Clinical Study Protocol	
Study Intervention	AZD7442 (Tixagevimab and Cilgavimab)
Study Code	D8850C00010
Version	4.0
Date	06 June 2023

A Phase II Randomized, Open-label, Multicenter, Dose-ranging Study in Adults and Pediatric Individuals ≥ 12 years of Age to Assess the Safety, Immunogenicity, Pharmacokinetics, and Pharmacodynamics of AZD7442, a Combination Product of Two Monoclonal Antibodies (Tixagevimab and Cilgavimab), for Pre-exposure Prophylaxis of COVID-19

Sponsor Name:	**AstraZeneca AB**
Legal Registered Address:	151, 85 Södertälje, Sweden
Regulatory Agency Identifier Number(s):	IND number: 150712

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: D8850C00010

Amendment Number: Amendment 3

Study Intervention: AZD7442 (a combination of 2 monoclonal antibodies tixagevimab [AZD8895] and cilgavimab [AZD1061])

Study Phase: II

Short Title: A Randomized, Open-label, Dose-ranging Study in Adults and Pediatric Individuals ≥ 12 years of Age to Assess the Safety, Immunogenicity, Pharmacokinetics, and Pharmacodynamics of AZD7442, for Pre-exposure Prophylaxis of COVID-19

Acronym: ENDURE (EvaluatiNg Dose in ImmUnocompRomisEd Participants at Risk of COVID-19)

Study Physician name and contact information will be provided separately

International Coordinating Investigator name and contact information will be provided separately

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Version 4.0 [Amendment 3]	06 June 2023
Version 3.0 [Amendment 2]	09 December 2022
Version 2.0 [Amendment 1]	08 July 2022
Original Protocol	10 March 2022

CSP Version 4.0 06-June-2023

Overall Rationale for the Modification:

On 30 March 2023, the FDA requested that the Sponsor halt further dosing for the ENDURE study effective immediately until the ICF has been updated to reflect the new benefit risk assessment as, given that AZD7442 (EVUSHELD) is not active against > 99% of the currently circulating SARS-CoV-2 variants in the USA, the benefit risk assessment may not be favorable.

After consideration of the FDA's request, the Sponsor has decided to terminate this study, including the permanent discontinuation of IMP administration. All actively enrolled participants will be reconsented and will remain in the study to complete visits/assessments (except those related to monitoring of IMP administration; see Section 1.3) for safety for at least 6 months after the last IMP administration. This would provide 12 months of safety, immunogenicity, pharmacokinetics, and pharmacodynamics of AZD7442 data from the initial dose of AZD7442 and 6 months of data following the last dose of IMP.

Summary of Changes:

List of Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
7.4 Study Suspension/Early Termination and throughout document	Study to be terminated early (including permanent discontinuation of IMP administration), with an early discontinuation visit to be completed at least 6 months after the last IMP administration. Sections have been updated to document what should happen to participants, should the study be terminated early by the Sponsor.	See above for overall rationale for the modification

List of Non-Substantial Modifications

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis; 9.4 Statistical Analysis	Removal of primary data readout	Study to be terminated early, therefore only final data readout required.
8.1.1 Monitoring of COVID-19 Symptoms	Language added to clarify initiation of illness visits based on Investigator judgement of symptom(s) relationship to COVID-19	Language clarified
8.1.3	Language added to clarify that illness visits will be performed at IL-D1a for symptomatic participants which have been evaluated and found to be related to COVID-19 by the investigator	Language clarified
8.1.4	Language added to clarify what the assessments at IL-D1a for symptomatic participants related to COVID-19 will include	Language clarified
8.3.10 Medication Error; Appendix A1; Appendix B4	CSP template changes – added Drug Abuse and Drug Misuse definition; added sub-heading “Regulatory Reporting Requirements for Serious Breaches”; added detailed Drug Abuse and Drug Misuse definition and examples	Update required to comply with global company requirement

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title

A Phase II Randomized, Open-label, Multicenter, Dose-ranging Study in Adults and Pediatric Individuals ≥ 12 years of Age to Assess the Safety, Immunogenicity, Pharmacokinetics, and Pharmacodynamics of AZD7442, a Combination Product of Two Monoclonal Antibodies (Tixagevimab and Cilgavimab), for Pre-exposure Prophylaxis of COVID-19

Short Title

A Randomized, Open-label, Dose-ranging Study in Adults and Pediatric Individuals ≥ 12 years of Age to Assess the Safety, Immunogenicity, Pharmacokinetics, and Pharmacodynamics of AZD7442, for Pre-exposure Prophylaxis of COVID-19

Rationale

AZD7442, a combination of 2 monoclonal antibodies (tixagevimab [investigational name, AZD8895] and cilgavimab [investigational name, AZD1061]), is being developed for the prophylaxis and treatment of coronavirus disease 2019 (COVID-19).

This Phase II dose-ranging study will investigate the safety, immunogenicity, pharmacokinetic (PK), and pharmacodynamic (PD) profiles of AZD7442 repeat dosing regimens for pre-exposure prophylaxis of COVID-19 in adults and pediatric individuals (≥ 12 years of age weighing at least 40 kg), who are moderately to severely immunocompromised.

Objectives and Endpoints

Objective	Endpoint
Primary	
To evaluate the safety and tolerability of AZD7442	AEs, SAEs, and AESIs
To evaluate the immunogenicity of AZD7442	Incidence of ADA in serum
Secondary	
To evaluate the PK of AZD7442 in serum	Serum AZD7442 concentrations PK parameters
To determine anti-SARS-CoV-2 nAb levels in serum after administration of AZD7442	Changes from baseline in GMTs and GMFRs values in SARS-CoV-2 nAbs (wild-type assay or pseudo-neutralization assay)

ADA, antidrug antibody; AE, adverse event; AESI, adverse event of special interest; GMT, geometric mean titers; GMFR, geometric mean fold rise; nAb, neutralizing antibody; PK, pharmacokinetic; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2.

For exploratory objectives and endpoints, see Section 3 of the protocol.

Overall Design

This is a Phase II randomized, open-label, dose-ranging study to assess the safety, immunogenicity, PK, and PD profiles of AZD7442 repeat dose regimens. The study will enroll adults and pediatric individuals (≥ 12 years of age weighing at least 40 kg) who are moderate to severely immunocompromised due to an underlying disease or are taking immunosuppressive medications and therefore unable to mount an adequate immune response to COVID-19 vaccine.

Approximately 200 participants who meet the eligibility criteria for the study will be randomized in a 1:1 ratio to one of 2 AZD7442 treatment arms:

- Arm A (100 participants): AZD7442 600 mg administered intramuscularly (IM) on Day 1 followed by 300 mg IM every 3 months (Q3M) for 12 months (a total of 5 doses)
- Arm B (100 participants): AZD7442 1200 mg administered intravenously (IV) on Day 1 followed by 600 mg IM every 6 months (Q6M) for 12 months (a total of 3 doses)

An End of Treatment (EoT) Visit will be conducted at 15 months for each arm (3 months after the final dose of AZD7442).

After the EoT Visit, the participant will enter the follow-up period. Participants will be followed for safety for an additional 9 months after the EoT Visit, ie, through 12 months after the participant's final dose of AZD7442.

Participants who discontinue IMP administration due to premature termination of the study will remain in the study to complete visits/assessments (except those related to monitoring of IMP administration; see Section 1.3) for at least 6 months after their final dose of AZD7442.

The study design is presented Figure 1.

Disclosure Statement

This is a parallel-group, safety, immunogenicity, PK, and PD study with 2 arms (both AZD7442 with different dosing regimens) that is not blinded.

Number of Participants

Approximately 200 eligible participants will be randomized in the study to one of 2 AZD7442 dosing regimens: Arm A or Arm B (100 participants per arm).

Intervention Groups and Duration

The AZD7442 dosing regimens to be evaluated in the study are:

- Arm A: AZD7442 600 mg IM on Day 1 followed by 300 mg IM Q3M for 12 months (ie, Days 92, 183, 274, and 365)

- Arm B: AZD7442 1200 mg IV on Day 1 followed by 600 mg IM Q6M for 12 months (ie, Days 183 and 365)

The total duration of the study for a participant is 105 weeks (approximately 24 months) for both arms which includes the screening period (up to one week), the treatment period (15 months), and the follow-up period (9 months).

Data Safety Monitoring Board

An independent Data Safety Monitoring Board will provide oversight, to ensure safe and ethical conduct of the study.

Cardiovascular Event Adjudication Committee

An independent cardiovascular (CV) Event Adjudication Committee will provide an independent, external, systematic, and unbiased assessment of de-identified blinded data to systematically evaluate CV events.

Statistical Methods

No statistical hypotheses will be tested. Results will generally be summarized by treatment arm using descriptive statistics: frequency and percentages for categorical variables; number of available observations, mean, standard deviation, median, minimum, and maximum, and quartiles where more appropriate for continuous variables.

The final data readout will occur once all participants have completed the follow-up period (at Month 24) or withdrawn due to premature termination of the study.

Primary Endpoints

- The safety and tolerability of AZD7442 will primarily be assessed by the incidence and exposure adjusted incidence of adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (AESIs).
- The incidence of antidrug antibodies (ADA) to AZD7442 will be assessed and summarized by number and percentage of participants who are ADA positive. The ADA titer will be summarized with descriptive statistics.

Secondary Endpoints

- Individual AZD7442 (tixagevimab and cilgavimab) serum concentration data will be listed and tabulated, along with descriptive statistics. Appropriate PK parameters may be calculated.
- Descriptive statistics for geometric mean titers (GMTs) and geometric mean fold rise (GMFR) in severe acute respiratory coronavirus-2 neutralizing antibodies will include number of participants, geometric mean, geometric standard deviation, 95% confidence interval, minimum, and maximum.

Sample Size

Approximately 200 participants will be randomized to one of 2 AZD7442 dosing regimens: 100 participants to Arm A and 100 participants to Arm B.

If the true AE rate is 3%, the probability of observing at least one AE in 100 participants is 95%. The number of participants in the study would also allow for assessment of immunogenicity based on ADA prevalence observed in PROVENT (D8850C00002; NCT04625725).

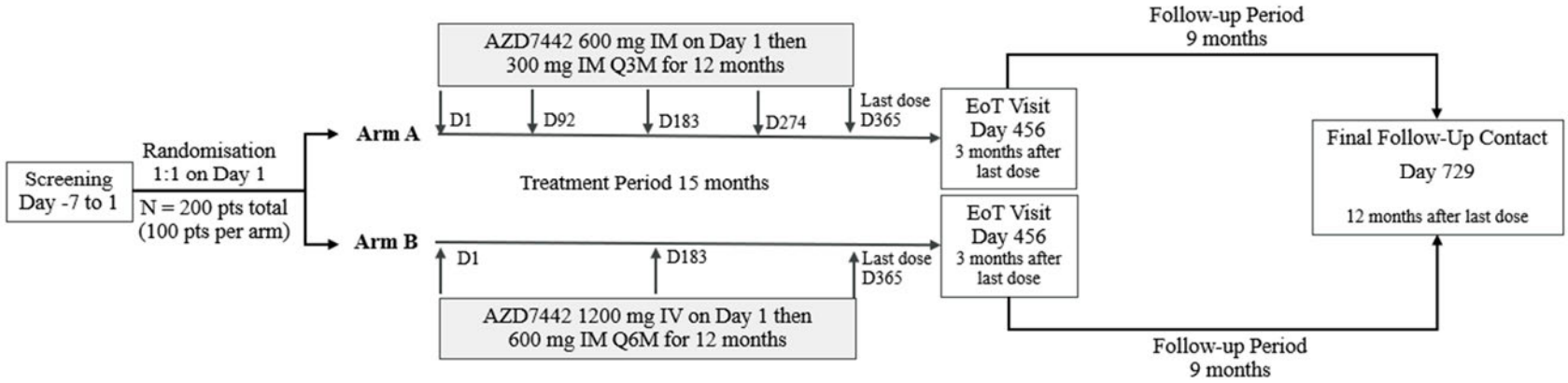
Interim Analyses

Interim analyses may be conducted to support regulatory requirements or at the discretion of the Sponsor, and will be specified in the statistical analysis plan if applicable.

