clinical adult studies.

Table 6 Planned Doses in the Different Indications in the Pediatric PK/PD/Safety Study

Participant weight range	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)
	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.

4.4 End of Study Definition

For the purpose of Clinical Trial Transparency, the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements define two completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with

different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the SoA in Section 1.3.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Age and Weight

1 Participant must be aged ≥ 29 weeks GA to < 18 years of age at the time of signing the informed consent (see Appendix A 3 for procedures around informed consent).

2 Participant must weigh a minimum of 1.5 kg.

Type of Participant and Disease Characteristics

COHORT 1: Participants who do not have COVID-19 and have not knowingly been exposed to a SARS-CoV-2 positive individual (pre-exposure prophylaxis):

3 At increased risk of severe COVID-19 for any of the following reasons:
   (a) Immunocompromised state
   (b) One or more comorbid conditions that increase the risk of severe COVID-19, eg, cardiovascular disease, including heart disease since birth, malignancy, chronic kidney disease, and genetic, neurologic, or metabolic conditions.

4 Medically stable defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the one month prior to enrollment, with no acute change in condition at the time of study enrollment as judged by the Investigator.

5 Documented negative SARS-CoV-2 RT-PCR test collected ≤ 3 days prior to Day 1 or a negative rapid SARS-CoV-2 antigen test at screening.

6 Prior to enrollment, participants must not have had COVID-19 symptoms (Table 13) within 10 days of dosing.

7 Increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19, based on available risk assessment at time of enrollment.

COHORT 2: Participants with COVID-19 and mild to moderate symptoms (treatment):

8 At increased risk of severe COVID-19 for any of the following reasons:
   (a) Immunocompromised state
   (b) One or more comorbid conditions that increase the risk of severe COVID-19 (see list in 3[b])
9 Medically stable defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the one month prior to enrollment, with no acute change in condition at the time of study enrollment as judged by the Investigator.
10 Documented positive SARS-CoV-2 RT-PCR test collected ≤ 3 days prior to Day 1 or a positive rapid SARS-CoV-2 antigen test at screening.
11 Participants who are symptomatic must be dosed with IMP no more than 7 days from self-reported or observed onset of COVID-19-related symptoms or measured fever, defined as the self-reported date of first reported sign/symptom from the list in Table 13. One or more COVID-19 signs/symptoms must also be present within 24 hours prior to Day 1 to be eligible for inclusion.
12 Oxygenation saturation of ≥ 92% obtained at rest by study staff within 24 hours prior to Day 1, unless the potential participant regularly receives chronic supplementary oxygen for an underlying lung condition.

Note that Cohort 2 will only be included if the indication is progressed in adults.

COHORT 3: Participants with severe COVID-19 (treatment):

13 Patients hospitalized with COVID-19 with a time between onset of symptoms and dosing AZD7442 of ≤ 7 days
14 Documented positive SARS-CoV-2 RT-PCR test collected ≤ 3 days prior to Day 1 or a positive rapid SARS-CoV-2 antigen test at screening.
15 Spontaneous blood ALT/AST levels ≤ 5 times the ULN
16 Glomerular filtration rate ≥ 30 mL/min/1.73 m^2

Note that Cohort 3 will only be included if the indication is progressed in adults.

Route of Administration:

Participants will receive IM AZD7442 unless they meet any of the following criteria for IV administration:

17 The participant has severe COVID-19

18 IM dosing is contraindicated due to:

(a) Thrombocytopenia (< 120000 cells/mm^3)

(b) Coagulation defects

(c) Any other condition that would compromise the absorption of AZD7442 or safety of the participant (eg, hypovolemic shock, myopathy, muscular atrophy, active infection other than SARS-CoV-2, cellulitis, and dermatitis at the injection site).

19 Any other participant for whom the enrolling physician considers an IV infusion the most appropriate route of administration.

Informed Consent

20 Provision of a signed and dated written informed consent form prior to any mandatory study specific procedures, sampling, and analyses. Informed assent is to be provided by participants who are capable of forming an opinion and assessing the information given to him or her; informed consent must be provided by the participant's legal guardian.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1 Cohort 1: Significant infection or other acute illness, including fever > 100 °F (> 37.8 °C) on the day prior to or day of receiving AZD7442.

2 History of infection with SARS-CoV-1 or MERS-CoV.

3 Cohorts 1 and 2: Current need for immediate medical attention in an emergency room service in the clinical opinion of the site Investigator or current need for hospitalization (Appendix E) in the following circumstances:

(a) Due to progressive COVID-19 as this implies severe disease (an exception is participants hospitalized with mild-moderate COVID-19 as a precautionary measure for isolation/infection prevention or for the purpose of conducting study procedures).

(b) For any underlying medical condition that requires hospitalization (suggestive of an unstable medical condition) with the following exceptions:

– Neonates aged ≥ 29 weeks GA to < 1 month in their birth hospitalization when discharge is expected within 7 days after receiving AZD7442.

- Children hospitalized for maintenance chemotherapy administration (induction, reinduction, relapse chemotherapy excluded). AZD7442 administration is to occur a minimum of 2 hours post chemotherapy administration (including any hydration or blood products) or post the institutional standards for observation after chemotherapy administration, whichever is longer. Only children who, in the opinion of the investigator, are at low risk for a hypersensitivity reaction to administration of chemotherapy or blood products should be considered for same day administration of AZD7442 during hospitalization for maintenance chemotherapy.

4 Requirement for mechanical ventilation or extracorporeal membrane oxygenation or anticipated impending need for mechanical ventilation at baseline for treatment of COVID-19 (CPAP and high flow O_2 is permitted).

5 Known history of allergy or reaction to any component of the study drug formulation.

6 Previous hypersensitivity, injection/infusion-related reaction, or severe adverse reaction following administration of a mAb for any indication.

7 Any co-morbidity requiring surgery within 7 days prior to study entry, or that is considered life-threatening in the opinion of the site Investigator within 30 days prior to study entry.

8 Any other significant disease, disorder, or finding that, in the judgment of the Investigator, may significantly increase the risk to the participant because of participation in the study, affect the ability of the participant to participate in the study, or impair interpretation of the study data.

Prior Therapy (Before Enrollment)

9 Prior receipt of convalescent COVID-19 plasma/sera or hyperimmune globulin therapy.

10 Prior receipt of mAb/biologic indicated for the prevention or of SARS-CoV-2 or treatment of COVID-19 or expected receipt during the period of study follow-up.

11 Prior receipt of a COVID-19 vaccine ≤ 14 days before screening or plan to receive a COVID-19 vaccination ≤ 14 days after IMP administration at study Visit 1 (see Section 6.5.1). Receipt of a COVID-19 vaccine > 14 days before screening is allowed.

Other Exclusions

12 Employees of the Sponsor involved in the planning, execution, supervising, or reviewing the AZD7442 program, clinical study site staff, or any other individuals involved with the conduct of the study, or immediate family members of such individuals.

13 Judgment by the Investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.

14 History of alcohol or drug abuse within the past 2 years that, according to the Investigator, might affect assessments of safety or ability of participant to comply with all study requirements.

15 Investigational Drugs or Devices: Treatment with investigational drug or device in another clinical trial within the last 30 days or 5 half-lives of the drug (whichever is longer) prior to screening. Note: Participation in observational studies (ie, studies that do not require medication, blood draws, or an additional intervention) is not exclusionary. Interventional trials which do not include investigational drugs (only include approved therapies), or investigational treatment regimens may be considered if the blood draw requirements and study interventions are minimal and not deemed by the Investigator to interfere with completion of the planned study sampling and follow-up.

16 Vulnerable persons (eg, ward of the state, kept in detention).

5.3 Lifestyle Considerations

- Restrictions related to concomitant medications and drugs of abuse and alcohol are described in Section 6.5.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if the eligibility criterion that resulted in screen failure has changed in a manner that meets eligibility.

Only a single rescreening is allowed in the study. Rescreened participants should be assigned the same participant number as for the initial screening. Individuals who are rescreened do not need to reconsent for the study.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilized by a study participant according to the study protocol.

6.1 Study Interventions Administered

6.1.1 Investigational Product

All eligible participants will receive a single dose of AZD7442 on Day 1, either IM (AZD8895 followed by AZD1061 administered separately) or a single IV infusion (AZD8895 and AZD1061 co-administered), and participants will be monitored for 365days after IMP administration (Table 7). Dose levels will be stratified by body weight range categories. Age-appropriate quantities of all excipients are used within the AZD7442 formulation. All excipients are of pharmaceutical grade and are not considered to pose any safety issues for children at the anticipated exposure levels.

Table 7 Investigational Product: AZD7442

Intervention name	AZD7442 (AZD8895 + AZD1061) (AstraZeneca)
Type	Biologic
Dose formulation	AZD7442 is comprised of 2 drug products supplied as separate vials of AZD8895 and AZD1061. Each vial contains a solution of 100 mg/mL active ingredient (AZD8895 or AZD1061), 20 mM histidine/histidine-HCl, 240 mM sucrose, 0.04% (w/v) PS80, pH 6.0. The label claim volume for each vial is 1.5 mL and each vial contains 150 mg (nominal) of active ingredient.
Unit dose strength(s)	100 mg/mL of AZD8895 in a single vial 100 mg/mL of AZD1061 in a single vial
Dosage level(s)	The dose levels are stratified by body weight range categories as shown in Table 6 (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).
Route of administration	IM (AZD8895 followed by AZD1061) or a single IV infusion (AZD8895 and AZD1061 concurrently)
Use	Experimental
Sourcing	AstraZeneca
Packaging and labeling	AZD7442 will be provided in glass vials. Each glass vial will be labeled as required per country requirement.

COVID-19, coronavirus 2019; IM intramuscular; IV, intravenous, w/v, weight per volume.

Details of the batch numbers will be included in the Trial Master File, and the final CSR. Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling.

6.2 Preparation/Handling/Storage/Accountability

1 Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

2 The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

6.2.1 Storage and Handling Procedures

AZD7442 vials (AZD8895 and AZD1061) are stored at 2 °C to 8 °C (36 °F to 46 °F) and must not be frozen. The Investigator, or an approved representative (eg, pharmacist), will ensure that all study intervention is stored in a secured area, in refrigerated temperatures (2 °C to 8 °C; 36 °F to 46 °F) and in accordance with applicable regulatory requirements. A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging are to be reported to the monitor upon detection. A calibrated temperature monitoring device will be used to record the temperature conditions in the drug storage facility. Storage conditions stated in the IB may be superseded by the label storage.

AZD7442 must be kept in original packaging until time of preparation to prevent prolonged light exposure.

AZD7442 is comprised of 2 drug products supplied as separate vials of AZD8895 and AZD1061. The product is a clear to slightly opalescent, colorless to slightly yellow solution.