1.2 Schema

The study design is presented in Figure 1.

Figure 1 Study Design



Interim analyses may be conducted to support regulatory requirements or at the discretion of the Sponsor, and will be specified in the statistical analysis plan if applicable.

D, day; EoT, End of Treatment; IM, intramuscular; IV, intravenous; N, number; pts, participants; Q3M, every 3 months; Q6M, every 6 months.

1.3 Schedule of Activities

Table 1 summarizes the SoA for the screening and treatment period for Arm A (AZD7442 Q3M).

Table 2 summarizes the SoA for the screening and treatment period for Arm B (AZD7442 Q6M).

Table 3 summarizes the SoA for the follow-up period for Arm A and Arm B.

Table 4 summarizes the assessments to be conducted when Illness Visits are initiated for participants who are suspected to have COVID-19.

Participants who permanently discontinue IMP administration due to the premature termination of the study will remain in the study to complete visits/assessments (except those related to monitoring of IMP administration) for at least 6 months after their final dose of AZD7442.

- If participants receive their last study drug administration on Day 183 visit, they will complete Day 190, Day 212, and Day 274 (no dosing) visits, followed by an Early Discontinuation visit in place of the Day 365 visit.

- If participants receive their last study drug administration on Day 274 visit, they will complete Day 281, and Day 365 (no dosing) visits, followed by an Early Discontinuation visit in place of the Day 456 visit.

- If participants have already completed visit/assessments up to 6 months after the last IMP administration (i.e. Day 365), the early discontinuation visit will be scheduled as early as possible. However, if early discontinuation scheduling is within one month of last completed in person visit and required samples were collected per protocol, then no additional sample collection is required (with the exception of a urine pregnancy test for WOCBP, and if positive or indeterminant, serum pregnancy will be collected).

- If participants are completing an illness visit series, they will be followed until completion or until the Early Discontinuation visit.

Table 1 Schedule of Activities: Treatment Period – Arm A (AZD7442 Q3M)

Period	**Screen [a]**	**Treatment (Days 1-456)**													**EoT**	**For details, see Section**
Day (* = IMP dosing day)	**-7 to 1**	**1***	**8**	**29**	**92***	**99**	**121**	**183***	**190**	**212**	**274***	**281**	**365***	**372**	**456**	
Week (Month)	**-**	**-**	**1**	**4**	**13 (3M)**	**14**	**17 (4M)**	**26 (6M)**	**27**	**30 (7M)**	**39 (9M)**	**40**	**52 (12M)**	**53**	**65 (15M)**	
Window (days)	**-**	**-**	**± 3**	**± 5**	**± 7**	**± 3**	**± 5**	**± 7**	**± 3**	**± 5**	**± 7**	**± 3**	**± 7**	**± 3**	**± 15**	
P = In-Person Visit RTM = Remote TM Visit [m]	**P**	**P**	**RTM/ P [m]**	**P**	**P**	**RTM/ P [m]**	**P**	**P**	**RTM/ P [m]**	**P**	**P**	**RTM/ P [m]**	**P**	**RTM/ P [m]**	**P**	
Procedure																
Informed consent	X															5.1
Informed assent for pediatric participants	X															5.1
Assignment PID number	X															-
Demographics	X															-
Medical and surgical history	X															-
Smoking status and pack-history (pack history for current and former smokers)	X															-
Complete physical examination, including height and weight	X															8.2.1

Table 1 Schedule of Activities: Treatment Period – Arm A (AZD7442 Q3M)

Period	**Screen [a]**	**Treatment (Days 1-456)**													**EoT**	**For details, see Section**
Day (* = IMP dosing day)	**-7 to 1**	**1***	**8**	**29**	**92***	**99**	**121**	**183***	**190**	**212**	**274***	**281**	**365***	**372**	**456**	
Week (Month)	**-**	**-**	**1**	**4**	**13 (3M)**	**14**	**17 (4M)**	**26 (6M)**	**27**	**30 (7M)**	**39 (9M)**	**40**	**52 (12M)**	**53**	**65 (15M)**	
Window (days)	**-**	**-**	**± 3**	**± 5**	**± 7**	**± 3**	**± 5**	**± 7**	**± 3**	**± 5**	**± 7**	**± 3**	**± 7**	**± 3**	**± 15**	
P = In-Person Visit RTM = Remote TM Visit [m]	**P**	**P**	**RTM/ P [m]**	**P**	**P**	**RTM/ P [m]**	**P**	**P**	**RTM/ P [m]**	**P**	**P**	**RTM/ P [m]**	**P**	**RTM/ P [m]**	**P**	
Targeted physical examination (predose on days of IMP administration) [n]		X		X	X		X	X		X	X		X		X	8.2.1
COVID-19 symptom screening	X															5.1, 5.2
Concomitant medications	←----------														----------→	6.5
Vital signs (including pulse oximetry) (pre and postdose on days of IMP administration) [b]	X	X [b]		X	X [b]		X	X [b]		X	X [b]		X [b]		X	8.2.2
12-lead ECG (postdose on days of IMP administration)	X	X			X			X			X		X		X	8.2.3

Table 1 Schedule of Activities: Treatment Period – Arm A (AZD7442 Q3M)

Period	**Screen [a]**	**Treatment (Days 1-456)**													**EoT**	**For details, see Section**
Day (* = IMP dosing day)	**-7 to 1**	**1***	**8**	**29**	**92***	**99**	**121**	**183***	**190**	**212**	**274***	**281**	**365***	**372**	**456**	
Week (Month)	**-**	**-**	**1**	**4**	**13 (3M)**	**14**	**17 (4M)**	**26 (6M)**	**27**	**30 (7M)**	**39 (9M)**	**40**	**52 (12M)**	**53**	**65 (15M)**	
Window (days)	**-**	**-**	**± 3**	**± 5**	**± 7**	**± 3**	**± 5**	**± 7**	**± 3**	**± 5**	**± 7**	**± 3**	**± 7**	**± 3**	**± 15**	
P = In-Person Visit RTM = Remote TM Visit [m]	**P**	**P**	**RTM/ P [m]**	**P**	**P**	**RTM/ P [m]**	**P**	**P**	**RTM/ P [m]**	**P**	**P**	**RTM/ P [m]**	**P**	**RTM/ P [m]**	**P**	
Verify eligibility criteria	X	X														5.1, 5.2
Randomization (after verification of eligibility)		X														6.3
Blood samples																
Cardiac/thrombosis biomarkers (predose on days of IMP administration); participants will be instructed to fast for ≥ 8 hours prior to collection		X		X	X			X			X		X		X	8.2.4
Serum chemistry (predose on days of IMP administration)		X			X			X			X		X		X	8.2.4
Hematology (predose on days of IMP administration)		X			X			X			X		X		X	8.2.4

Table 1 Schedule of Activities: Treatment Period – Arm A (AZD7442 Q3M)

Period	**Screen [a]**	**Treatment (Days 1-456)**													**EoT**	**For details, see Section**
Day (* = IMP dosing day)	**-7 to 1**	**1***	**8**	**29**	**92***	**99**	**121**	**183***	**190**	**212**	**274***	**281**	**365***	**372**	**456**	
Week (Month)	**-**	**-**	**1**	**4**	**13 (3M)**	**14**	**17 (4M)**	**26 (6M)**	**27**	**30 (7M)**	**39 (9M)**	**40**	**52 (12M)**	**53**	**65 (15M)**	
Window (days)	**-**	**-**	**± 3**	**± 5**	**± 7**	**± 3**	**± 5**	**± 7**	**± 3**	**± 5**	**± 7**	**± 3**	**± 7**	**± 3**	**± 15**	
P = In-Person Visit RTM = Remote TM Visit [m]	**P**	**P**	**RTM/ P [m]**	**P**	**P**	**RTM/ P [m]**	**P**	**P**	**RTM/ P [m]**	**P**	**P**	**RTM/ P [m]**	**P**	**RTM/ P [m]**	**P**	
Coagulation (predose on days of IMP administration)		X			X			X			X		X		X	8.2.4
FSH (suspected postmenopausal women, < 50 years) [c]	X															5.3, 8.2.4
Nasopharyngeal samples																
Documented negative SARS-CoV-2 RT-PCR test from NP specimen taken ≤ 3 days before Day 1 [d] OR SARS-CoV-2 rapid antigen test (local laboratory)	X [e]															8.2.4
SARS-CoV-2 RT-PCR (central laboratory) (predose)		X [f]														8.2.4

Table 1 Schedule of Activities: Treatment Period – Arm A (AZD7442 Q3M)

Period	**Screen [a]**	**Treatment (Days 1-456)**													**EoT**	**For details, see Section**
Day (* = IMP dosing day)	**-7 to 1**	**1***	**8**	**29**	**92***	**99**	**121**	**183***	**190**	**212**	**274***	**281**	**365***	**372**	**456**	
Week (Month)	**-**	**-**	**1**	**4**	**13 (3M)**	**14**	**17 (4M)**	**26 (6M)**	**27**	**30 (7M)**	**39 (9M)**	**40**	**52 (12M)**	**53**	**65 (15M)**	
Window (days)	**-**	**-**	**± 3**	**± 5**	**± 7**	**± 3**	**± 5**	**± 7**	**± 3**	**± 5**	**± 7**	**± 3**	**± 7**	**± 3**	**± 15**	
P = In-Person Visit RTM = Remote TM Visit [m]	**P**	**P**	**RTM/ P [m]**	**P**	**P**	**RTM/ P [m]**	**P**	**P**	**RTM/ P [m]**	**P**	**P**	**RTM/ P [m]**	**P**	**RTM/ P [m]**	**P**	
Urine samples																
Pregnancy test – urine (WOCBP only) [g]; (predose on days of IMP administration)	X	X [h]		X	X		X	X		X	X		X		X	5.3, 8.2.4, 8.3.9.1
Urinalysis (predose on days of IMP administration)		X			X			X			X		X		X	8.2.4
PK, PD, ADA assessments																
Serum sample for AZD7442 PK assessment (predose on days of IMP administration unless otherwise noted)		D3 (±1d) [i]	D11 (±3d) [j]	X	X		X	X		X	X		X		X	8.5.1
Serum sample for AZD7442 ADA assessment (predose on days of IMP administration)		X		X	X		X	X		X	X		X		X	8.5.2.1