Each vial selected for dose preparation should be inspected. If there are any defects noted with the IMP (ie, it is visually different to the description provided above), the Investigator and site monitor should be notified immediately.

The dose of AZD7442 (AZD8895 and AZD1061) for administration must be prepared by the Investigator's or site's designated IMP manager using aseptic technique. Total time from needle puncture of the vial to the start of administration must not exceed:

- 24 hours at 2 °C to 8 °C (36 °F to 46 °F)
- 4 hours at room temperature.

If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hours, otherwise a new dose must be prepared from new vials. AZD7442

(AZD8895 and AZD1061) does not contain preservatives; any unused portion of the vial must be discarded immediately after use.

No incompatibilities between AZD7442 (AZD8895 and AZD1061) and the following component materials of construction have been observed:

- IV bags made of polyvinylchloride (PVC) or polyolefin (PO)
- Polypropylene (PP) syringes
- Filters made of polyethersulfone (PES)

AstraZeneca will be permitted upon request to audit the supplies, storage, dispensing procedures and records.

6.2.2 Preparation and Administration

6.2.2.1 Intramuscular Administration

The volumes for IM administration are provided by participant weight range and indication in Table 8. AZD8895 and AZD1061 (comprising AZD7442), must both be administered separately to the participant in sequential order, with no participant receiving doses of AZD8895 without also receiving the matching dose of AZD1061.

Accurately withdraw the required volume for each of the injections. Use a single disposable polycarbonate or polypropylene syringe for each of the injections.

Administer the injections of AZD7442 (comprised of AZD8895 and AZD1061) using a needle of appropriate gauge and length for each of the injections, according to standard procedures for IM injections for patients in each weight bracket. AZD8895 should be administered first in the anterolateral thigh followed by administration of AZD1061 in the alternate anterolateral thigh.

Table 8 Volume of AZD7442 for IM Administration by Participant Weight Range and Indication

Participant weight range (kg)	Dose	Injection volume (mL) of AZD8895 100 mg/mL	Injection volume (mL) of AZD1061 100 mg/mL	Total injection volume (mL) of AZD7442 100 mg/mL (AZD8895 + AZD1061)
Prophylaxis of COVID-19 (Cohort 1)/Treatment of mild to moderate COVID-19 (Cohort 2)				
≥ 1.5 to < 5 kg	60 mg (30 mg AZD8895 and 30 mg AZD1061)	0.3	0.3	0.6
≥ 5 to < 15 kg	150 mg (75 mg AZD8895 and 75 mg AZD1061)	0.75	0.75	1.5
≥ 15 to < 40 kg	Participants in this weight range will be administered AZD7442 via IV infusion			
≥ 40 kg	600 mg (300 mg AZD8895 and 300 mg AZD1061)	3	3	6

AZD8895 must be administered first followed by AZD1061.
COVID-19, coronavirus disease 2019; IM, intramuscular; IV, intravenous.

6.2.2.2 Intravenous Administration

AZD7442 is dosed by co-administration of AZD8895 and AZD1061 in a single IV infusion.

The dose volume to be administered to each participant depends on the weight of the participant, the indication (ie, prophylaxis, inpatient, or outpatient treatment), and the concentration of the prepared dilution as indicated in Table 9 and Table 10. The dose of AZD7442 (AZD8895 and AZD1061) should be administered as an admixture of AZD7442 (AZD8895 and AZD1061) and diluent. The diluent is to be selected per the standard of care of the participant and may consist of 0.9% sodium chloride for injection or 5% dextrose for injection.

Dose Preparation

AZD7442 (AZD8895 and AZD1061) for administration should be prepared by combining the required volume of AZD7442 (AZD8895 and AZD1061) with an appropriate volume of diluent to give a final AZD7442 admixture with a concentration ranging from 10 mg/mL to 50 mg/mL. Refer to Table 10 for recommended volumes for AZD7442 (AZD8895 and AZD1061) and diluent in order to achieve the required concentrations. The AZD7442 admixture should be prepared by following the procedure below:

- Withdraw the AZD7442 (AZD8895 and AZD1061) dose volume into a suitable size syringe. Prepare a separate syringe containing required amount of diluent.
- Transfer the AZD7442 (AZD8895 and AZD1061) solution into the diluent syringe; once capped (or secured with an attached needle), mix the solution using gentle inversion. Do not shake.

Table 9 Preparation of AZD7442 Admixture for IV Administration

Concentration of AZD7442 Admixture (mg/mL)	Number of AZD8895 (100 mg/mL) vials required	Number AZD1061 (100 mg/mL) vials required	AZD8895 Volume for Dilution (mL)	AZD1061 Volume for Dilution (mL)	Diluent volume for dilution (mL)	Total volume post-dilution (mL)[a]
10	1	1	1.5	1.5	27	30
20	1	1	1.5	1.5	12	15
50	1	1	1.5	1.5	3	6
50	2	2	3.0	3.0	6	12

[a] The volume of the prepared diluted AZD7442 admixture will exceed the volume that will be required for dose administration

IV, intravenous.

Dose Administration

Following dilution, the required volume of the AZD7442 admixture for the intended dose will be drawn into an appropriately sized syringe or IV bag and administered intravenously. Refer to Table 10 for the volume of admixture to be administered.

The dose volumes, infusion rates, and infusion times for each weight range were determined by considering the maintenance fluid rate and maintenance volume requirements. It is not recommended to deviate from these values unless the participant has a particular medical requirement that deems it necessary to adjust.

- AZD7442 (AZD8895 and AZD1061) infusion is to be administered through an IV administration set with a 0.2 or 0.22 µm low protein binding filter; acceptable configurations include an IV set containing an in-line filter or the attachment of a separate filter to the distal end of the IV tubing.
- AZD7442 (AZD8895 and AZD1061) infusion can be administered through the same IV line as other medications when local practices for flushing the line with each administration are followed.
- Administration set volume should not exceed 2 mL in order to minimize the flush volume.

- The IV line and catheter will be flushed according to local practices to ensure the full dose is administered. It is recommended to flush at the same rate as the drug infusion rate (listed in Table 10).
- **Important**: The timing of the PK sample must be well coordinated such that the PK sample is immediately obtained after the full dose is delivered. Sampling should occur immediately after the IV line and catheter are flushed.

The approximate infusion time and target rates are listed in Table 10; however, if there are interruptions, the total allowed time must not exceed 4 hours with the infusion syringe maintained at room temperature, otherwise a new dose must be prepared from new vials.

Table 10 Doses and AZD7442 Admixture Concentration Selection per Cohort and Participant Weight Range for IV Administration

Participant weight range (kg)	Dose of AZD7442 (mg)	Concentration of AZD7442 Admixture (mg/mL)[a]	Volume of AZD7442 Admixture for administration (mL)	Infusion rate (mL/minute; mL/hour)	Approximate infusion time (minutes)[b]
Prophylaxis (Cohort 1)/Treatment – Outpatient (Cohort 2)					
≥ 1.5 to < 5 kg	50	20	2.50	0.1 mL/min; 6.0 mL/hour	25
≥ 5 to < 15 kg	110	50	2.20	0.3 mL/min; 18 mL/hour	7
≥ 15 to < 40 kg	300	50	6.00	0.8 mL/min; 48 mL/hour	8
≥ 40 kg	440	50	8.80	1.0 mL/min; 60 mL/hour	9
Treatment – Inpatient (Cohort 3)					
≥ 1.5 to < 5 kg	60	20	3.00	0.1 mL/min; 6 mL/hour	30
≥ 5 to < 15 kg	150	50	3.00	0.3 mL/min; 18 mL/hour	10
≥ 15 to < 40 kg	400	50	8.00	0.8 mL/min; 48 mL/hour	10
≥ 40 kg	600	50	12.00	1.0 mL/min; 60 mL/hour	12

[a] Refer to Table 9 for instructions on preparation of the AZD7442 admixture.
[b] Infusion time does not account for flush time
AZD7442 is to be administered as a single IV infusion (AZD8895 and AZD1061 co-administered).
IV, intravenous; min, minute.

6.3 Measures to Minimize Bias: Randomization

This is an open-label study and all eligible participants will receive AZD7442.

For the PK sample collected post Day 1 during the first 14 days, participants will be randomized to have a blood sample collected on either Day 4, Day 8, Day 11, or Day 15 (1:1:1:1) using the IRT.

The Investigator(s) will:

1 Obtain signed informed consent or assent from the potential participant, or their guardian/legal representative, before any study specific procedures are performed.
2 Determine participant eligibility.
3 Assign the eligible participant unique SID via the IRT.
4 Participants will be allocated to receive AZD7442 administered IM or IV
5 Participants will be assigned the Day of PK sampling (Day 4, Day 8, Day 11, or Day 15)

If a participant withdraws from the study, then his/her enrollment/SID cannot be reused. Withdrawn participants will not be replaced.

6.4 Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

Dosing will take place under the guidance of study personnel, and may occur at study sites, mobile units, or other health care facilities. The date, and time if applicable, of dose administered will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. If a problem occurs during dosing, such as needle break, no re-dosing is permitted.

6.5 Concomitant Therapy

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 must be recorded along with:

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

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

Permitted, prohibited, and restricted medications are summarized in Table 11. Restricted drugs of abuse and alcohol are summarized in Table 12.

Table 11 Summary of Permitted, Prohibited, or Restricted Medications

Use category	Type of medication/treatment	Timeline/instructions
Permitted	Routine vaccines[a]	Licensed influenza vaccines are permitted at any time. All other routine vaccines are permitted beginning > 30 days after IMP dose COVID-19 vaccines are permitted before (> 14 days before study entry) and during the study, > 14 days after IMP administration study Day 1. For guidance during the study, see Section 6.5.1).
	Allergen immunotherapy	Allowed if participant has been receiving stable desensitization therapy for allergies for at least 30 days prior to Day 1 and there is no anticipated change during the treatment period. Allergen immunotherapy should not be administered on the same day as IMP. Non-prescription treatments for allergies such as antihistamines, decongestants, and nasal steroids are permitted.
	Commercial biologics (except for COVID-19 prophylaxis or treatment), prednisone, immunosuppressive medications (eg, azathioprine, tacrolimus, cyclosporine, methotrexate, hydroxychloroquine, or cytotoxic chemotherapy)	Allowed, provided the participant is stable on maintenance dose (at steady state) prior to Day 1 and up to Day 29, OR Allowed if participant is hospitalized for treatment of COVID-19 Biologics (eg, palivizumab) should not be administered on the same day as IMP
	Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance. Primary care providers, or where appropriate Investigators, should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study.	

Table 11 Summary of Permitted, Prohibited, or Restricted Medications

Use category	Type of medication/treatment	Timeline/instructions
Prohibited	Products indicated for the treatment or prevention of SARS-CoV-2 or COVID-19 (including those under investigation or authorized under early access provisions) Convalescent COVID-19 plasma and sera	Note: For participants who become hospitalized with COVID-19, receipt of approved/licensed treatment options are permitted, and they should be treated according to local standard of care, including investigational agents under Emergency Use Authorization or equivalent regulations.
	Hydroxychloroquine	Use of hydroxychloroquine is acceptable if used chronically for autoimmune disease, and the dose is stable prior to Day 1 and up to Day 29.
	Chloroquine	Use of chloroquine is acceptable if used to treat a parasitic infection.
	Ivermectin	Use of ivermectin is acceptable if used to treat a parasitic infection.
	HIV protease inhibitors	HIV protease inhibitors are acceptable if used chronically for HIV infection, and the dose is stable prior to Day 1 and up to Day 29.
	Hyperimmune globulin and immune globulin products	Previous use of hyperimmune globulin/ immune globulin is allowed if there is an adequate washout period prior to study start ≥ 5 half-lives of the drug with no plan to dose during the study period.
Restricted	Contraceptive methods	See Section 5.1

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

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

Table 12 Summary of Restricted Drugs of Abuse and Alcohol

Amphetamine	Benzodiazepines
Ethanol	Methadone Metabolites
Cannabinoids	Barbiturates
Cocaine	Phencyclidine
Opiates	Methamphetamines
Tricyclic anti-depressants (TCA)	

6.5.1 Receipt of COVID-19 Vaccines During the Study

Individual participants are encouraged to receive a COVID-19 vaccination when they become eligible and it is locally available. If a participant plans to receive a COVID-19 vaccine within 14 days of study Day 1 (AZD7442 administration) they should delay starting in the study until > 14 days after their last dose of vaccine (Section 5.2). Available data suggests that AZD7442 may provide 6 months of protection against pre-Omicron SARS-CoV-2 variants but due to a reduced in vitro neutralization against the Omicron variant, AZD7442 may provide a different duration of protection against Omicron. Protection has not yet been demonstrated in children.

Theoretically, in the presence of adequate neutralizing antibody titers, expected for the durations noted, an appropriate and effective response to the vaccine could be impaired. Data from animal studies reported that prior AZD7442 administration did not alter either the cellular or the humoral immune responses elicited by subsequent COVID-19 vaccinations. Based on these results, AZD7442 is not anticipated to interfere with vaccine efficacy. If the participant decides to receive the vaccination the participant can proceed and continue in the study. If a participant has a breakthrough case of COVID-19 during the study despite being previously vaccinated, they should be managed using standard of care.

For participants who have received IMP and develop symptomatic COVID-19 at some point in the study:

- There is no reason to believe that administration of a vaccine during acute COVID-19 illness will ameliorate the illness.
- In most mAb recipients, an infection-induced immune response will occur, and this response should be protective.
- The risk associated with receiving a vaccine after resolution of the illness should be low.

6.6 Dose Modification

The DSMB may recommend modifications to the doses outlined in Table 6 based on available safety and tolerability data. See Appendix A 5.

6.7 Intervention After the End of the Study

No intervention will be provided at the end of this study.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Participants will receive a single IM dose of AZD7442 (administered as a single IM injection containing AZD8895 followed by a single IM injection containing AZD1061) or a single IV

dose of AZD7442 (administered by co-infusion of AZD8895 and AZD1061 in the same bag).

It may be necessary for a participant to temporarily interrupt their injection/infusion of IMP. If the injection of IMP is not resumed (ie, it is discontinued), the participant should remain in the study to be evaluated.

Note that discontinuation of IMP is NOT the same thing as withdrawal from the study.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, the request of their parent or legal guardian, or at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time a participant withdraws consent or is withdrawn from the study, if possible, an Early Discontinuation visit should be conducted, as shown in the SoA (Table 3). See the SoA for data to be collected at the time a participant withdraws consent or is withdrawn from the study and follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before consent was withdrawn.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she withdraws consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants enrolled, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A 9.

7.4 Stopping Rules, Progression to Next Study Part, and Termination of Study

7.4.1 Stopping Rules for an Individual Participant, at Any Time in the Study

Each participant in this study will receive a single dose of IMP. An individual participant will not receive IMP if any of the following occur in the participant in question:

- Withdraws consent after signing informed consent.
- Meets one or more of the exclusion criteria or fails to meet all inclusion criteria for study participation.

Each participant who has received IMP will be followed for the full study period unless consent is withdrawn specifically from further study participation, or the participant is lost to follow-up. Participants who have not received IMP, regardless of reason, will not be followed. Unless consent for follow-up is withdrawn, participants discontinued after receiving a partial dose of IMP will be followed for the full study period (up to and including Day 366, 52 weeks after IMP dosing) with all laboratory and clinical evaluations collected as defined in this CSP.

7.4.2 Stopping Rules for a Whole Cohort, Progression to Next Study Part, and Termination of Study

The Sponsor reserves the right to temporarily suspend or permanently terminate this study or a component of the study at any time.

Stopping rules as detailed below (general, cardiovascular, laboratory, and AZD7442 specific).

General Criteria

The study will be put on temporary hold (defined as stop of enrollment of participants into the study) pending further safety data analysis if any of the following criteria occur in participants receiving AZD7442:

- An SAE (including death) where there is a reasonable possibility that it is related to the IMP administration in any one participant.
- A severe non-serious adverse reaction where there is a reasonable possibility that it is related to the IMP administration in 2 or more participants in the same cohort, independent of, within, or not within the same system organ class.

The risk to all participants will be evaluated thoroughly prior to a decision as to whether to terminate the study prematurely or continue dosing in agreement with the regulatory authorities.

The DSMB will carefully review the totality of data, taking into account moderate non-serious AEs where there is a reasonable possibility that the AE is related to the IMP administration, the number of participants in which the AE occurs, and concurrency of more than one AE within the same participant.

Cardiovascular Criteria

- Two or more participants, that receive AZD7442, have QTc prolongation defined as QTcF > 500 ms, or a prolongation from baseline (pre-dose on Day 1) of > 60 ms, confirmed (persistent for at least 5 minutes) and determined post dose either during continuous 12 lead ECG monitoring or on a repeat 12 lead ECG.

Laboratory Findings

- One or more participants, who receive AZD7442, fulfill Hy's Law defined as "An increase in AST or ALT ≥ 3 × ULN and TBL ≥ 2 × ULN, where no other reason can be found to explain the combination of increases, eg, elevated serum ALP indicating cholestasis, viral hepatitis, another drug". The elevations do not have to be at the same time or within a specified time frame (see Appendix D for follow-up procedures).

Study Specific Stopping Criteria Related to AZD7442

- Anaphylactic reaction (Appendix F) considered related to the IMP in any participant.

- Any safety finding assessed as related to the IMP that, in the opinion of the Sponsor or the Investigator, warrants suspension of further dosing of participants until more fully assessed.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- A hierarchy of blood tests and wide visit windows are defined in Section 8.5.1 to provide flexible blood collection schedules. This will allow Investigators to determine the blood volume that can be safely drawn from each child based on the child's individual circumstances (eg, tests already conducted as part of the child's routine clinical management) without exceeding local recommendations. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

8.1.1 Monitoring COVID-19 Symptoms

Progression of COVID-19 will be captured and recorded in the eCRF.

To determine the incidence of infection in Cohort 1, when a participant develops at least one of the COVID-19 qualifying symptoms listed in Table 13 after Day 1, the participant, his/her caretaker, or his/her legal representative must contact the study site. A sample will be collected for SARS-CoV-2 RT-PCR to confirm the participant is positive (see Section 8.6.1). COVID-19 qualifying symptom(s), SARS-CoV-2 positive test results, and/or COVID-19 diagnosis will be collected and recorded in the eCRF as AEs.

In Cohorts 2 and 3, COVID-19 symptoms or signs listed in Table 13 will only be recorded as

AEs when any of the following occur:

- The sign or symptom is serious according to the definition in Appendix B 2.
- The participant discontinues the study due to the sign or symptom.
- In the Investigator's judgment, the sign or symptom is not considered COVID-19 related.

Table 13 COVID-19 Qualifying Symptoms

Participant must present with at least one of the following symptoms:	
Duration	**Symptom**
No minimum duration	Fever
	Shortness of breath
	Difficulty breathing
Must be present for ≥ 2 days	Chills
	Cough
	Fatigue
	Muscle aches
	Body aches
	Headache
	New loss of taste
	New loss of smell
	Sore throat
	Congestion
	Runny nose
	Nausea
	Vomiting
	Diarrhea
	Abdominal pain
	Poor appetite/feeding problems

CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019.
Adapted from CDC 2020.

8.1.2 Severe COVID-19 Criteria

In all cohorts, severe COVID-19 will be characterized by a minimum of either pneumonia (fever, cough, tachypnea, or dyspnea, and lung infiltrates) or hypoxemia (SpO_2 < 90% in room air and/or severe respiratory distress) and a WHO Clinical Progression Scale score of 5 or higher (Table 14). Severe COVID-19 will be collected and recorded in the eCRF as an SAE.

Table 14 WHO Clinical Progression Scale

Patient state	Descriptor	Score
Uninfected	Uninfected, no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalized: moderate disease	Hospitalized; no oxygen therapy[a]	4
	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized: Severe Disease	Hospitalized; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$	7
	Mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors	8
	Mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO	9
Dead	Death	10

[a] If hospitalized for isolation only, record status as for ambulatory patient.
ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; NIV, non-invasive ventilation; pO_2, partial pressure of oxygen; SpO_2, oxygen saturation, WHO, World Health Organization.
(Marshall et al 2020)

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical Examinations

A complete physical examination will be performed at screening followed by targeted physical examinations as specified in the SoA (Section 1.3).

- 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. Each clinically significant abnormal finding at screening will be recorded in the medical history.
- A targeted physical examination will include areas suggested by the medical history. Each clinically significant abnormal finding following IMP dosing will be recorded as an AE (Section 8.2).

All physical examinations will be performed by a licensed healthcare provider (eg, physician, physician assistant, or licensed nurse practitioner).

8.2.2 Vital Signs

Vital signs, including heart rate, respiratory rate, pulse oximetry, BP, and body temperature, will be performed as specified in the SoA (Section 1.3). The participant should be resting prior to the collection of vital signs.

Situations in which vital sign results should be reported as AEs are described in Section 8.3.7.

8.2.3 Electrocardiograms

A triplicate 12-lead ECG will be performed at time points specified in the SoA (Section 1.3). A 12-lead safety ECG will be obtained after 5 minutes' supine rest, using the sites' own ECG machines.