Table 1 Schedule of Activities: Treatment Period – Arm A (AZD7442 Q3M)

Period	**Screen [a]**	**Treatment (Days 1-456)**													**EoT**	**For details, see Section**
Day (* = IMP dosing day)	**-7 to 1**	**1***	**8**	**29**	**92***	**99**	**121**	**183***	**190**	**212**	**274***	**281**	**365***	**372**	**456**	
Week (Month)	**-**	**-**	**1**	**4**	**13 (3M)**	**14**	**17 (4M)**	**26 (6M)**	**27**	**30 (7M)**	**39 (9M)**	**40**	**52 (12M)**	**53**	**65 (15M)**	
Window (days)	**-**	**-**	**± 3**	**± 5**	**± 7**	**± 3**	**± 5**	**± 7**	**± 3**	**± 5**	**± 7**	**± 3**	**± 7**	**± 3**	**± 15**	
P = In-Person Visit RTM = Remote TM Visit [m]	**P**	**P**	**RTM/ P [m]**	**P**	**P**	**RTM/ P [m]**	**P**	**P**	**RTM/ P [m]**	**P**	**P**	**RTM/ P [m]**	**P**	**RTM/ P [m]**	**P**	
Serum sample for SARS-CoV-2 nAbs assessment (predose on days of IMP administration)		X		X	X		X	X		X	X		X		X	8.5.3.1
NLF sample for mucosal response assessments [k] (predose on days of IMP administration unless otherwise noted)		D3 (±1d) [i]	D11 (±3d) [j]	X	X		X	X		X	X		X		X	8.5.2.3
Serum sample for SARS-CoV-2 serology (anti-nucleocapsid) testing (predose on days of IMP administration)		X		X	X		X	X		X	X		X		X	8.5.2.2

Table 1 Schedule of Activities: Treatment Period – Arm A (AZD7442 Q3M)

Period	**Screen [a]**	**Treatment (Days 1-456)**													**EoT**	**For details, see Section**
Day (* = IMP dosing day)	**-7 to 1**	**1***	**8**	**29**	**92***	**99**	**121**	**183***	**190**	**212**	**274***	**281**	**365***	**372**	**456**	
Week (Month)	**-**	**-**	**1**	**4**	**13 (3M)**	**14**	**17 (4M)**	**26 (6M)**	**27**	**30 (7M)**	**39 (9M)**	**40**	**52 (12M)**	**53**	**65 (15M)**	
Window (days)	**-**	**-**	**± 3**	**± 5**	**± 7**	**± 3**	**± 5**	**± 7**	**± 3**	**± 5**	**± 7**	**± 3**	**± 7**	**± 3**	**± 15**	
P = In-Person Visit RTM = Remote TM Visit [m]	**P**	**P**	**RTM/ P [m]**	**P**	**P**	**RTM/ P [m]**	**P**	**P**	**RTM/ P [m]**	**P**	**P**	**RTM/ P [m]**	**P**	**RTM/ P [m]**	**P**	
IMP Administration																
Arm A: AZD7442 administration		X			X			X			X		X			6.1, 6.2
Postdose safety monitoring [l]		X	X		X	X		X	X		X	X	X	X		8.2.5
Safety assessments																
AEs/SAEs/AESIs	SAEs only	←----------												----------→		8.3
Monthly contact between visits																
Monthly telephone/email/text contacts - monitoring for COVID-19 symptoms and safety [o]				←----------										----------→		8.1.1, 8.3

[a] Screening activities may be collected over more than one visit if necessary; if screening and dosing occur at the same visit, only one evaluation is required, unless otherwise specified.

[b] Days 1, 92, 183, 274, and 365 (AZD7442 IM administration): Perform vital signs (including pulse oximetry) predose (within 15 minutes prior to first injection) and postdose (15 minutes [± 5 minutes] after both injections are complete).

[c] FSH will be analyzed at screening to confirm postmenopausal status only in women < 50 years of age who have been amenorrhoeic for ≥ 12 months. Until FSH is documented to be within menopausal range, the participant is to be considered of childbearing potential. For women aged ≥ 50 years, postmenopausal is defined as having a history of ≥ 12 months' amenorrhea prior to Day 1, without an alternative cause, following cessation of exogenous sex-hormonal treatment.

[d] This test is not performed as part of the clinical study but must be available prior to enrollment.

[e] If a documented (negative) SARS-CoV-2 RT-PCR test is not available at screening, a SARS-CoV-2 rapid antigen test will be performed. Either test must be negative before dosing (see inclusion criteria in Section 5.1).

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

[g] If the urine pregnancy test is positive or indeterminate, a quantitative serum β-hCG will be performed by the central laboratory for confirmation.

[h] On Day 1, a negative urine pregnancy test is required before the participant receives IMP.

[i] For a subset of 20 participants, PK and NLF samples will be collected at 24 to 72 hours after the Day 1 AZD7442 dose.

[j] For a subset of 20 participants, PK and NLF samples will be collected at Day 11 (± 3 days).

[k] When test supplies are available, sampling should be performed.

[l] Includes monitoring participants for at least one hour postdose, checking injection sites, and monitoring for hypersensitivity (including anaphylaxis). See Section 8.2.5 for required safety monitoring.

[m] If local facilities or local regulations do not allow for an RTM visit, an In-person visit can be performed.

[n] Targeted physical examination per investigator discretion will include areas suggested by medical history, vulnerable conditions and reported clinical complaints during the study visit and may require height and weight.

[o] Monthly contact with participants to remind them to present to the study site for SARS-CoV-2 testing if they have qualifying symptoms. The Investigator will enquire about any COVID-19 symptoms from previous 30 days and other adverse events.

Note: In agreement with the Sponsor, In-person visits may be replaced with home or mobile visits if required to protect participants from COVID-19 infection and as per Investigator's discretion provided they are operationally feasible.

ADA, antidrug antibody; AE, adverse event; AESI, adverse event of special interest; β-hCG, beta-human chorionic gonadotropin; COVID-19, coronavirus disease 2019; D, day; ECG, electrocardiogram; EoT, End of Treatment; FSH, follicle-stimulating hormone; IM, intramuscular; IMP, investigational medicinal product; M, month; nAb, neutralizing antibody; NLF, nasal lining fluid; NP, nasopharyngeal; PD, pharmacodynamics; PID, participant identification; PK, pharmacokinetics; Q3M, every 3 months; RT-PCR, reverse transcriptase polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; TM, telemedicine; WOCBP, women of childbearing potential.

Table 2 Schedule of Activities: Treatment Period – Arm B (AZD7442 Q6M)

Period	**Screen [a]**	**Treatment (Days 1-456)**										**EoT**	**For details, see Section**
Day (* = IMP dosing day)	**-7 to 1**	**1***	**8**	**29**	**92**	**183***	**190**	**D212**	**274**	**365***	**372**	**456**	
Week (Month)	**-**	**-**	**1**	**4**	**13 (3M)**	**26 (6M)**	**27**	**30 (7M)**	**39 (9M)**	**52 (12M)**	**53**	**65 (15M)**	
Window (days)	**-**	**-**	**± 3**	**± 5**	**± 7**	**± 7**	**± 3**	**± 5**	**± 7**	**± 7**	**± 3**	**± 15**	
P = In-Person Visit RTM = Remote TM Visit[n]	**P**	**P**	**RTM/ P [n]**	**P**	**P**	**P**	**RTM/ P [n]**	**P**	**P**	**P**	**RTM/ P [n]**	**P**	
Procedure													
Informed consent	X												5.1
Informed assent for pediatric participants	X												5.1
Assignment PID number	X												-
Demographics	X												-
Medical and surgical history	X												-
Smoking status and pack-history (pack history for current and former smokers)	X												-
Complete physical examination, including height and weight	X												8.2.1
Targeted physical examination (predose on days of IMP administration)[o]		X		X	X	X		X	X	X		X	8.2.1
COVID-19 symptom screening	X												5.1, 5.2
Concomitant medications	←----------											----------→	6.5
Vital signs (including pulse oximetry) (pre and postdose on days of IMP administration) [b]	X	X [b]		X	X	X [b]		X	X	X [b]		X	8.2.2
12-lead ECG (postdose on days of IMP administration)	X	X				X				X		X	8.2.3

Table 2 Schedule of Activities: Treatment Period – Arm B (AZD7442 Q6M)

Period	**Screen [a]**	**Treatment (Days 1-456)**										**EoT**	**For details, see Section**
Day (* = IMP dosing day)	**-7 to 1**	**1***	**8**	**29**	**92**	**183***	**190**	**D212**	**274**	**365***	**372**	**456**	
Week (Month)	**-**	**-**	**1**	**4**	**13 (3M)**	**26 (6M)**	**27**	**30 (7M)**	**39 (9M)**	**52 (12M)**	**53**	**65 (15M)**	
Window (days)	**-**	**-**	**± 3**	**± 5**	**± 7**	**± 7**	**± 3**	**± 5**	**± 7**	**± 7**	**± 3**	**± 15**	
P = In-Person Visit RTM = Remote TM Visit[n]	**P**	**P**	**RTM/ P [n]**	**P**	**P**	**P**	**RTM/ P [n]**	**P**	**P**	**P**	**RTM/ P [n]**	**P**	
Verify eligibility criteria	X	X											5.1, 5.2
Randomization (after verification of eligibility)		X											6.3
Blood samples													
Cardiac/thrombosis biomarkers (predose on days of IMP administration); participants will be instructed to fast for ≥ 8 hours prior to collection		X		X	X	X			X	X		X	8.2.4
Serum chemistry (predose on days of IMP administration)		X			X	X			X	X		X	8.2.4
Hematology (predose on days of IMP administration)		X			X	X			X	X		X	8.2.4
Coagulation (predose on days of IMP administration)		X			X	X			X	X		X	8.2.4
FSH (suspected postmenopausal women, < 50 years) [c]	X												5.3, 8.2.4

Table 2 Schedule of Activities: Treatment Period – Arm B (AZD7442 Q6M)

Period	**Screen [a]**	**Treatment (Days 1-456)**										**EoT**	**For details, see Section**
Day (* = IMP dosing day)	**-7 to 1**	**1***	**8**	**29**	**92**	**183***	**190**	**D212**	**274**	**365***	**372**	**456**	
Week (Month)	**-**	**-**	**1**	**4**	**13 (3M)**	**26 (6M)**	**27**	**30 (7M)**	**39 (9M)**	**52 (12M)**	**53**	**65 (15M)**	
Window (days)	**-**	**-**	**± 3**	**± 5**	**± 7**	**± 7**	**± 3**	**± 5**	**± 7**	**± 7**	**± 3**	**± 15**	
P = In-Person Visit RTM = Remote TM Visit[n]	**P**	**P**	**RTM/ P [n]**	**P**	**P**	**P**	**RTM/ P [n]**	**P**	**P**	**P**	**RTM/ P [n]**	**P**	
Nasopharyngeal samples													
Documented negative SARS-CoV-2 RT-PCR test from NP specimen taken ≤ 3 days before Day 1 [d] OR SARS-CoV-2 rapid antigen test	X [e]												8.2.4
SARS-CoV-2 RT-PCR (central laboratory) (predose)		X [f]											8.2.4
Urine samples													
Pregnancy test – urine (WOCBP only) [g]; (predose on days of IMP administration)	X	X [h]		X	X	X		X	X	X		X	5.3, 8.2.4, 8.3.9.1
Urinalysis (predose on days of IMP administration)		X			X	X			X	X		X	8.2.4
PK, PD, ADA assessments													
Serum sample for AZD7442 PK assessment (predose on days of IMP administration unless otherwise noted)		D1 [i], D3 (±1d) [j]	D11 (±3d) [k]	X	X	X		X	X	X		X	8.5.1
Serum sample for AZD7442 ADA assessment (predose on days of IMP administration)		X		X	X	X		X	X	X		X	8.5.2.1
Serum sample for SARS-CoV-2 nAbs assessment (predose on days of IMP administration)		X		X	X	X		X	X	X		X	8.5.3.1