A pediatrician will judge the overall interpretation as normal or abnormal. If abnormal, it will be documented as to whether or not the abnormality is clinically significant by the Investigator. For neonates, ECGs must be evaluated by a physician who is experienced in reading neonatal ECGs. For all abnormalities (regardless of clinical significance), the specific type and nature of the abnormality will be documented. Clinically significant findings should also be documented on the AE page of the eCRF, if applicable.

The Investigator may add extra 12 lead resting ECG safety assessments if there are any abnormal findings or if the Investigator considers it is required for any other safety reason. These assessments should be entered as an unscheduled assessment.

All ECG readings will be digitally stored as source documents.

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, hematology, coagulation, and urinalysis will be taken at the visits indicated in the SoA (Section 1.3).

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The clinical chemistry, hematology, urinalysis, and coagulation will be performed at a central laboratory. Instruction for the collection and handling of the samples will be provided in the study-specific Laboratory Manual.

The following laboratory variables will be measured.

8.2.4.1 Hematology

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)	

8.2.4.2 Serum Clinical Chemistry

Serum Clinical Chemistry	
Sodium	Alkaline phosphatase (ALP)
Potassium	Alanine aminotransferase (ALT)
Urea	Aspartate aminotransferase (AST)
Creatinine	Gamma glutamyl transpeptidase (GGT)
Albumin	Total bilirubin (TBL)
Calcium	Unconjugated bilirubin
Phosphate	Conjugated bilirubin
Glucose	Creatine Kinase

8.2.4.3 Urinalysis

Urinalysis
Glucose
Protein
Blood
Microscopy (if positive for protein or blood): RBC, WBC, Casts (Cellular, Granular, Hyaline)

8.2.4.4 Coagulation Tests

Coagulation Tests
International normalized ratio (INR)
Activated partial thrombin time (aPTT)
Prothrombin Time (PT)

8.2.4.5 Pregnancy Testing

Pregnancy test (Females of Childbearing Potential)	
Serum human-beta chorionic gonadotrophin (screening)	Urine human-beta chorionic gonadotrophin (screening)

8.3 Adverse Events and Serious Adverse Events

The Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from the time of IMP administration throughout the study, up to and including the last visit. After IMP administration on Day 1, participants will be monitored on site for a minimum of one hour for general safety, including injection/infusion site reactions and hypersensitivity reactions (including anaphylaxis).

Serious adverse events will be recorded from the time of signing of the ICF throughout the study, up to and including the last visit.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the IMP that occurs after the end of the clinical study in a participant treated by him or her, the Investigator shall, without undue delay, report the SAE to the Sponsor.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant’s last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse Event Variables

The following variables will be collected for each AE:

- AE diagnosis and description (verbatim)
- The date and time when the AE started and stopped

- Severity grade/maximum severity
- Whether the AE is serious or not
- Investigator causality rating against the IMP(s) (yes or no)
- Action taken with regard to the IMP(s)
- AE caused participant to withdraw from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE is serious due to
- Date of hospitalization (if hospitalized)
- Date of discharge
- Probable cause of death (if death occurred)
- Date of death (if death occurred)
- Autopsy performed (if death occurred)
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

The following severity ratings will be used, adapted from the Common Terminology Criteria for Adverse Events version 5.0 (NIH 2017):

- Grade 1: An event of mild intensity that is usually transient and may require only clinical or diagnostic observations. The event does not generally interfere with usual activities of daily living.
- Grade 2: An event of moderate intensity that is usually alleviated with additional, specific therapeutic intervention, which is minimal, local, or non-invasive. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the participant.
- Grade 3: A severe event that requires intensive therapeutic intervention but is not immediately life-threatening. The event interrupts usual activities of daily living, or significantly affects the clinical status of the participant.
- Grade 4: An event, and/or its immediate sequelae, that is associated with an imminent risk of death and urgent intervention is indicated.
- Grade 5: Death, as result of an event.

It is important to distinguish between serious and severe AEs:

- Severity is a measure of intensity, whereas seriousness is defined by the criteria in Appendix B 2.
- An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

8.3.3 Causality Collection

The Investigator should assess causal relationship between IMP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IMP?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

8.3.4 Adverse Events of Special Interest

Adverse events of special interest will be collected according to the time points specified in the SoA (Section 1.3).

Adverse events of special interest are events of scientific and medical interest, specific to the further understanding of the IMP safety profile, and require close monitoring and rapid communication by the Investigators to the Sponsor. An AESI can be serious or non-serious. All AESIs will be recorded in the eCRF. Serious AESIs will be recorded and reported as per Section 8.3.9. See also the AZD7442 IB, for additional information on AESIs.

Adverse events of special interest for AZD7442 are listed below. They include:

- Anaphylaxis and other serious hypersensitivity reactions, including immune complex disease (Section 8.3.4.1).
- Injection site and infusion site reactions (Section 8.3.4.2).
- MIS-C (Section 8.3.4.3)
- Thrombotic events, heart failure, and cardiac ischemia (Section 8.3.4.4)

8.3.4.1 Anaphylaxis and Hypersensitivity Reactions

The definition and management of anaphylaxis and serious hypersensitivity reactions are provided in Appendix F. After IMP administration, participants will be monitored for at least one hour for general safety, including anaphylaxis and other hypersensitivity reactions (Section 8.3.1).

8.3.4.2 Injection and Infusion Site Reactions

An injection/infusion site inspection will be performed on Day 1 and at any in-person visits up to and including Day 6 (see SoA in Section 1.3 and Table 15). If evidence of injection or infusion site reaction persists, the site will be rechecked at each visit until no evidence of an active reaction remains. The inspection will include assessment of size, redness/erythema, swelling, itching/pruritis, pain or tenderness, induration, discoloration). Any injection/infusion site reaction will be recorded as an AE and a photograph taken, at the discretion of the Investigator, with visible measuring tape.

Table 15 Injection/infusion Site Inspection

Procedure/time after injections or infusions have been administered	Immediately after IMP administration	30 minutes (± 10 minutes)	Immediately prior to participant release
Visual inspection of site	X	X	X
Palpation of site	X	X	X
Participant will be asked:			
Are you experiencing any discomfort?	X	X	X
If yes, has the feeling of discomfort changed since you received the injection?	NA	X	X

IMP, investigational medicinal product; NA, not applicable.

Any AEs should be reported as described in Section 8.3.

8.3.4.3 Multisystem Inflammatory Syndrome - Children

For this study, MIS-C is defined as follows (CDC 2021d):

- Fever > 38.0 °C for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (> 2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND
- No alternative plausible diagnoses; AND
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.

8.3.4.4 Cardiac and Thromboembolic Events

Cardiovascular AEs will be referred to a CV Event Adjudication Committee (Section 9.7). Only adjudicated events will be included as AESIs.

8.3.5 Medically Attended Adverse Events

Medically attended adverse events will be collected according to the time points specified in the SoA (Section 1.3).

Medically attended adverse events are defined as AEs leading to medically attended visits that were not routine visits for physical examination or vaccination, such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (eg, a medical doctor or equivalent) for any reason. AEs, including abnormal vital signs, identified on a routine study visit will not be considered medically attended adverse events.

8.3.6 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider or reported in response to the open question from the study site staff: 'Have you/the child had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.7 Adverse Events Based on Examinations and Tests

The results from the CSP mandated laboratory tests and vital signs will be summarized in the CSR.

Deterioration as compared to baseline in protocol-mandated safety assessments should therefore only be reported as AEs if they fulfill any of the SAE criteria, are the reason for discontinuation of treatment with the investigational product or are considered to be clinically relevant as judged by the Investigator (which may include, but are not limited to, consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.8 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN *and* confirmed as a Hy's Law (HL) case should be reported as SAEs.

Occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug should be evaluated. The elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of HL.

8.3.9 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

For further guidance on the definition of a SAE, see Appendix B.

The reference document for definition of expectedness/listedness is the IB for AZD7442.

8.3.10 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except when the pregnancy is discovered before the study participant has received any IMP.

8.3.10.1 Maternal Exposure

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.9) and **within 30 days** for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

8.3.10.2 Paternal Exposure

In case of pregnancy of the partner of a male participant, the partner's pregnancy should be reported on the pregnancy form (consent from the partner must be obtained before the pregnancy form is completed) following the same timeframe and routing as described for any participant's pregnancy. Pregnancy of the participant's partner is not considered to be an AE. These pregnancies will also be followed up, and the outcome of the pregnancy (spontaneous

miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should, if possible, be obtained and documented.

8.3.11 Medication Error, Drug Abuse, and Drug Misuse

8.3.11.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.9) and **within 30 days** for all other medication errors.

8.3.11.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The definition of a Medication Error can be found in Appendix B 4.

8.3.11.3 Drug Abuse

Events of drug abuse with IMP or AstraZeneca NIMP are collected in all studies where drug abuse is possible.

For guidance, refer to AstraZeneca SOP ‘Management of Individual Case Safety Reports (ICSR) in Clinical Trials’, SOP-0108717.

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

8.3.11.4 Drug Misuse

Events of drug misuse with IMP or AstraZeneca NIMP are collected in all studies where drug misuse is possible.

For guidance, refer to AstraZeneca SOP ‘Management of Individual Case Safety Reports (ICSR) in Clinical Trials’, SOP-0108717.

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

8.4 Overdose

For this study, any dose of AZD7442 greater than a planned weight-based dose presented in Table 6 will be considered an overdose.

AstraZeneca does not recommend a specific treatment for an overdose. Symptoms of overdose should be treated as per clinical judgment.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study intervention occurs during the study, the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.9) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed.

- Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.

  - Pharmacokinetic samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

- Remaining ADA sample aliquots will be retained at AstraZeneca or its designee for a maximum of 15 years following issue of the CSR. Additional use includes but is not limited to further characterization of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

8.5.1 Total Blood Volume

Blood volume estimates are provided in Table 16. For participants other than neonates, the total estimated blood volume to be collected during the study is approximately 73 mL per participant. For neonates, only safety and PK samples will be collected and the total estimated blood volume to be collected during the study is approximately 22 mL per participant. The total volume can be adjusted by age and the body weight of the participant per local ethics requirements. Where necessary, the visit windows in the SoA can be used to collect samples across a number of days. When sample collection occurs over ≥ 2 days for a given study visit, participants are required to visit the site at least once per study visit. If practical, additional sample collection can take place at home visits as long as the samples are obtained per protocol by qualified personnel. If it is not possible to obtain sufficient blood from a participant at a given study visit, the order of the samples will be prioritized according to the key requirements of the study and the following hierarchy will be applied: safety (ie, serum chemistry, hematology, coagulation), PK, SARS-CoV-2 neutralizing antibodies, and ADA (see Laboratory Manual). For participants receiving IV infusions of AZD7442, blood samples are to be collected from the opposite side of the body to the IV infusion at Visit 1.

Table 16 Blood Volume Estimates

Visit (study day ± visit window)	Estimated blood volume for neonates[a]	Estimate blood volume for all other participants[b]
Screening Visit (Day -7 to Day 0)	3.7 mL	6.3 mL
Visit 1 (Day 1 ± 0)	1.2 mL (IV only)	6.0 to 8.5 mL[c, d]
Visit 2 (Day 4 to 15 ± 2)	1.2 mL	2.5 mL
Visit 3 (Day 31 + 5)	4.9 mL[e]	14.8 mL
Visit 4 (Day 92 ± 5)	2.6 mL[e]	10.3 to 12.8 mL[d]
Visit 5 (Day 183 ± 10)	3.5 mL[e]	13.0 mL
Visit 6 (Day 366 ± 15)	4.9 mL[e]	14.8 mL
Total from screening to Day 366	**20.8 to 22.0 mL**	**67.7 to 72.7 mL**

[a] For neonates, only safety and PK samples will be collected.

[b] For participants other than neonates, the following hierarchy will apply if it is not possible to obtain blood for all samples: (1) safety, (2) pharmacokinetics, (3) SARS-CoV-2 neutralizing antibodies, and (4) anti-drug antibodies.
[c] At Visit 1, participants receiving AZD7442 IV will have an extra 2.5mL blood sample taken for post-dose PK sampling.
[d] At Visit 4, participants in Cohort 1 will also have an additional 2.5mL taken for SARS-CoV-2 serology.
[e] For Visits 3 to 6 blood samples should be taken on at least 2 different days and at least 24 h apart
Blood samples can be taken on different days within the sampling window specified in the Schedule of Activities (Section 1.3).
COVID-19, coronavirus disease 2019; IM, intramuscular; IV, intravenous; PK, pharmacokinetic; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Repeat blood samples may be collected for safety reasons.

8.5.2 Pharmacokinetics

- Serum samples will be collected for measurement of serum concentrations of AZD7442 (AZD8895 and AZD1061) at either Day 4, 8, 11, or 15 (one sample) and Days 31, 92, 183, and 366 (one sample on each day), as specified in the SoA (Section 1.3). For participants who receive AZD7442 via an IV infusion, a serum sample should also be taken at the end of the infusion on Day 1 from the opposite side of the body. Serum samples should still be taken even if the participant is outside the visit window specified in the SoA.
- Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.
- Serum samples will be used to assess the PK of AZD7442 following IM and IV administration. Samples collected for analyses of AZD7442 serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Samples will be collected, labeled, stored, and shipped, as detailed in the Laboratory Manual.
- AZD7442 PK parameters (eg, maximum serum concentration, AUC), if data permit, will be calculated based on AZD7442 serum concentrations following IM and IV administration.

8.5.2.1 Determination of Drug Concentration in Serum

Samples for determination of drug concentration in serum will be assayed by bioanalytical test sites operated on behalf of AstraZeneca, using an appropriately validated bioanalytical method. The bioanalytical sample results and the analytical method used will be described in a

separate Bioanalytical Report.

8.5.2.2 Determination of Drug Concentration in Nasal Secretions

Nasal samples to measure AZD7442 concentrations in nasal mucosa will be collected when test supplies are available and assessed using an appropriately qualified bioanalytical assay.

8.5.3 Immunogenicity Assessments

Serum samples for immunogenicity assessments will be collected according to the SoA (Section 1.3). Samples will be collected, labeled, stored, and shipped, as detailed in the Laboratory Manual.

8.5.3.1 Anti-drug Antibody

Blood samples for determination of ADA in serum will be assayed using an appropriately validated bioanalytical method. The results and the method details will be described in a separate report.

8.5.3.2 SARS-CoV-2 Serology

Serum samples will be collected to assess SARS-CoV-2 antigen-specific antibody levels at baseline from all participants. Serostatus will also be collected from non-neonates in Cohort 1 according to the SoA (Table 3). Baseline serostatus and time to seroconversion in participants receiving AZD7442 will be determined using a validated SARS-CoV-2 nucleocapsid antigen assay operated by an authorized laboratory. Serologic assessment to S (spike), RBD, and nucleocapsid antigens may also be assessed quantitatively using a validated multiplexed meso scale discovery immunoassay.

8.5.4 Pharmacodynamics: Neutralizing Antibody Assessments

8.5.4.1 SARS-CoV-2 Neutralizing Antibody Assessments

Serum samples to measure SARS-CoV-2 neutralizing antibody titers will be collected from participants according to the time points specified in the SoA (Section 1.3). Authorized laboratories may measure neutralizing antibodies to SARS-CoV-2 using validated wild-type live virus or pseudovirus neutralization assays.

For storage, re-use, and destruction of pharmacodynamic samples, see Section 8.5 and Appendix C.

8.6 Human Biological Sample Biomarkers

8.6.1 Virologic Assessments

Instructions for obtaining and processing samples for RT-PCR are provided in the Laboratory Manual. A SARS-CoV-2 rapid antigen test can be performed at each site at screening to enable same-day assignment to study cohorts. During the study, samples will also be assessed by authorized RT-PCR assays for the detection of SARS-CoV-2 by the central laboratories

according to the time points specified in the SoA (Section 1.3). Unscheduled RT-PCR testing may be performed in participants in Cohort 1 who present with COVID-19 qualifying symptom(s) (Section 8.1.1).

For Cohorts 2 and 3, viral load will be assessed in samples collected on Day 1 (at the site) and on Day 8 (at the site or at home) by an authorized RT-PCR assay for the quantitative measurement of SARS-CoV-2. The type of sample (eg, saliva, blood, nasopharyngeal) should be consistent between all study visits for each participant, but particularly for the samples collected on Day 1 and Day 8 which will be used to estimate the change in viral load.

8.6.2 Other Study-related Biomarker Research

Already collected samples may be analyzed for different biomarkers thought to play a role in COVID-19 severity or outcomes, including, but not limited to, serum, plasma or mucosal cytokines, quantification of RNA, micro-RNA, and/or non-coding RNA, using quantitative RT-PCR, microarray, sequencing, or other technology in blood, saliva, or mucosal specimens to evaluate their association with observed clinical responses to AZD7442. Other study-related biomarker research excludes genetic analysis.

For storage, re-use, and destruction of biomarker samples, see Section 8.5 and Appendix C.

8.7 Optional Genomics Initiative Sample

Collection of optional samples for Genomics Initiative research are out of scope for pediatric studies.

8.8 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics are not applicable in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

No hypotheses are planned in this PK, PD, safety study.

9.2 Sample Size Determination

Approximately 120 participants will be screened/enrolled to achieve 100 evaluable participants.

Note: “Enrolled” means a participant’s, or their legally acceptable representative’s, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, can be rescreened once. If they are not subsequently assigned to receive AZD7442 in the study, they are considered “screen failures”.

The total sample size of 100 participants across all pediatric age groups is the minimum number required to adequately characterize the AZD7442 safety profile in pediatric participants following IM or IV administration (based on FDA 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 CL with a 95% confidence interval that remained within 60% to 140% of the point estimate in each pediatric subgroup.

9.3 Populations for Analyses

The analysis populations are defined in Table 17.

Table 17 Populations for Analysis

Population/Analysis Set	Description
Screened population set	All participants who signed the ICF. Unless otherwise stated, the enrolled set will be used for the presentation of disposition data.
Full Analysis Set	All participants who received 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.
Safety Analysis Set	All participants who have received IMP.
PK Analysis Set	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.
ADA Evaluable Analysis Set	All participants who are AZD8895 ADA evaluable and/or AZD1061 ADA evaluable. A participant is AZD1061 ADA evaluable if they are in the Safety Analysis Set and have a non-missing baseline AZD1061 ADA result and at least one non-missing post-baseline AZD1061 ADA result. A participant is AZD8895 ADA evaluable if they are in the Safety Analysis Set and have a non-missing baseline AZD8895 ADA result and at least one non-missing post-baseline AZD8895 ADA result.
SARS-CoV-2 nAb Evaluable Analysis Set	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.

ADA, anti-drug antibodies; COVID-19, coronavirus disease 2019; ICF, informed consent form; IMP, investigational medicinal product; nAb, neutralizing antibody; PK, pharmacokinetic, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

9.4 Statistical Analyses

The SAP will be finalized before the first DSMB review and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

The statistical methodology below describes the statistical analysis as it is foreseen when the study is being planned.

If circumstances should arise during the study rendering the analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be performed. Any deviations from the statistical methodology defined in this protocol, reasons for such deviations and all alternative/additional statistical analyses that may be performed will be described in the SAP. The verification and review of all statistical modeling assumptions will be documented appropriately.

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.

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, then only $n = 0$ 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.

All statistical analyses and production of tables, figures, and listings will be performed using SAS® version 9.4 or higher.

9.4.2 Pharmacokinetics

9.4.2.1 Primary Endpoint(s)

The serum AZD7442 mAbs (AZD8895 and AZD1061) concentrations and PK parameters following IM and IV administration will be listed and presented separately in tabular and graphical form.

Serum Concentration Data

For AZD7442 mAbs (AZD8895 and AZD1061), the serum concentrations for each scheduled time point will be summarized by weight categories, dose, and route of administration using

appropriate descriptive statistics, based on the PK analysis set. A listing of all serum concentration-time data, ie, PK scheduled times, actual sample collection times, sample actual relative times, as well as derived sampling time deviations will be presented by weight categories, dose, and route of administration for all participants in the Safety Analysis Set.

Individual serum concentration-time data will be graphically presented on linear and semi-logarithmic scales, for all participants in the PK analysis set. Combined individual serum concentration versus actual times will be plotted on both the linear and semi-logarithmic scales for all participants in the PK analysis set. Plots will be grouped by weight categories, dose, and route of administration. Figures for the geometric mean (± geometric SD) serum concentration-time data will be presented by weight categories, dose, and route of administration on both a linear and semi-logarithmic scale (no geometric SD presented), for all participants in the PK analysis set.

All plots will be based on the PK analysis set.

Serum Pharmacokinetic Parameters

All reportable AZD7442 (AZD8895 and AZD1061) PK parameters, obtained by non-compartmental analysis method, including individual diagnostic and λ_z-related parameters, will be listed for each participant by weight categories, dose, and route of administration, based on the PK analysis set. All PK parameters will be summarized by weight categories, dose, and route of administration using appropriate descriptive statistics, based on the PK analysis set.