Table 2 Schedule of Activities: Treatment Period – Arm B (AZD7442 Q6M)

Period	**Screen [a]**	**Treatment (Days 1-456)**										**EoT**	**For details, see Section**
Day (* = IMP dosing day)	**-7 to 1**	**1***	**8**	**29**	**92**	**183***	**190**	**D212**	**274**	**365***	**372**	**456**	
Week (Month)	**-**	**-**	**1**	**4**	**13 (3M)**	**26 (6M)**	**27**	**30 (7M)**	**39 (9M)**	**52 (12M)**	**53**	**65 (15M)**	
Window (days)	**-**	**-**	**± 3**	**± 5**	**± 7**	**± 7**	**± 3**	**± 5**	**± 7**	**± 7**	**± 3**	**± 15**	
P = In-Person Visit RTM = Remote TM Visit[n]	**P**	**P**	**RTM/ P [n]**	**P**	**P**	**P**	**RTM/ P [n]**	**P**	**P**	**P**	**RTM/ P [n]**	**P**	
NLF sample for mucosal response assessments [l] (predose on days of IMP administration unless otherwise noted)		D1 [i], D3 (±1d) [j]	D11 (±3d) [k]	X	X	X		X	X	X		X	8.5.2.3
Serum sample for SARS-CoV-2 serology (anti-nucleocapsid) testing (predose on days of IMP administration)		X		X	X	X		X	X	X		X	8.5.2.2
IMP Administration													
Arm B: AZD7442 administration		X				X				X			6.1, 6.2
Postdose safety monitoring [m]		X	X			X	X			X	X		8.2.5
Safety assessments													
AEs/SAEs/AESIs	SAEs only	←----------									----------→		8.3
Monthly contact between visits													
Monthly telephone/email/text contacts - monitoring for COVID-19 symptoms and safety [p]				←----------							----------→		8.1.1, 8.3

[a] Screening activities may be collected over more than one visit if necessary; if screening and dosing occur at the same visit, only one evaluation is required, unless otherwise specified.

[b] Day 1 (AZD7442 IV administration): Perform vital signs (including pulse oximetry) within 15 minutes prior to the start of infusion, every 15 minutes (± 5 minutes) during the infusion, and 15 minutes (± 5 minutes) after end of infusion.
Days 183 and 365 (AZD7442 IM administration): Perform vital signs (including pulse oximetry) predose (within 15 minutes prior to first injection) and postdose (15 minutes [± 5 minutes] after both injections are complete).

[c] FSH will be analyzed at screening to confirm postmenopausal status only in women < 50 years of age who have been amenorrhoeic for ≥ 12 months. Until FSH is documented to be within menopausal range, the participant is to be considered of childbearing potential. For women aged ≥ 50 years, postmenopausal is defined as having a history of ≥ 12 months' amenorrhea prior to Day 1, without an alternative cause, following cessation of exogenous sex-hormonal treatment.

[d] This test is not performed as part of the clinical study but must be available prior to enrollment.

[e] If a documented (negative) SARS-CoV-2 RT-PCR test is not available at screening, a SARS-CoV-2 rapid antigen test will be performed. Either test must be negative before dosing (see inclusion criteria in Section 5.1).

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

[g] If the urine pregnancy test is positive or indeterminate, a quantitative serum β-hCG will be performed by the central laboratory for confirmation.

[h] On Day 1, a negative urine pregnancy test is required before the participant receives IMP.

[i] For all participants, the PK and NLF samples will be collected postdose within 30 minutes after the end of infusion on Day 1.

[j] For a subset of 20 participants, PK and NLF samples will be collected at 24 to 72 hours after the Day 1 AZD7442 dose.

[k] For a subset of 20 participants, PK and NLF samples will be collected at Day 11 (± 3 days).

[l] When test supplies are available, sampling should be performed.

[m] Includes monitoring participants for at least one hour postdose, checking injection sites, and monitoring for hypersensitivity (including anaphylaxis), and infusion-related reactions (applicable for Day 1 IV administration). On Day 1, the minimum of one hour postdose monitoring will start at the end of the IV infusion. See Section 8.2.5 for required safety monitoring.

[n] If local facilities or local regulations do not allow for an RTM visit, an In-person visit can be performed.

[o] Targeted physical examination per investigator discretion will include areas suggested by medical history, vulnerable conditions and reported clinical complaints during the study visit and may require height and weight.

[p] Monthly contact with participants to remind them to present to the study site for SARS-CoV-2 testing if they have qualifying symptoms. The Investigator will enquire about any COVID-19 symptoms from previous 30 days and other adverse events.

Note: In agreement with the Sponsor, In-person visits may be replaced with home or mobile visits if required to protect participants from COVID-19 infection and as per Investigator's discretion provided they are operationally feasible.

ADA, antidrug antibody; AE, adverse event; AESI, adverse event of special interest; β-hCG, beta-human chorionic gonadotropin; COVID-19, coronavirus disease 2019; D, day; ECG, electrocardiogram; EoT, End of Treatment; FSH, follicle-stimulating hormone; IM, intramuscular; IMP, investigational medicinal product; IV, intravenous; M, month; nAb, neutralizing antibody; NLF, nasal lining fluid; NP, nasopharyngeal; PD, pharmacodynamics; PID, participant identification; PK, pharmacokinetics; Q6M, every 6 months; RT-PCR, reverse transcriptase polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; TM, telemedicine; WOCBP, women of childbearing potential.

Table 3 Schedule of Activities: Follow-up Period (Arm A and Arm B)

Period	**Follow-up (Days 457-729)**			**Early Discontinuation [a]**	**For details, see Section**
Day	**547**	**638**	**729**		
Week (Month)	**78 (18M)**	**91 (21M)**	**104 (24M)**		
Window (days)	**± 15**	**± 15**	**± 15**		
P = In-Person Visit **RTM = Remote TM Visit**	**RTM/ Telephone call**	**RTM/ Telephone call [b]**	**P**	**P**	
Procedure					
Targeted physical examination			X	X	8.2.1
Concomitant medications	X	X	X	X	6.5
Vital signs (including pulse oximetry)			X	X	8.2.2
12-lead ECG				X	8.2.3
Blood samples					
Cardiac/thrombosis biomarkers; participants will be instructed to fast for ≥ 8 hours prior to collection			X	X	8.2.4
Serum chemistry			X	X	8.2.4
Hematology			X	X	8.2.4
Coagulation			X	X	8.2.4
Urine samples					
Urinalysis			X	X	8.2.4
Pregnancy test – urine (WOCBP only) [c]			X	X	8.2.4
PK, PD, and ADA assessments					
Serum sample for AZD7442 PK assessment				X	8.5.1
Serum sample for AZD7442 ADA assessment			X	X	8.5.2.1
Serum sample for SARS-CoV-2 nAbs assessment				X	8.5.3.1
NLF sample for mucosal response assessments [d]				X	8.5.2.3

Table 3 Schedule of Activities: Follow-up Period (Arm A and Arm B)

Period	**Follow-up (Days 457-729)**			**Early Discontinuation [a]**	**For details, see Section**
Day	**547**	**638**	**729**		
Week (Month)	**78 (18M)**	**91 (21M)**	**104 (24M)**		
Window (days)	**± 15**	**± 15**	**± 15**		
P = In-Person Visit **RTM = Remote TM Visit**	**RTM/ Telephone call**	**RTM/ Telephone call [b]**	**P**	**P**	
Serum sample for SARS-CoV-2 serology (anti-nucleocapsid) testing				X	8.5.2.2
Safety assessments					
AEs/SAEs/AESIs	X	X	X	X	8.3
Monthly contact between visits					
Monthly telephone/email/text contacts - monitoring for COVID-19 symptoms and safety[f]	←----------			----------→	8.1.1, 8.3

[a] The Early Discontinuation Visit is only applicable for participants who withdraw from the study and for premature termination of the study . See Section 7.2. and Section 7.4.

[b] If local facilities or local regulations do not allow for an RTM visit, contact with participants should be made by telephone.

[c] If the urine pregnancy test is positive or indeterminate, a quantitative serum β-hCG will be performed by the central laboratory for confirmation.

[d] When test supplies are available, sampling should be performed.

[e] Targeted physical examination per investigator discretion will include areas suggested by medical history, vulnerable conditions and reported clinical complaints during the study visit and may require height and weight.

[f] Monthly contact with participants to remind them to present to the study site for SARS-CoV-2 testing if they have qualifying symptoms. The Investigator will enquire about any COVID-19 symptoms from previous 30 days and other adverse events.

ADA, antidrug antibody; AE, adverse event; AESI, adverse event of special interest; β-hCG, beta-human chorionic gonadotropin; ECG, electrocardiogram; FSH, follicle-stimulating hormone; M, month; nAb, neutralizing antibody; NLF, nasal lining fluid; PK, pharmacokinetics; PD, pharmacodynamics; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; TM, telemedicine; WOCBP, women of childbearing potential.

Table 4 Schedule of Activities: Illness Visits (Participants with COVID-19 Clinical Symptoms)

Procedure	**Site Visit**		**Site Visit for SARS-CoV-2 positive participants only [a, b]**					**Long COVID-19 monitoring**	**For details, see Section**
Day [c]	**IL-D1a**	**IL-D1b [d]**	**IL-D5**	**IL-D7**	**IL-D14**	**IL-D28**	**IL-D90**	**Every 3 months until symptoms resolve or end of study [g]**	
Window (days)	**NA**	**NA**	**± 2**	**± 2**	**± 2**	**± 7**	**± 7**		
Illness history	X		X	X	X				-
COVID-19 symptom assessment	X		X	X	X	X	X	X	8.1.1
Targeted physical examination[h]	X		X	X	X				8.2.1
Vital signs (including pulse oximetry)	X		X	X	X				8.2.2
12-lead ECG					X				8.2.3
Concomitant medication	←----------							----------→	6.5
Nasopharyngeal swab									
SARS-CoV-2 rapid antigen test (local laboratory)	X								8.2.4
SARS-CoV-2 RT-PCR (local laboratory)	X								8.2.4, 8.6.1.1
SARS-CoV-2 RT-PCR (central laboratory), sequencing, respiratory panel	X		X	X	X	X	X		8.6.1.1
Immunogenicity, PD, PK, coagulation									
PBMCs for B-cell and T-cell responses [e]		X			X				8.5.2.4
Serum sample for AZD7442 PK assessment		X							8.5.1
Serum sample for AZD7442 ADA assessment		X			X				8.5.2.1
Serum sample for SARS-CoV-2 nAbs assessment		X			X				8.5.3.1
NLF sample for SARS-CoV-2 mucosal responses and mucosal response assessments [f]		X							8.5.2.3

Table 4 Schedule of Activities: Illness Visits (Participants with COVID-19 Clinical Symptoms)

Procedure	Site Visit		Site Visit for SARS-CoV-2 positive participants only [a, b]					Long COVID-19 monitoring	For details, see Section
Day [c]	**IL-D1a**	**IL-D1b** [d]	**IL-D5**	**IL-D7**	**IL-D14**	**IL-D28**	**IL-D90**	**Every 3 months until symptoms resolve or end of study** [g]	
Window (days)	**NA**	**NA**	**± 2**	**± 2**	**± 2**	**± 7**	**± 7**		
Serum sample for exploratory assessments		X			X				8.5.2.5
Serum sample for coagulation assessment		X			X				8.2.4
Safety assessments									
SAEs and AESIs	←----------							----------→	8.3
Telephone contact for safety monitoring	←----------							----------→	8.1.1, 8.3

[a] Where supported, home or mobile visits by study staff may substitute for site visits.

[b] Only applicable for participants with SARS-CoV-2 RT-PCR positive result from local test performed on IL-D1a.

[c] To distinguish between illness episodes the visits will be labeled as follows. For the first episode Illness Visit Day 1 = 1IL-D1, Illness Visit Day 5 = 1IL-D5 etc, and for the second episode 2IL-D1, 2IL-D5, and so on as applicable.

[d] IL-D1b assessments should only be performed if either the SARS-CoV-2 rapid antigen or RT-PCR local test result is positive. If the rapid antigen local test result is negative and the RT-PCR local test result is subsequently determined as positive (ie, rapid antigen was false negative), then IL-D1b assessments should be performed as soon as possible (but no later than 2 days) after the positive RT-PCR local test result is available. If the rapid antigen local test result is positive and the RT-PCR local test result is subsequently determined as negative (ie, rapid antigen was false positive), the participant will be instructed to discontinue Illness Visits.

[e] To be collected when operationally viable.

[f] When test supplies are available, sampling should be performed.

[g] Symptom assessment to continue every 3 months until symptoms have resolved or end of study occurs. A separate visit is not required, the assessment should be performed at the next scheduled visits per Table 1 for Arm A and Table 2 for Arm B.

[h] Targeted physical examination per investigator discretion will include areas suggested by medical history, vulnerable conditions and reported clinical complaints during the study visit and may require height and weight.

Note: The Illness Visit schedule is to be performed in addition to the scheduled visits in the treatment period (Table 1 for Arm A and Table 2 for Arm B) and follow-up period (Table 3 for Arm A and Arm B). Where visits coincide, all assessments from the scheduled visit and the Illness Visit should be performed.

ADA, antidrug antibody; AESI, adverse events of special interest; COVID-19, coronavirus disease 2019; D, day; ECG, electrocardiogram; IL, illness; NA, not applicable; nAb, neutralizing antibody; NLF, nasal lining fluid; PBMC, peripheral blood mononuclear cell; PK, pharmacokinetics; PD, pharmacodynamics; RT-PCR, reverse transcriptase polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.

2 INTRODUCTION

2.1 Study Rationale

AZD7442, a combination of 2 mAbs (tixagevimab [investigational name, AZD8895] and cilgavimab [investigational name, AZD1061]), is being developed for the prophylaxis and treatment of COVID-19.

This Phase II dose-ranging study will investigate the safety, immunogenicity, PK, and PD profiles of AZD7442 repeat dosing regimens (600 mg IM on Day 1 then 300 mg IM Q3M and 1200 mg IV on Day 1 then 600 mg IM Q6M) for pre-exposure prophylaxis of COVID-19 in adults and pediatric individuals (≥ 12 years of age weighing at least 40 kg), who are moderately to severely immunocompromised due to an underlying disease or are taking immunosuppressive medications and therefore unable to mount an adequate immune response to COVID-19 vaccine. Pharmacokinetic data will be generated to evaluate the AZD7442 doses and whether repeat dosing can maintain serum levels associated with protection against COVID-19. Pharmacodynamic data will include measurement of neutralizing antibodies levels in serum after AZD7442 repeat dosing.

2.2 Background

Severe acute respiratory coronavirus-2 is the causative agent of the ongoing COVID-19 pandemic that, as of 19 January 2022, has caused over 332 million confirmed cases of COVID-19, including 5.5 million deaths, reported to WHO (WHO 2022). The majority of CoVs cause mild disease in humans and animals, however SARS-CoV-2 can replicate in the lower respiratory tract to cause acute respiratory distress syndrome and fatal pneumonia. This is also a characteristic of the genetically similar SARS-CoV and the more distantly related MERS-CoV, both of which were responsible for prior outbreaks in 2002 to 2003 and 2012, respectively (Gorbalenya et al 2020). The original SARS-CoV-2 virus first detected in Wuhan had a basic reproduction number R0 value estimated between 2.43 to 3.10 and was highly transmissible from person to person, which has contributed to its rapid dissemination worldwide (D'Arienzo and Coniglio 2020). Mortality risk factors associated with SARS-CoV-2 infection include age > 60 years (significantly greater for those 80 years and older), male sex, and chronic medical conditions, including hypertension, diabetes, obesity, chronic obstructive pulmonary disease, and CV disease (Zhou et al 2020). Clinical management of COVID-19 is based on supportive care and a limited number of treatment interventions, which results in healthcare resources being stretched (Tangcharoensathien et al 2021).

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, and variant alerts for further monitoring. For the Omicron BA.1 variant, independent laboratories have generated in vitro potency data showing that AZD7442 maintains neutralizing activity, although increases the IC_{50} compared to the original SAR-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 VLP neutralization assays correlate with clinical outcomes.

The interim analysis for the Phase I FTIH study (D8850C00001; NCT04507256) with AZD7442 in healthy adults indicated that tixagevimab and cilgavimab have a mean terminal $t_{1/2\lambda z}$ of approximately 90 days. The minimum serum protective concentration threshold was reached on average 6 hours (interquartile range of 3.4 to 11.7 hours) after administration of 300 mg AZD7442 and remained above this threshold for 6 months in 96% of participants.

The primary analyses of the Phase III PROVENT (D8850C00002; NCT04625725) and STORM CHASER (D8850C00003; NCT04625972) trials support the use of AZD7442 for prophylaxis of COVID-19. PROVENT met its primary endpoint: AZD7442 administered in a prophylactic setting, before participant exposure to SARS-CoV-2, reduced the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness by 76.73% compared to placebo, which was statistically significant. In addition, there were no cases of severe COVID-19 or COVID-19 related deaths in the AZD7442 group, compared to 3 cases of severe COVID 19, including 2 COVID-19 related deaths, in the placebo group. STORM CHASER did not meet its primary endpoint: the reduction in risk of developing symptomatic COVID-19 of 33.31% compared to placebo was not statistically significant in this post-exposure to SARS-CoV-2 population. However, in a predefined subgroup analysis, AZD7442 reduced the risk of developing symptomatic COVID-19 by 73.17% in participants with a negative or missing SARS-CoV-2 RT-PCR at baseline. This subpopulation of participants, who had not been exposed to infection prior to receiving AZD7442, is similar to the PROVENT study population.

The primary analysis of the Phase III TACKLE trial (D8851C00001; NCT04723394) supports the use of AZD7442 for the treatment of COVID-19 in non-hospitalized adults. TACKLE met

its primary endpoint with a 50.49% relative risk reduction for developing severe COVID-19 or death compared with placebo in participants dosed ≤ 7 days from symptom onset. Pre-specified analyses showed that this rose to 88.01% and 66.93% relative risk reduction if the participants were dosed ≤ 3 days and ≤ 5 days of symptom onset, respectively. Approximately 90% of trial participants were from populations at high risk of progression to severe COVID-19, including those with co-morbidities.

AZD7442 has generally been well tolerated in the Phase I to Phase III studies. Doses from 300 mg IM (150 mg each of tixagevimab and cilgavimab) to 3000 mg IV (1500 mg each of tixagevimab and cilgavimab) have been administered without dose limiting toxicity.

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

2.3 Benefit/Risk Assessment

The risks and benefits of AZD7442 are briefly summarized below. More detailed information about the known and expected benefits and potential risks of AZD7442 can be found in the AZD7442 IB.

2.3.1 Risk Assessment

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

Potential risks based on clinical data include cardiac and thromboembolic events. Due to observations in the adult population in the Phase III pre-exposure prophylaxis study PROVENT (D8850C00002 [NCT04625725]; n = 5197), cardiac ischemia, cardiac failure, and thrombotic events have been included as AESIs in this study. In PROVENT, a numerical imbalance in SAEs in the Cardiac Disorders system organ class 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. In STORM CHASER (D8850C00003; NCT04625972), a 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 (D8851C00001; NCT04723394), a Phase III outpatient treatment study of AZD7442 in adults (n = 903), there were 2 (0.4%) SAEs in the Cardiac Disorders system organ class 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. The SAEs from SMQ embolic and thrombotic events were also reviewed from these 2 studies (PROVENT and STORM CHASER), and there was no clinically meaningful imbalance in thromboembolic events between participants who received AZD7442 and those who received placebo. Across the cases, many participants had confounding cardiac-related medical histories and risk present at baseline.

The identified risks based on class effect include injection site reactions and hypersensitivity including rash and urticaria. 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.

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

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.

2.3.2 Benefit Assessment

The primary analyses of the Phase III PROVENT (D8850C00002; NCT04625725) and STORM CHASER (D8850C00003; NCT04625972) trials support the use of AZD7442 for prophylaxis of COVID-19. 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 2.2).

Despite the rollout of effective SARS-CoV-2 vaccines, there remains a clear unmet medical need to provide effective prophylaxis 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 2021a), and those for whom vaccination is not suitable.

The individuals to be included in this study, adults and pediatric individuals (≥ 12 years old) who are moderately or severely immunocompromised and who may not mount an adequate immune response to COVID-19 vaccination, may benefit from AZD442 repeat dosing regimens for ongoing protection against 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 participants who are immunocompromised and at risk of COVID-19.

3 OBJECTIVES AND ENDPOINTS

Table 5 lists the objectives and endpoints for the study.