Population PK Analysis

Pharmacokinetic data from all age group/weight categories, doses, and route of administration will be analyzed simultaneously by population methods based on the PK analysis set. Population PK parameter estimates from the final model will be presented. Additionally, the post-hoc individual PK parameter estimates (including $AUC_{0\text{-}inf}$) will be summarized by weight categories, dose, and route of administration using descriptive statistics, when appropriate.

Full details of the analyses to be performed will be provided in the SAP.

9.4.3 Pharmacodynamics

9.4.3.1 Secondary Endpoint: Neutralizing Antibody Titers

Samples will be collected for the evaluation of the functional inhibition of SARS-CoV-2 by AZD7442 concentrations in serum. Results will be listed for each participant and time point. Descriptive statistics for geometric mean titers and geometric mean fold rises will include number of participants, geometric mean, geometric SD, 95% CI, minimum, and maximum.

9.4.4 Safety

The safety of AZD7442 will primarily be assessed by:

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

Adverse event intensity will be graded according to Appendix B 2. Adverse events will be presented for each treatment group by system organ class and preferred term. Summaries will include the number and percentage of participants reporting at least one event, number of events, and exposure adjusted rates, where appropriate.

An overview of AEs will be presented for each treatment group, including the number and percentage of participants with any AE and SAEs. Summaries will present the relationship to IMP as assessed by the Investigator, maximum intensity, seriousness, and death.

A listing will cover details for each individual AE. Full details of all AE analyses will be provided in the SAP.

Other safety endpoints include the following:

- Laboratory parameters (hematology, clinical chemistry, coagulation, and urinalysis)
- Vital signs (pulse rate, pulse oximetry, BP, and body temperature)
- Physical examination
- ECG

Laboratory assessments will be performed for hematology, clinical chemistry, coagulation, and urinalysis parameters.

All parameters from laboratory, vital signs, physical examination, and ECG assessments will be summarized with descriptive statistics based on data type (continuous, categorical, etc). No hypothesis testing or CIs will be performed or calculated, unless otherwise specified. Full details of safety endpoints analysis will be provided in the SAP.

9.4.5 Anti-drug Antibody

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 titers and neutralizing antibody status of the positive samples. 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 ADA evaluable analysis set.

In addition, the ADA titers (n, median, minimum, and maximum) will be summarized by weight categories, dose, and route of administration as well as overall by route of administration 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 may be assessed.

9.5 Interim Analyses

At least one interim analysis is planned to be conducted in this study. The first will be conducted after a minimum of 12 adolescent patients, age ≥ 12 to < 18 years old, complete the Day 92 study visit. Additional interim analyses may be conducted to support regulatory requirements or at the discretion of the Sponsor. No hypotheses are planned in this PK, PD, safety study so multiplicity is not a concern.

9.6 Data Monitoring Committee

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 as soon as practical after dosing of the study's sixth participant plus 14 days. Subsequent DSMB meetings will review safety data after 21, 36, 51, 66, 81, and 96 participants have been dosed with AZD7442.

For details on the DSMB, refer to Appendix A 5. Further details, composition, and operation of the independent DSMB will be described in a DSMB Charter.

9.7 Cardiovascular Event Adjudication Committee

An independent CV Event Adjudication Committee will provide an independent, external, systematic, and unbiased assessment of de-identified blinded data to systematically evaluate CV events. The adjudicated CV events will be included in descriptive analyses of safety data. Further details of the CV Event Adjudication Committee composition, operation, and listings of preferred terms to identify events are provided in a separate CV Event Adjudication Committee Charter.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

- An Investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the [IB or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
  - A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency (EMA) Clinical Trial Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
  - The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
  - A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

Investigators and Sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

A 3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants and their legally authorized representative must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants will be required to provide their assent, where appropriate, and their legally authorized representative (defined as a parent or guardian) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The Investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant and their legally authorized representative must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.

- The participant and their legally authorized representative must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

The safety of all Sponsor clinical studies is closely monitored on an ongoing basis by Sponsor representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the CSP and letters to Investigators.

Data and Safety Monitoring Board

An independent DSMB will monitor and protect the safety of the participants throughout the study. The DSMB members will be selected for their expertise. The voting members of the DSMB will be comprised of external individuals including the DSMB chair. Data summaries will be prepared and provided to the DSMB. To minimize the potential introduction of bias, DSMB members will not have direct contact with the study site personnel or participants. The data for review will be outlined in the DSMB Charter and will be agreed to in advance by the DSMB members. Data Review Meetings will review data relating to participant safety and quality of study conduct.

The DSMB will review safety data on a regular basis as set out in the DSMB Charter, including, but not limited to, reviewing cumulative safety data. These reviews will take place as soon as practical after 14 days of follow-up for the first 6 participants recruited into the study. Subsequent DSMB meetings will review safety data after 21, 36, 51, 66, 81, and 96 participants have been dosed with AZD7442. Recruitment will continue during the safety review unless a pause is requested by the DSMB.

Safety summaries will be prepared prior to each meeting. During the study, the benefit/risk assessment will be continuously monitored by the DSMB to ensure that the balance remains favorable.

The DSMB can recommend modifications of the protocol to enhance participant safety and to recommend early termination of the study if there is strong evidence that AZD7442 or continuation of the study poses a safety concern to participants.

Morbidity Adjudication Committee

An independent Morbidity Adjudication Committee will provide an independent, external, systematic, and unbiased assessment of de-identified data to evaluate whether the causes of death for participants are considered COVID-19 associated. Only adjudicated deaths will be included in efficacy endpoints. All fatal events will be further assessed as part of safety

evaluation. Further details of this adjudication are provided in a separate Morbidity Adjudication Committee Charter.

Cardiovascular Event Adjudication Committee

An independent CV Event Adjudication Committee will provide an independent, external, systematic, and unbiased assessment of de-identified blinded data to systematically evaluate CV events. Further details of the CV Event Adjudication Committee composition, operation, and listings of preferred terms to identify events are provided in a separate CV Event Adjudication Committee Charter.

A 6 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a half a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).

- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the study monitoring plan.

A 9 Study and Site Start and Closure

The first act of recruitment is the first participant screened and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator

- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), 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

Adverse events for **malignant tumors** reported during a study should generally be assessed as **Serious AEs**. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-serious AE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life-threatening

"Life-threatening" means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the participant's death. "Life-threatening" does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Severity Rating Scale:

- Grade 1: An event of mild intensity that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Grade 2: An event of moderate intensity that is usually alleviated with additional, specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the participant.

- Grade 3: A severe event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the participant.
- Grade 4: An event, and/or its immediate sequelae, that is associated with an imminent risk of death.
- Grade 5: Death as result of an event.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in this appendix. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in this appendix.

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error, Drug Abuse, and Drug Misuse

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study intervention that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- Occurred
- **Was identified and** participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error.

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet

- Drug not stored as instructed eg, kept in the refrigerator when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors).

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the Data Entry Site (DES) using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug

misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- Someone who is not enrolled in the study intentionally takes the drug.

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each center keeps full traceability of collected biological samples from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing information related to the samples while at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.

- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, the action is documented, and study site is notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf)
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

D 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the IMP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

D 2 Definitions

Potential Hy's Law

Aspartate aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3 × Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2× ULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law

AST or ALT ≥ 3× ULN **together with** TBL ≥ 2× ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

D 3 Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

Central Laboratories Being Used:

When a participant meets any of the PHL identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the PHL identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the participant meets PHL criteria (see Appendix D 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

Local Laboratories Being Used:

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative

- Determine whether the participant meets PHL criteria (see Appendix D 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

D 4 Follow-up

D 4.1 Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

D 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria "Important medical event" and causality assessment "yes/related" according to CSP process for SAE reporting
- For participants that met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change[1] in the participant's condition
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to this contact the Investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.

[1] A 'significant' change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the Study Physician if there is any uncertainty.

- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the Hy's Law lab kit should be used.
- Complete the 3 Liver eCRF Modules as information becomes available.

D 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Head or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term "Hy's Law") according to AstraZeneca standard processes.
  - The "Medically Important" serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of "related" should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now "Hy's Law case") ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

D 6 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory. For studies using a local laboratory, the list may be modified based on clinical judgment. Any test results need to be recorded.

Hy's Law Lab Kit for Central Laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HBsAg IgM and IgG anti-HBc HBV DNA [a] IgG anti-HCV HCV RNA [b] IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin) [c]
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)

Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin [c] Transferrin saturation

[a] HBV DNA is only recommended when IgG anti-HBc is positive
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive
[c] CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly

D 7 References

Aithal et al, 2011
Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

FDA Guidance for Industry, July 2009
FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'. Available from; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

Appendix E Hospitalization Definition

Amid a rising number of COVID-19 hospitalizations across the world, leading to a shortage of hospital beds, temporary facilities are being utilized increasingly to manage severe COVID-19 patients who would have usually been treated in a traditional hospital setting.

Please note that in this protocol, "hospitalization" is defined as ≥ 24 hours of acute care, in a hospital or similar acute care facility, including emergency rooms or temporary facilities instituted to address medical needs of those with severe COVID-19 during the COVID-19 pandemic.

For the purposes of ascertaining an exclusion criterion or an endpoint event, individuals with COVID-19 will be considered "hospitalized" if they are:

1 Managed in an alternative care site set up or authorized by states, provinces, or equivalent jurisdictions or
2 Provided with acute hospital care at home meeting the criteria below:
   (a) Physician determines the patient's condition as being appropriate for "acute inpatient hospitalization"
   (b) Treating physician should have appropriate screening protocols before care at home begins, to assess both medical and non-medical factors, including patient's preference, working utilities and assessment of physical barriers
   (c) Patients are evaluated daily either in person or remotely by a qualified health care provider/treating physician and are managed appropriately based on the patient's treatment plan and local standards for COVID-19 management.

The appropriate WHO Clinical Progression Scale for COVID-19 score assigned to grade the participant's condition would depend on the level of oxygen/ventilation support provided in these acute care settings.

Appendix F Anaphylaxis

Anaphylaxis is highly likely when either of the following criteria are fulfilled:

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips, tongue and/or uvula) plus features of anaphylaxis involving one or more system (Table 18) OR
2 Hypotension, bronchospasm, or upper airway obstruction

Table 18 Clinical Features of Anaphylaxis in Children

System	Features of anaphylaxis
Respiratory (most common in children)	Persistent cough Wheeze, stridor, hoarse voice, difficulty talking or change in character of cry Tongue swelling Chest pain or dyspnoea Subjective feeling of swelling, tightness or tingling the throat or mouth
Cardiovascular	Pale and floppy (infant) Palpitations, tachycardia, bradycardia Hypotension, pallor Collapse with or without unconsciousness Cardiac arrest
Neurological	Headache (usually throbbing) Dizziness Altered consciousness, confusion, sudden behavior change
Gastrointestinal	Nausea, vomiting, dysphagia Diarrhoea Abdominal or pelvic pain
Dermatological	Urticarial rash Erythema, flushing, tearing Angioedema Pruritus (skin, eyes, nose, throat, mouth)

Source: RCH 2021.