Table 5 Objectives and Endpoints

Objective	Endpoint
Primary	
To evaluate the safety and tolerability of AZD7442	AEs, SAEs, and AESIs
To evaluate the immunogenicity of AZD7442	Incidence of ADA in serum
Secondary	
To evaluate the PK of AZD7442 in serum	Serum AZD7442 concentrations PK parameters
To determine anti-SARS-CoV-2 nAb levels in serum after administration of AZD7442	Changes from baseline in GMTs and GMFRs values in SARS-CoV-2 nAbs (wild-type assay or pseudo-neutralization assay)
Exploratory	
To estimate the efficacy of AZD7442 for the prevention of COVID-19	Incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness Incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies
To estimate the efficacy of AZD7442 for the prevention of severe or critical symptomatic COVID-19	Incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness and COVID-19 deaths
To evaluate the PK of AZD7442 in nasal fluid	Nasal AZD7442 concentrations
To quantify SARS-CoV-2 viral loads in infected participants treated with AZD7442 (Illness Visits)	Viral genome copies in NP swabs at Illness Visits as determined by RT-PCR

Table 5 Objectives and Endpoints

Objective	Endpoint
To characterize resistance to AZD7442 (Illness Visits)	Genotypic analysis and biochemical and/or susceptibility analysis of SARS-CoV-2 variants to AZD7442
To assess additional immune responses in participants treated with AZD7442 (Illness Visits)	Other exploratory assays for humoral, mucosal, and cellular immune responses may be performed based upon emerging safety, efficacy, and pharmacodynamic data

ADA, antidrug antibody; AE, adverse event; AESI, adverse event of special interest; COVID-19, coronavirus disease 2019; GMT, geometric mean titers; GMFR, geometric mean fold rise; nAb, neutralizing antibody; NP, nasopharyngeal; PK, pharmacokinetic; RT-PCR, reverse transcriptase polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase II randomized, open-label, multicenter, dose-ranging study to assess the safety, immunogenicity, PK, and PD profiles of AZD7442 repeat dose regimens. The study will enroll adults and pediatric individuals (≥ 12 years of age weighing at least 40 kg) who are moderate to severely immunocompromised due to an underlying disease or are taking immunosuppressive medications and therefore unable to mount an adequate immune response to COVID-19 vaccine.

Approximately 200 adults and pediatric individuals, who meet the eligibility criteria, will be randomized in a 1:1 ratio to one of 2 AZD7442 treatment arms:

- Arm A (100 participants): AZD7442 600 mg administered intramuscularly (IM) on Day 1 followed by 300 mg IM Q3M for 12 months (a total of 5 doses)
- Arm B (100 participants): AZD7442 1200 mg administered intravenously (IV) on Day 1 followed by 600 mg IM Q6M for 12 months (a total of 3 doses)

An EoT Visit will be conducted at 15 months in both arms (3 months after the final dose of AZD7442).

After the EoT Visit, the participant will enter the follow-up period. Participants will be followed for safety for an additional 9 months after the EoT Visit, ie, through 12 months after the participant's final dose of AZD442.

Participants who permanently discontinue IMP administration due to the premature termination of the study will remain in the study to complete visits/assessments (except those

related to monitoring of IMP administration) for at least 6 months after their final dose of AZD7442.

The total duration of the study for a participant is 105 weeks (approximately 24 months) for both arms which includes the screening period (up to one week), the treatment period (15 months), and the follow-up period (9 months).

An independent DSMB will provide oversight, to ensure safe and ethical conduct of the study (see Section 9.6 and Appendix A 5.1).

The study design is presented Figure 1.

4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The Investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with Good Clinical Practice, and minimize risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The Investigator should confirm this with the designated study physician prior to any rescreening during study conduct mitigation.
- Home or Remote visit in lieu of on-site visit: Performed by a site qualified HCP or HCP provided by a TPV.
- Telemedicine visit in lieu of on-site visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- At-home IMP administration: permitted only for redosing with no major safety issues after initial dose. Performed by a site qualified HCP, HCP provided by a TPV. Additional information related to the visit can be obtained via telemedicine.

Any modifications or changes in study conduct as a part of mitigation under this section, will be documented as a protocol deviation for tracking purposes.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix E.

4.2 Scientific Rationale for Study Design

This is a Phase II randomized, open-label study with 2 treatment arms. Randomization will minimize potential bias in dose selection.

The study will enroll adults and pediatric individuals (≥ 12 years of age weighing at least 40 kg) who are moderate to severely immunocompromised due to an underlying disease or are taking immunosuppressive medications and therefore unable to mount an adequate immune response to COVID-19 vaccine.

The primary objective of the study is to assess safety and immunogenicity (ADA) of AZD7442 dose regimens (600 mg IM followed by 300 mg IM Q3M and 1200 mg IV followed by 600 mg IM Q6M) in this population. The repeat dosing treatment regimens with a duration of 12 months will allow for collection of safety endpoints (AEs, SAEs, and AESIs) and ADA data after repeat dosing with AZD7442. A follow-up of 12 months after the participant's last dose will provide additional safety and immunogenicity data on AZD7442.

4.3 Justification for Dose

The loading dose and frequency of repeat dosing in Study D8850C00010 have been chosen taking into account the current prophylaxis dosing schedules approved in PROVENT substudy (D8850C00002; NCT04625725) of 300 mg Q6M and 300 mg Q12M.

The 2 repeat dose regimens planned in this study for 2 different dosing intervals with a loading dose (Arm A: 600 mg IM then 300 mg Q3M; Arm B: 1200 mg IV then 600 mg Q6M) will provide over 18 months of safety and immunogenicity data for serum AZD7442 concentrations ≥ 2-fold higher than what was needed for at least 6 months of protection against the original SARS-CoV-2 strain and variants of concern in a moderately to severely immunocompromised population due to an underlying disease or are taking immunosuppressive medications. The either 3-month or 6-month repeat administration frequency will inform if immunogenicity differs by administration frequency with similar overall AZD7442 exposure. These data will further inform the safety profile of AZD7442 and will therefore allow for flexibility in dose level and dosing interval of AZD7442 by establishing a wider safety margin for C_{max} and AUC when dosing chronically.

A higher overall dose over a 12-month period will provide safety data for a higher loading dose and higher maintenance dose than have been assessed in clinical studies to date. A

6-month dosing interval at a higher dose of 600 mg IM may minimize the potential risk of ADA.

4.4 End of Study Definition

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 (see Section 1.3).

The end of the study is defined as the date of the last scheduled procedure shown in the SoA (see Section 1.3) for the last participant in the study globally.

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 of the following criteria apply:

Informed Consent

1 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this protocol. For pediatric participants: informed assent is to be provided by the participant; informed consent must be provided by the participant's legal guardian (see Appendix A 3).

2 Ensure that participants who are considered by the Investigator clinically unable to consent at screening and who are entered into the study by the consent of a legally acceptable representative show evidence of assent, as applicable in accordance with local regulations. See Appendix A for further details.

Age

3 Participant must be an adult (≥ 18 years of age) or pediatric individual (≥ 12 to < 18 years of age weighing ≥ 40 kg) at the time of signing the ICF or assent (for pediatric participants).

Type of Participant and Disease Characteristics

4 Individuals with medical conditions or treatments that may result in moderate to severe immune compromise or an inadequate immune response to COVID-19 vaccination include but are not limited to:

(a) Active treatment for solid tumor and hematologic malignancies.

(b) Receipt of solid-organ transplant and taking immunosuppressive therapy.

(c) Receipt of chimeric antigen receptor T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy).

(d) Moderate or severe primary immunodeficiency (eg, DiGeorge syndrome, Wiskott-Aldrich syndrome).

(e) Advanced or untreated HIV infection (people with HIV and history of CD4 cell counts < 200/mm^3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV).

(f) Active treatment with systemic high-dose corticosteroids (ie, ≥ 20 mg prednisone or equivalent per day when administered for ≥ 2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor necrosis factor blockers, and other biologic agents that are immunosuppressive or immunomodulatory (eg, B-cell depleting agents).

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

5.2 Exclusion Criteria

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

Medical Conditions

1 Any clinical signs and symptoms consistent with COVID-19, eg, fever, dry cough, dyspnea, sore throat, fatigue for ≥ 5 days or confirmed COVID-19 infection by appropriate laboratory test within 28 days prior to screening. Prior COVID-19 infection is not an exclusion.

2 History or current hospitalization for worsening disease during the one month prior to screening, with no change in condition at the time of study enrollment as judged by the Investigator.

3 Current need for hospitalization or immediate medical attention in a clinic or emergency room service in the clinical opinion of the Investigator.

4 Previous hypersensitivity, infusion-related reaction, or severe adverse reaction following administration of a mAb.

5 Known history of allergy to any component of the IMP formulation.

6 History of clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IV infusions or venepuncture.

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

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

Prior/Concomitant Therapy

9 Any prior receipt of investigational or licensed mAb or other biologic indicated for the prevention or treatment of SARS-CoV-2 or COVID-19 within 5 half-lives prior to screening or expected administration immediately after enrollment.

10 Have received a COVID-19 vaccination ≤ 14 days before Day 1 or plan to receive a COVID-19 vaccination ≤ 14 days after Day 1. (Such participants can subsequently be included in the study once they have reached > 14 days after their last dose of vaccine).

11 Receipt of convalescent COVID-19 plasma treatment within 90 days prior to screening.

Prior/Concurrent Clinical Study Experience

12 Receipt of any IMP in the preceding 90 days or 5 half-lives, whichever is longer, or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

Other Exclusions

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 For women only - currently pregnant (confirmed with positive pregnancy test) or breastfeeding.

15 Previous randomization in the present study.

16 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to randomization.

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

18 In nations, states, or other jurisdictions that for legal or ethical reasons bar the enrollment of participants who lack capacity to provide their own informed consent, such participants are excluded.

5.3 Lifestyle Considerations and Restrictions

- Restrictions relating to concomitant medications are described in Section 6.5.
- Participants must abstain from donating blood or plasma from the time of informed consent and for 12 months after the final dose of AZD7442.

Female Participants

- Participants should be advised to discuss the use of highly effective contraception with the Investigator, including the risks and benefits of a contraception versus a potential pregnancy during this study.

  Participants should be advised to discuss ova donation with the Investigator prior to donation.
- Participants should be advised to discuss breastfeeding with the Investigator in advance. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IMP and any potential adverse effects on the breastfed infant from the IMP.
- Pregnancy testing will be performed for women of childbearing potential per the SoA (Section 1.3). Pregnancy testing is not required for women who are not of childbearing potential.

Women not of childbearing potential are defined as either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or postmenopausal (amenorrhoeic for 12 months prior to the planned date of randomization without an alternative medical cause). The following age-specific requirements apply:

- Women < 50 years old will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and FSH levels in the postmenopausal range.
- Women ≥ 50 years old will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.

Male Participants

- Participants should be advised to discuss sperm donation with the Investigator prior to donation.
- Participants should be advised to discuss the use of barrier methods during sexual intercourse with the Investigator.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to IMP. 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 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 and must be started within 2 weeks of the initial screening. When possible, the Investigator should consult the Study Physician prior to rescreening. 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 Intervention(s) Administered

6.1.1 Investigational Medicinal Products

The IMP to be administered in this study is described in Table 6.

Table 6 Investigational Medicinal Products

Intervention name	AZD7442 (tixagevimab [AZD8895] + cilgavimab [AZD1061])
Type	Biologic
Dose formulation	**Liquid Product** AZD7442 will be supplied as separate vials of tixagevimab (AZD8895) and cilgavimab (AZD1061) as 150 mg colorless to slightly yellow, clear to opalescent solutions for injection. The solutions contain 100 mg/mL of active ingredient (tixagevimab [AZD8895] or cilgavimab [AZD1061]) in 20 mM L-histidine/L-histidine hydrochloride, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0. The label-claim volume is 1.5 mL.
Unit dose strength(s)	150 mg (nominal) tixagevimab (AZD8895) and 150 mg (nominal) cilgavimab (AZD1061) per vial.