The following definitions are provided for the purposes of this study:

Hypersensitivity reaction: An acute onset of an illness with involvement of the skin, mucosal tissue, or both after injection of IMP (but does not meet the definition of anaphylaxis described above).

To assist with the mitigation of these AEs, see Table 19, which categorizes reactions by severity of symptoms and proposes severity-specific treatment and offers guidance on management of IMP. Final treatment is at the discretion of the Investigator and should reflect local standard of care.

Table 19 An Approach to Management of Anaphylactic, Hypersensitivity, and Post Injection/Infusion Reactions

Severity of symptoms	Treatment	Investigational product
Mild local reactions (During and post injection/infusion and hypersensitivity) Mild injection/infusion site reactions such as redness, mild swelling, pain at the injection site or headache, nausea, non-pruritic rash, or mild hypersensitivity reactions including localized at the injection site or generalized cutaneous reactions such as mild pruritus, flushing, rash, dizziness, headache, ≤ 20 mmHg change in systolic BP from pre-administration measurement.	Evaluate participant, including close monitoring of vital signs. At the discretion of the Investigator, treat participant, for example, with: Localized cold pack or heat to the injection site. If more generalized reaction: • Diphenhydramine or equivalent and/or • Acetaminophen or equivalent dose of paracetamol and/or • Topical antihistamines and/or low-potency topical corticosteroid preparations and/or • Anti-nausea medication, as needed. Doses and route of administration as per local standard of care.	Pause or hold additional IMP injection immediately. At the discretion of the Investigator, resume current IMP administration under observation.
Moderate reactions (during or immediately post injection) Injection/infusion site reaction such as those listed above under mild reactions but excluding moderate hypersensitivity reactions (see below).	Evaluate participant, including close monitoring of vital signs. Treat participant, for example, with: • Normal saline IV and/or • Diphenhydramine 50 mg IV or equivalent and/or • Acetaminophen 500 to 650 mg or equivalent dose of paracetamol and/or • Anti-nausea and/or antiemetic intramuscular, as needed. Doses and route of administration as per local standard of care.	Stop or hold additional IMP administration immediately. At the discretion of the Investigator, resume current IMP administration under observation.
Moderate hypersensitivity reactions Reactions which may include generalized rash or urticaria, palpitations, chest discomfort, shortness of breath, hypo- or hypertension with	Evaluate participant, including close monitoring of vital signs. Treat participant, for example, with: • Normal saline IV and/or	Stop IMP administration immediately.

Table 19 An Approach to Management of Anaphylactic, Hypersensitivity, and Post Injection/Infusion Reactions

Severity of symptoms	Treatment	Investigational product
> 20 mmHg change in systolic BP from pre-infusion measurement.	• Diphenhydramine or equivalent and/or • Acetaminophen or equivalent dose of paracetamol and/or • IV corticosteroids, such as hydrocortisone or methylprednisolone. Doses and route of administration as per local standard of care.	
Severe Above plus fever with rigors, hypo- or hypertension with ≥ 40 mmHg change in systolic BP, signs of end-organ dysfunction (eg, symptomatic hypotension such as hypotonia, syncope, incontinence, seizure) from pre-infusion measurement, or wheezing, angioedema, or stridor OR **Life-threatening** Defined as a reaction that is life-threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to tissue hypoperfusion	Evaluate participant, including close monitoring of vital signs. Maintain airway, oxygen if available. Treat participant immediately, for example with: • Normal saline IV • Epinephrine for bronchospasm, hypotension unresponsive to IV fluids, or angioedema • IV corticosteroids, such as hydrocortisone or methylprednisolone • Diphenhydramine or equivalent • Acetaminophen or equivalent dose of paracetamol Doses and route of administration as per local standard of care. Call emergency medical transport for transport to emergency hospital based on judgment of the Investigator. Grade 3 wheezing, hypotension or angioedema is unresponsive to single dose of epinephrine Grade 4 event At the discretion of the Investigator	Stop IMP administration immediately. Do not resume current dosing. Permanently discontinue IMP administration. Consider need for additional oral antihistamine administration or oral corticosteroid administration to prevent reoccurrence of symptoms over subsequent 2 to 3 days.

BP, blood pressure; IMP, investigational medicinal product; IV, intravenous;

RCH 2021
The Royal Children's Hospital (RCH) Melbourne. Clinical Practice Guidelines. Anaphylaxis. Available from: https://www.rch.org.au/clinicalguide/guideline_index/Anaphylaxis/ Accessed 22 September 2021.

Appendix G Abbreviations

Abbreviation or special term	Explanation
ACE2	angiotensin converting enzyme 2
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase/transaminase
AST	aspartate aminotransferase/transaminase
AZ	AstraZeneca
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-}inf}$	area under the serum concentration versus time curve extrapolated to infinity
BP	blood pressure
CFR	Code of Federal Regulations
CI	confidence interval
CL	systemic clearance
COVID-19	coronavirus disease 2019
CPAP	continuous positive airway pressure
CRO	Contract Research Organization
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTIS	Clinical Trial Information System
CV	cardiovascular
DES	Data Entry Site
DILI	drug-induced liver injury
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EU	European Union
EUA	Emergency Use Authorization
Fc	fragment crystallizable region
FDA	Food and Drug Administration
FTIH	first time in human
GA	gestational age

Abbreviation or special term	Explanation
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HL	Hy's Law
IATA	International Airline Transportation Association
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration or 50% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IM	intramuscular
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
λ_z	terminal disposition rate constant/terminal rate constant
mAb(s)	monoclonal antibody(ies)
MERS-CoV	Middle East respiratory syndrome coronavirus
MIS-C	multisystem inflammatory syndrome in children
NIMP	non-investigational medicinal product
PD	pharmacodynamic(s)
PHL	Potential Hy's Law
PK	pharmacokinetic(s)
QT	ECG interval measured from the onset of the QRS complex to the J point
QTcF	QT interval corrected for heart rate using Fridericia's formula
R_0	basic reproduction number
RBD	receptor binding domain
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RT-PCR	reverse transcriptase polymerase chain reaction
RTSM	Randomization and Trial Supply Management
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

Abbreviation or special term	Explanation
SD	standard deviation
SID	subject identification
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reactions
TBL	total bilirubin level
ULN	upper limit of normal
USA	United States of America
WHO	World Health Organization

Appendix H Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Version 4.0, 22 September 2022

Key amendment and rationale for change:

The CSP was amended with the following substantial changes: revised eligibility criteria to include females who are pregnant or breastfeeding, females of childbearing potential, and females and males who are sexually active and do not use contraception; removed the urine drug and alcohol screening and related laboratory variables, and updated the related exclusion criterion and restrictions; removed the urine collection requirement for participants who are unable to provide a urine sample; and specified how the minimum recruitment numbers in other cohorts will be impacted if Cohort 3 is not opened. Other changes are administrative and non-substantial and include clarifications, corrections, template alignments, and formatting updates.

Section No and Name	Description of Change	Brief Rationale
1.1 Synopsis; 4.1 Overall Design, Table 5	Defined "≥ 29 weeks GA" and added text on the reallocation of minimum participant numbers if a cohort is not opened.	Clarification
1.1 Synopsis, 4.1 Overall Design, Table 5	Specified how the minimum number of participants in other cohorts will increase if Cohort 3 is not opened; shifted the minimum participant numbers for the ≥ 29 wk GA to < 1 mo age group to either IM or IV for Cohorts 1 and 2; and added text on the route of administration for the ≥ 29 wk GA to < 1 mo age group for Cohorts 1 and 2.	Clarification in the language to allow redistribution of participants in case a particular cohort is not opened. Clarification to allow flexibility in route of administration per local practice for neonates.
1.1 Synopsis, 6.1.1 Investigational Product	Clarified what comprises a "single dose of AZD7442" per route of administration	Clarification
1.1 Synopsis, 9.5 Interim Analyses	Clarified that additional interim analyses may be conducted as needed at the discretion of the Sponsor.	Clarification
1.3 Schedule of Activities Tables 1 and 3,	Removed urine pregnancy testing from all visits except	To amend eligibility criteria to allow this population to be included in the study.

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5.1 Inclusion Criteria, 5.2 Exclusion Criteria, 5.3 Lifestyle Considerations, 8.2.4.5 Pregnancy Testing, 8.3.10 Pregnancy	Screening (Day -7 to Day 1) and Day 1 and added clarifying note; removed inclusion criterion and restrictions on females and males who are sexually active and who do not use contraception, and criterion excluding pregnant or breastfeeding females and other related text throughout the CSP.	Pregnancy: AZD7442 (EVUSHELD™) is approved or authorized for early access/emergency use in several markets worldwide. There is no requirement to use contraception in women of child bearing potential. In a tissue cross-reactivity study with tixagevimab and cilgavimab using human fetal tissues, no binding was detected. No signals pertinent to development and reproductive toxicology have been seen in the pivotal toxicology study in nonhuman primates. EVUSHELD should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus. Breastfeeding: The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EVUSHELD. AZD7442 is a combination of 2 human mAbs with nonoverlapping epitopes directed against the receptor binding domain of the SARS-CoV-2 S protein for neutralization of the virus with neither mAb having any human target. There are no potential risks based on mechanism of action.
1.3 Schedule of Activities Tables 1 and 3, 5.2 Exclusion Criteria, 5.3 Lifestyle Considerations, 6.5 Concomitant Therapy, 8.2.4 Clinical Safety Laboratory Assessments	Removed urine drug and alcohol screening, and updated the related exclusion criterion and restrictions.	Removed the urine drug and alcohol screening test as it does not provide sufficient information on chronic drug and alcohol use. Investigator assessment of the participant is sufficient for ensuring the participants do not have a history of drug or alcohol abuse that would compromise their ability to comply with study requirements as well as affect PK and safety.
1.3 Schedule of Activities Tables 1, 2, and 3	Urine collection requirement updated so that while collection should still be attempted, it is not mandatory, and clarified follow-up call language.	While there should be a reasonable attempt to collect a urine sample from participants, it is not a mandatory sample collection for any participant who is unable to provide a urine sample. The phone call language has been updated for clarification.
1.3 Schedule of Activities Table 3	Removed collection of SARS-CoV-2 serum sample at Day 1.	Serology test at Screening (Day -7 to Day 1) is sufficient.