Table 6 Investigational Medicinal Products

Dosage level(s) and route of administration	AZD7442 doses (combined doses of tixagevimab [AZD8895] and cilgavimab [AZD1061]) to be administered: <u>Arm A (AZD7442 600 mg IM on Day 1 then 300 mg IM Q3M for 12 months)</u> • Day 1 600 mg AZD7442 administered sequentially as a 3 mL IM injection containing 300 mg tixagevimab (AZD8895) and a 3 mL IM injection containing 300 mg cilgavimab (AZD1061), one injection in each gluteal region. • Days 92, 183, 274, 365 300 mg AZD7442 administered sequentially as a 1.5 mL IM injection containing 150 mg tixagevimab (AZD8895) and a 1.5 mL IM injection containing 150 mg cilgavimab (AZD1061), one injection in each gluteal region. <u>Arm B (AZD7442 1200 mg IV on Day 1 then 600 mg IM Q6M for 12 months)</u> • Day 1 1200 mg AZD7442 (600 mg tixagevimab [AZD8895] and 600 mg cilgavimab [AZD1061]) administered by IV infusion. • Days 183, 365 600 mg AZD7442 administered sequentially as a 3 mL IM injection containing 300 mg tixagevimab (AZD8895) and a 3 mL IM injection containing 300 mg cilgavimab (AZD1061), one injection in each gluteal region.
Use	Experimental
IMP or NIMP	IMP
Sourcing	AZD7442 (tixagevimab [AZD8895] + cilgavimab [AZD1061]): AstraZeneca.
Packaging and labeling	IMP will be provided in a glass vial. Each glass vial will be labeled as required per country requirement.

IM, intramuscular; IMP, investigational medicinal product; IV, intravenous; Q3M, every 3 months; Q6M, every 6 months; w/v, weight per volume.

6.2 Preparation/Handling/Storage/Accountability

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IMP received, and any discrepancies are reported and resolved before use of the IMP.
- Only participants randomized in the study may receive IMP, and only authorized site staff may supply or administer IMP. All IMP 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.

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

6.2.1 Dose Preparation and Administration Instructions

Each vial selected for dose preparation should be inspected. If there are any defects noted with the IMP, the Investigator and site monitor should be notified immediately.

AZD7442 IMP is comprised of 2 separate DPs, tixagevimab (AZD8895) and cilgavimab (AZD1061). Tixagevimab (AZD8895) and cilgavimab (AZD1061) DPs are each supplied as sterile clear to opalescent, colorless to slightly yellow solutions, with a label-claim of 150 mg at 100 mg/mL per vial.

The dose of tixagevimab (AZD8895) and cilgavimab (AZD1061) for administration must be prepared 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. Each tixagevimab (AZD8895) and cilgavimab (AZD1061) vial must be used only once to prepare a single dose. AZD7442 (tixagevimab [AZD8895] and cilgavimab [AZD1061]) does not contain preservatives, and any unused portion must be discarded.

6.2.1.1 AZD7442 IV 1200 mg (600 mg Tixagevimab [AZD8895] and 600 mg Cilgavimab [AZD1061]) Dose Preparation and Administration Instructions (Arm B; Day 1 Only)

Use a single IV bag with diluent of 0.9% (w/v) sodium chloride or 5% dextrose to co-administer tixagevimab (AZD8895) and cilgavimab (AZD1061) infusion. The admixture can be prepared using IV bag volumes ranging between 50 mL and 250 mL and the IV bag material of construction may consist of polyolefin, polyvinylchloride, or polyethylene.

To prepare the IV bag, accurately withdraw 6 mL of tixagevimab (AZD8895) and 6 mL of cilgavimab (AZD1061) and transfer both to the same IV bag. Mix the contents of the bag until visually uniform.

Administer the entire contents of the IV bag using IV administration sets containing low protein binding 0.2 micrometre or 0.22 micrometre filters made of polyethersulfone. The target infusion rate is 20 mg/minute.

The IV line and catheter must be flushed according to local practices to ensure the full dose is administered.

Monitoring for safety, including infusion-related reactions and hypersensitivity reactions is described in Section 8.2.5.

6.2.1.2 AZD7442 IM Administration Dose Preparation and Administration Instructions

The 2 DPs tixagevimab (AZD8895) and cilgavimab (AZD1061), comprising AZD7442, must both be administered separately to the participant in sequential order, with no participant receiving doses of tixagevimab (AZD8895) without also receiving the matching dose of cilgavimab (AZD1061).

No incompatibilities have been observed between AZD7442 and disposable polypropylene or polycarbonate syringes used for IM administration. Use a separate disposable syringe with a 22 – 25 gauge and 1 – 1.5 in (25 – 38 mm) length needle for each tixagevimab (AZD8895) and cilgavimab (AZD1061) DP injection. Tixagevimab (AZD8895) and cilgavimab (AZD1061) should be administered according to standard practice procedures for IM injections, with one injection in each gluteal region.

Monitoring for safety, including injection site reactions and hypersensitivity reactions is described in Section 8.2.5.

6.3 Measures to Minimize Bias: Randomization and Blinding

This is an open-label study in which all eligible participants will be randomized in a 1:1 ratio to treatment with AZD7442 in Arm A (600 mg IM on Day 1 then 300 mg IM Q3M) or Arm B (1200 mg IV on Day 1 then 600 mg IM Q6M). AZD7442 will be administered at the study visits summarized in SoA (Section 1.3).

All eligible participants will be centrally assigned to randomized IMP using an IRT. Before the study is initiated, user guides, the log-in information, and directions for the IRT will be provided to each site.

Where a participant does not meet all the eligibility criteria but incorrectly received IMP, the Investigator should inform the Study Physician immediately, and a discussion should occur between the Study Physician and the Investigator regarding whether to continue or discontinue the participant.

6.4 Study Intervention Compliance

Participants will receive IMP directly from the Investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of IMP 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 IMP.

6.5 Concomitant Therapy

Any medication or vaccine (including COVID-19 vaccines, 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.

Table 7 lists the permitted, restricted, and prohibited medications during the study.

Table 7 Permitted, Restricted, and Prohibited Medications

Use Category	Type of medication/treatment	Timeline/instructions
Permitted	Routine Vaccines	Licensed influenza vaccines are permitted at any time. All other routine vaccines are permitted; however, they should not be given within 14 days before or after any dose of IMP. Vaccines for the prevention of SARS-CoV-2 or COVID-19 are not considered routine vaccines in this protocol and are allowed; however, they should not be given within 14 days before or after any dose of IMP (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 screening and there is no anticipated change during the treatment period. Allergen immunotherapy should not be administered on the same day as IMP. Non-prescription over-the-counter treatments for allergies such as antihistamines, decongestants, and nasal steroids are permitted for such participants.

Table 7 Permitted, Restricted, and Prohibited Medications

Use Category	Type of medication/treatment	Timeline/instructions
	Commercial biologics, prednisone, immunosuppressive medications (eg, azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy)	Allowed. Biologics (eg, palivizumab, adalimumab) should not be administered on the same day as IMP.
	IVIG	Allowed for participants with primary or secondary immunodeficiency who have hypoglobulinemia and need replacement IVIG. IVIG 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. Participants who develop COVID-19 after receiving IMP should be treated according to local standard of care, including investigational agents outside a clinical trial setting.	
	• Contraceptive methods	• Allowed, with guidance from health care professional taking into consideration any risks and benefits.
Restricted	• Investigational or authorized under early access or EUA products indicated for the treatment or prevention of SARS-CoV-2 or COVID19) • Convalescent COVID-19 plasma and sera	• Note: For participants who develop COVID-19, receipt of approved/licensed products options are permitted, and they should be treated according to local standard of care, including investigational agents under EUA or equivalent regulations. • Receipt of approved/licensed treatments for the prevention of COVID-19 are permitted during the follow-up period (starting ≥ 3 months after last dose of AZD7442) as per local guidelines/standard of care and should be documented as concomitant medication.

COVID-19, coronavirus disease 2019; EUA, Emergency Use Authorization; HIV, Human immunodeficiency virus; IMP, investigational medicinal product; IVIG, intravenous immunoglobulin; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.

6.5.1 COVID-19 Vaccines

Participants who have received a previous dose or doses of a COVID-19 vaccine are permitted to be included in the study; however, participants must not receive a dose of a COVID-19 vaccine within 14 days before or after any dose of IMP.

6.6 Dose Modification

The IMP will be administered as described in Section 6.1.1. Dose modification is not permitted.

6.7 Intervention After the End of the Study

There is no intervention after the end of study (see Section 4.4 for definition of end of study).

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

At any time, participants are free to discontinue IMP (Section 7.1) or withdraw from the study (Section 7.2), without prejudice to further treatment.

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue (definitive discontinuation) IMP. If IMP is permanently discontinued, the participant should remain in the study to complete visits/assessments (except those related to IMP administration) through the final visit in the study (Day 729). If the participant is unwilling to complete all visits/assessments through the end of study, modified follow-up options (eg, modified visit schedule and/or telephone contact) may be offered.

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

Reasons for permanent discontinuation from IMP include but are not limited to:

- Participant/participant's parent or legal guardian decision to discontinue IMP
- Participant/participant’s parent or legal guardian decision to withdraw from the study (see Section 7.2)

See the SoA (Section 1.3) for data to be collected at the time of IMP discontinuation and follow-up and for any further evaluations that need to be completed.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or at the request of their parent or legal guardian or may be withdrawn at any time 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, modified visit schedule, telephone contact, a contact with a relative or treating physician, or information from medical records; see Section 7.1). A participant who agrees to modified follow-up options will not be considered to have withdrawn from the study.
- At the time of withdrawal from the study, if possible, an Early Discontinuation Visit should be conducted as shown in the SoA (Table 3; Section 1.3). See the SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The participant will discontinue the IMP and be withdrawn from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if the participant still agrees for existing samples to be used in line with the original consent. If the participant requests withdrawal of 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 or not 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, a minimum of 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. If after every effort to regain contact with the participant, they do not come in for their next visit, the participant may be considered lost to follow-up.
- 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 randomized, 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.

7.4 Study Suspension/Early Termination

The Sponsor reserves the right to temporarily suspend or permanently terminate this study or a component of the study at any time. The reasons for temporarily suspending the study may include, but are not limited to, the following:

- One or more participant experiences a Grade 4 hypersensitivity reaction or hypersensitivity reaction classified as an SAE, and assessed as related to the IMP, in the opinion of the Sponsor.
- Any death, SAE, or other safety finding assessed as related to IMP that, in the opinion of the Sponsor, may preclude further administration of IMP.

If the Sponsor prematurely terminates this study, including the permanent discontinuation of IMP administration, all actively enrolled participants will remain in the study to complete visits/assessments (except those related to monitoring of IMP administration) and complete an early discontinuation visit, at least 6 months after the last IMP administration.

Refer to Section 1.3 for details of activities to be completed if the Sponsor permanently terminates this study.

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 to determine if the participant should continue or discontinue IMP.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), 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 (Section 1.3).

- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 350 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

The primary objectives of this study are to evaluate safety and immunogenicity. Efficacy assessments described in this section are exploratory.

8.1.1 Monitoring COVID-19 Symptoms

To capture the incidence of infection, study sites will contact participants monthly (telephone/email/text) as indicated in the SoA (Section 1.3) with reminders to monitor for COVID-19 symptoms. During these monthly contacts the Investigator will enquire about any COVID-19 symptoms (see Table 8) since the previous visit/contact. If such symptoms are evaluated and found to be related to COVID-19 by the investigator, an illness visit will be initiated as soon as possible. Participants who experience suspected COVID-19 symptoms such as those listed in Table 8, will be given instructions to contact the study site.