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2 Introduction	Streamlined the section by referring to the AZD7442 IB for the most current information.	To minimize redundancy and provide the most current information on AZD7442
4.1 Overall Design	Clarified the maximum study duration of 479 days.	Clarification
4.4 End of Study Definition	Added text on end of study definitions.	To align with the newest TransCelerate protocol template
5.1 Inclusion Criteria	Added a missing unit to the glomerular filtration rate inclusion criterion for Cohort 3; deleted the inclusion criterion on the route of administration for a participant who already has a central IV line.	Correction of a unit; criterion removed to allow participants with a central IV line to receive the investigational product either IM or IV in alignment with the investigator's judgement for the most appropriate route of administration
5.2 Exclusion Criteria	Modified the criterion excluding those involved in the planning and/or conduct of the study to ensure exclusion of family members; clarified the criterion on vulnerable persons since the list is not inclusive of all vulnerable persons	Clarification and/or consistency with the rest of the clinical program
6.3 Measures to Minimize Bias: Randomization	Revised an oversight.	Correction
8.3.11 Medication Error, Drug Abuse, and Drug Misuse	Added information on Drug Abuse and Drug Misuse.	To align with the newest TransCelerate protocol template
8.4 Overdose	Added text on doses of AZD7442 considered to be an overdose.	Correction of a previous oversight
8.5.1 Total Blood Volume	Updated blood volume totals.	To ensure alignment and accuracy of planned collections
9.2 Sample Size Determination	Clarified the minimum sample size by route of administration for each of the 4 age groups.	Clarification
9.7 Morbidity Adjudication Committee	Removed the entire section and text on the Morbidity Adjudication Committee.	Activities of the Morbidity Adjudication Committee are covered by the DSMB and Cardiovascular Adjudication Committee.
Appendix A1 Regulatory and Ethical Considerations	Added a section on regulatory reporting requirements for serious breaches.	To align with the newest TransCelerate protocol template

Version 4.0, 22 September 2022		
Appendix A6 Dissemination of Clinical Study Data	Added text around clinical trial transparency.	To align with the newest TransCelerate protocol template
Appendix A7 Data Quality Assurance	Revised an oversight.	Correction
Appendix B4 Medication Error, Drug Abuse, and Drug Misuse	Added information on drug abuse and drug misuse.	To align with the newest TransCelerate protocol template
Various sections	Corrections, consistency alignments, and formatting updates throughout as needed	Corrections and updates for clarity

Version 3.0, 03 March 2022

Key amendment and rationale for change:

The CSP was amended to incorporate changes to the recruitment strategy, with Cohort 1 being recruited first, followed by Cohorts 2 and 3 if the corresponding indications are progressed in adults. The AZD7442 dose for prophylaxis of COVID-19 (Cohort 1) has been adjusted to reflect the change in the authorized adult dose from 300 mg to 600 mg IM. Other changes include updates to the Introduction, changes to the safety sample schedule and total blood volume collected, updates to the inclusion and exclusion criteria, addition of a Cardiovascular Event Adjudication Committee, and other minor changes to clarify study procedures. All changes are considered non-substantial.

Section No and Name	Description of Change	Brief Rationale
1.1 Synopsis	Updated in line with the changes in the body of the protocol	See below
1.2 Schematic, 4.1 Study Design, 5.1 Inclusion Criteria	Updated in line with the changed recruitment plan for the cohorts	In response to health authority feedback
1.3 Schedule of Activities, 4.2.1 Rationale for Choice of Endpoints, Section 8.5.1 Total Blood Volume	Changed Visit 3 from Day 29 to Day 31	In response to health authority feedback. The change puts Visit 3 outside the 30-day window from Visit 1 for blood collection.
1.3 Schedule of Activities (Table 2 and Table 3)	Deleted samples for serum chemistry and hematology at	To further reduce the blood volume required for collection

Version 3.0, 03 March 2022		
	Visit 4 and coagulation tests at Visit 5	
1.3 Schedule of Activities (Table 3); Section 8.5.3.2 SARS-CoV-2 Serology	Serostatus will be collected from all participants in Cohort 1 (non-neonates)	To confirm whether Cohort 1 have previously been infected with SARS-CoV-2
1.3 Schedule of Activities, 8.6.1 Virologic Assessments	Addition of an unscheduled sample for SARS-CoV-2 RT-PCR in participants in Cohort 1 that have COVID-19 qualifying symptoms during the study	To assess SARS-CoV-2 infections in the prophylaxis cohort during the study
1.3 Schedule of Activities, 2.3.1 Risk Assessment, 4.1 Study Design, 8.3 Adverse Events and Serious Adverse Events	Clarification of the requirement to monitor participants on site for adverse reactions for one hour after IMP injection/infusion	In response to health authority feedback
2 Introduction	Added language regarding neutralizing capacity of AZD7442 against SARS-CoV-2 variants, including Omicron	To provide the latest information relative to the currently dominant Omicron variant
2 Introduction, 2.3.1 Risk Assessment	Updated with TACKLE data (treatment of mild to moderate COVID-19 in adults)	To provide information about the TACKLE primary analysis and CV events
2.3.1 Risk Assessment	Updated the unmet need statement	To reflect the current situation for pediatrics
3 Objectives and Endpoints and 5.1 Inclusion Criteria	Removed lower respiratory tract infection as a risk factor for severe COVID-19	To align with current understanding of risk for severe COVID-19 in children
4 Study Design, 6.1.1 Investigational Product, 6.2.2 Preparation and Administration	The dose for Cohort 1 (prophylaxis of COVID-19) has been adjusted. The minimum number of participants in the IM route of administration has been adjusted to reflect the maximum volume restriction in the ≥15 to <40 kg weight band.	To reflect the change in the authorized adult dose from 300 mg to 600 mg IM
5.2 Exclusion Criteria	Further refinement of Exclusion Criteria #3	To accommodate safely administering AZD7442 to immunocompromised children while they are hospitalized for maintenance chemotherapy

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5.2 Exclusion Criteria, Section 6.5 Concomitant Therapy	Added receipt of COVID-19 vaccine ≤ 14 days before screening or planned vaccine ≤ 14 days of study Day 1	To align criteria across the AZD7442 program
5.2 Exclusion Criteria	Added criteria to exclude participants currently enrolled in other clinical trials with investigational drugs or devices	Lack of this exclusion criteria was an oversight
5.2 Exclusion Criteria	Exclude vulnerable persons (ie, wards of the state)	To exclude vulnerable persons
6.1.1 Investigational Product	Updated the follow-up time from 365 days to 456 days after IMP administration	To align with the additional follow-up time added in Amendment 1.
6.2.2.2 Intravenous Administration	Clarified the procedures for IV infusion, simplified Table 11 and corrected the dose for 15 to 40 kg weight within table (it was correct in other parts of the protocol)	To simplify the table for easier interpretation and align doses throughout protocol
6.5 Concomitant Therapy	Added guidance around the use of immune globulin and hyperimmune globulin Added guidance around the use of biologics	To allow for inclusion of participants who have used immune globulin if it has fully cleared from their system (5 half-lives of the drug) To align with other studies in the AZD7442 clinical program
6.5.1 Receipt of COVID-19 Vaccines During the Study	Amended language on need for COVID-19 vaccination	To allow COVID-19 vaccination per local guidelines and availability
6.6 Dose Modification, 9.6 Data Monitoring Committee	Removed reference to the DSMB receiving PK data	PK data are not part of DSMB review/aligning with the DSMB Charter
8 Study Assessment and Procedures	Clarification that a hierarchy of tests and wide visit windows will be used for blood collection to provide flexibility to blood collection schedules.	To clarify that Investigators will be able to determine a safe blood volume for withdrawal based on a participant's individual circumstances.
8.3.4.4 Cardiac and Thromboembolic Events, 9.8 Cardiovascular Event Adjudication Committee	A Cardiovascular Event Adjudication Committee has been added	To provide an independent, external, systematic, and unbiased assessment of de-identified blinded data to systematically evaluate CV events
8.5.1 Total Blood Volume	Updated blood volume totals	To ensure alignment and accuracy of planned collections

Version 3.0, 03 March 2022		
9.3 Populations for Analyses	Updated the definition of the ADA analysis set	To align with the statistical analysis plan

Version 2.0, 16 December 2021

Key amendment and rationale for change:

The CSP was amended to incorporate updated AESI language and include further safety follow-up, until 5 half-lives of the IMP. All changes are considered non-substantial.

Section No and Name	Description of Change	Brief Rationale
Global	Updated safety follow-up from Day 366 to Day 457	To follow for adverse events for at least 5 half-lives of the investigational product
1.3 Schedule of Activities Table 1	Removed the requirement for a finger prick Rapid SARS-CoV-2 antigen test	To allow for any antigen test authorized for screening diagnosis per standard of care
1.3 Schedule of Activities Table 2 and Table 3	Clarified language pertaining to SARS-CoV-2 RT-PCR	Quantitative RT-PCR should not be performed on participants who have a negative qualitative RT-PCR result
1.3 Schedule of Activities Table 2	Removed the requirement for RT-PCR in neonates to be a saliva sample	Limitations on validated method for saliva collection and analysis in this population, sample collection method will be per local standard
1.3 Schedule of Activities Table 3	Added UPT on Day 1 pre-dose	UPT should be performed pre-dose in case screening UPT does not occur on Day 1
1.3 Schedule of Activities Table 3	Removed Nasal PK pre-dose sample	Not required for evaluation of Nasal PK
2.3.1 Risk Assessment	Updated safety language	To include text on the imbalance of cardiovascular events seen in the PROVENT study in adults
5.1 Inclusion Criteria	Removed requirement for serum pregnancy test	Urine pregnancy test (UPT) is sufficient for eligibility evaluation; serum pregnancy test should only be used for confirmation of positive or indeterminate UPT
5.2 Exclusion Criteria	Clarification of hospitalization exclusion for Cohorts 1 and 2	To allow inclusion of those hospitalized for mild to moderate COVID-19 disease as a precautionary measure (Cohort 2) and neonates in their birth hospitalization
6.2.2.2 Intravenous Administration	Removed requirement for a separate infusion line for AZD7442	AZD7442 can be administered through the same infusion line as other medications as long as the line is flushed

Version 2.0, 16 December 2021		
8.3.4 Adverse Events of Special Interest	Added thrombotic events, heart failure, and cardiac ischemia	Cardiac AESI added due to a small number of events creating an imbalance in the PROVENT study, occurring in participants with cardiac disease and/or CV risk factors
A5 Committees Structure	Removed reference to double-blind	Blinding not applicable for study

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Document Name: d8850C00006-csp-v5		
Document Title:	D8850C00006 Clinical Study Protocol Version 5	
Document ID:	Doc ID-004527750	
Version Label:	5.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
26-Oct-2023 08:31 UTC	PPD	Management Approval
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