Participants with suspected COVID-19 symptom(s) after Day 1 will be instructed to initiate Illness Visits and will be tested locally for SARS-CoV-2 (see Section 8.1.3). If negative, the participant will be instructed to stop Illness Visits and continue with the study scheduled assessments for the treatment period (Table 1 for Arm A; Table 2 for Arm B) and follow-up period (Table 3 for both arms). If positive, the participant will be instructed to continue Illness Visits and will have additional assessments per Table 4. Diagnoses of suspected or confirmed COVID-19, confirmed asymptomatic SARS-CoV-2 infection, post-COVID-19 (“long COVID”), or recurrence of COVID-19 (or of SARS-CoV-2 reinfection) will be collected and recorded in the eCRF as an AE (see Section 8.3.5). Post the IL-D90 visit, participants diagnosed with long COVID-19 will have their COVID-19 symptoms reassessed and recorded every 3 months until their symptoms resolve or end of study occurs.

Table 8 COVID-19 Symptoms

Typical presenting symptoms of COVID-19 may include:	
Pediatric 12 - < 18 years of age	**Adult ≥ 18 years of age**
• Fever • Fatigue • Headache • Myalgia • Cough • Nasal congestion or rhinorrhea • New loss of taste or smell • Sore throat • Shortness of breath or difficulty breathing • Abdominal pain • Diarrhea • Nausea or vomiting • Poor appetite Note: Children infected with SARS-CoV-2 may have many of these nonspecific symptoms, only have a few (such as only upper respiratory symptoms or only gastrointestinal symptoms) or may be asymptomatic. The most common symptoms in children are cough and/or fever.	• Fever • Shortness of breath • Difficulty breathing • New onset confusion (only for participants ≥ 60 yo) • Appetite loss or decrease food intake (only for participants ≥ 60 yo) • Increased supplemental oxygen requirement (only for participants ≥ 60 yo on baseline supplemental oxygen) • Chills • Cough • Fatigue • Muscle aches • Body aches • Headache • New loss of taste • New loss of smell • Sore throat • Congestion • Runny nose • Nausea • Vomiting • Diarrhea

CDC, Centers for Disease Control and Prevention; COVID, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2; yo, years old.

Adapted from CDC 2021b.

8.1.2 Severe or Critical Criteria

Severe COVID-19 is characterized by a minimum of either pneumonia (fever, cough, tachypnea or dyspnea, and lung infiltrates) or hypoxemia (oxygen saturation < 90% in room air and/or severe respiratory distress) and a WHO Clinical Progression Scale score of 5 or higher (Table 9). Each confirmed positive case of COVID-19 must have a WHO clinical progression score recorded in the eCRF. Additionally, the highest WHO clinical progression score during the clinical course of the severe case will be recorded in the eCRF.

Table 9 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; RNA, ribonucleic acid; pO_2, partial pressure of oxygen; SpO_2, oxygen saturation; WHO, World Health Organization.

Marshall et al 2020.

8.1.3 Illness Visits

Symptomatic participants (as defined in Section 8.1.1) will be instructed to visit the study site for initiation of illness assessments (Table 4); where supported, home or mobile visits may be substituted for the site visits. Assessments will be performed at IL-D1a for all participants who have reported symptoms of COVID-19 which have been evaluated and found to be related to COVID-19 by the investigator. (Table 4). Assessments will include collection of NP specimens for SARS-CoV-2 rapid antigen and RT-PCR tests (local laboratory; see Sections 8.2.4 and 8.6.1.1) and RT-PCR (central laboratory; see Section 8.6.1.1).

The local laboratory SARS-CoV-2 tests (rapid antigen and RT-PCR) performed at IL-D1a will be used to determine if the participant should continue with the Illness Visits. IL-D1b assessments (ie, blood sample collection) should only be performed if either the SARS-CoV-2 rapid antigen or RT-PCR local test result is positive. If the rapid antigen test result is negative and the RT-PCR is subsequently determined as positive (ie, rapid antigen was false negative), then the participant will be instructed to return to the site, and IL-D1b assessments should be performed as soon as possible (but no later than 2 days) after the positive RT-PCR test result

is available. If the rapid antigen test result is positive and the RT-PCR is subsequently determined as negative (ie, rapid antigen was false positive), the participant will be instructed to discontinue Illness Visits. Only participants with a positive RT-PCR test result will be instructed to continue with the Illness Visits. The results of the SARS-CoV-2 rapid antigen and RT-PCR testing should also be reported to the participant's primary care providers.

Participants will continue with follow-up visits per the SoA for the treatment period (Table 1 for Arm A and Table 2 for Arm B) and follow-up period (Table 3 for both arms). The Illness Visit schedule is to be performed in addition to the scheduled visit in the SoA. Where visits coincide, all assessments from the scheduled visit and Illness Visit should be performed.

To distinguish between the scheduled visits for the treatment period (Table 1 for Arm A; Table 2 for Arm B) and follow-up period (Table 3 for both arms) and the Illness Visits (Table 4), and to distinguish between illness episodes the visits will be labeled as follows: for the first episode Illness Visit Day 1 = 1IL-D1, Illness Visit Day 5 = 1IL-D5, etc, and for the second episode 2IL-D1, 2IL-D5 and so on as applicable.

8.1.4 SARS-CoV-2 Testing and Other Virology Assessments

Participants who have reported symptoms of COVID-19 which have been evaluated and found to be related to COVID-19 by the investigator will undergo assessments at IL-D1a (Table 4). Assessments will include collection of NP specimens for SARS CoV-2 rapid antigen and RT-PCR tests (local laboratory; see Sections 8.2.4 and 8.6.1.1) and RT-PCR (central laboratory; see Section 8.6.1.1).

Resistance monitoring as performed by genotypic and phenotypic characterization of virus isolated from Illness Visits may be conducted per the SoA (see Table 4 and Section 8.6.1.1). Additionally, a respiratory panel to investigate the presence of additional viral pathogens may be carried out at time points per Table 4, and as outlined in Section 8.6.1.1.

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 (see Section 1.3).

- A complete physical examination will include, but will not be limited to, assessment of height, weight, general appearance, head, ears, eyes, nose, throat, neck, skin, as well as CV, respiratory, abdominal, and nervous systems. Each clinically significant abnormal finding at screening will be recorded in the medical history.

- Targeted physical examination per investigator discretion will include areas suggested by medical history, vulnerable conditions and reported clinical complaints during the study visit and may require height and weight.

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, blood pressure, and body temperature, will be performed as specified in the SoA (see 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 8.3.6.

8.2.3 Electrocardiograms

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

The Investigator 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 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, urinalysis, and cardiac biomarkers will be taken at the visits indicated in the SoA (see 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, coagulation, urinalysis, cardiac/thrombosis biomarkers, serum β-hCG, and FSH 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.

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)	Reticulocytes absolute count

Serum clinical chemistry	
Sodium	Alkaline phosphatase (ALP)
Potassium	Alanine aminotransferase (ALT)
Urea	Aspartate aminotransferase (AST)
Creatinine (and estimated glomerular filtration rate [eGFR])	Gamma glutamyl transpeptidase (GGT)
Albumin	Total bilirubin
Calcium	Conjugated bilirubin
Phosphate	Creatine kinase
Glucose	
C-reactive protein (CRP)	

Note: In case a participant shows an AST **or** ALT ≥ 3 × ULN together with TBL ≥ 2 × upper limit normal (ULN) please refer to Appendix D. Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law, for further instructions.

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

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

Cardiac/thrombosis biomarkers [a]	
D-dimer	High-sensitivity C-reactive protein (hs-CRP)
P-selectin	
Thrombin	Total serum cholesterol
Factor VIII levels	Serum-low-density lipoprotein (LDL) cholesterol
Troponin T/I	Serum-high density lipoprotein (HDL) cholesterol

[a] Participants will be instructed to fast for ≥ 8 hours prior to collection.

SARS-CoV-2 Testing

SARS-CoV-2 rapid antigen test (local laboratory)	SARS-CoV-2 RT-PCR (local and central laboratory)

Females Only

Pregnancy test (women of childbearing potential only)	
Urine human beta chorionic gonadotrophin (β-hCG) (predose on days of IMP administration)	Serum β-hCG[a]
Suspected postmenopausal women < 50 years only	
Follicle-stimulating hormone (FSH)[b]	

[a] If urine tests positive or indeterminate, a quantitative serum β-hCG will be performed for confirmation.

[b] FSH will be analyzed at the screening visit to confirm postmenopausal status only in women < 50 years of age who have been amenorrhoeic for ≥ 12 months. Until FSH is documented to be within menopausal range, the participant is to be considered of childbearing potential. For women aged ≥ 50 years, postmenopausal is defined as having a history of ≥ 12 months' amenorrhea prior to randomization, without an alternative cause, following cessation of exogenous sex-hormonal treatment.

8.2.5 Monitoring of IMP Administration and Injection Site Inspection

Participants will be clinically monitored closely on site for a minimum of one hour after each administration of IMP for general safety, including injection site reactions, infusion-related reactions (applicable for Arm B Day 1 IMP IV administration), and hypersensitivity reactions, and per local standard of care. Vital signs, including pulse oximetry, will be measured within 15 minutes before and 15 minutes (± 5 minutes) after administration of IMP. Note that on Day 1 in Arm B, vital signs will also be measured every 15 minutes (± 5 minutes) during the infusion, and the minimum one-hour postdose monitoring period will start at the end of the IV infusion. See the SoA (Section 1.3; Table 1 for Arm A and Table 2 for Arm B).

As with any biologic product, hypersensitivity reactions (including anaphylaxis), injection site reactions, and infusion-related reactions are possible. Therefore, appropriate drugs and medical equipment to treat these reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

Additionally, all participants will have a remote telemedicine visit or, if required due to local facilities, an In-person visit one week (± 3 days) after each dose of IMP for general safety monitoring and follow-up (see the SoA [Section 1.3]).

Any AEs should be reported as described in Section 8.3.

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 Adverse Event and Serious Adverse Event Information

Non-serious AEs will be collected from the time of IMP administration through the last contact with the participant.

Serious adverse events will be recorded from the time of signing of the ICF through the last contact with the participant.

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 Adverse Events and Serious Adverse Events

Any AEs that are unresolved at the participant's last AE assessment 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:

- Adverse event (verbatim)
- The date and time when the AE started and stopped
- Severity grade/maximum severity grade/changes in severity grade

- Whether the AE is serious or not
- Investigator causality rating against the IMP(s) (yes or no)
- Action taken with regard to IMP(s)
- If the AE caused participant's withdrawal from the 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
- Date of discharge
- Probable cause of death
- Cause of death related to COVID-19 (yes/no/unknown)
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

The following severity ratings will be used, adapted from the CTCAE v5.0 (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 an 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 investigational product?'

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 (see 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 8.3.8. See also the AZD7442 IB, for additional information on AESIs.

If the Investigator has any questions as to whether an AE is an AESI, the Investigator should consult with the Study Physician.

The AESIs for AZD7442 include:

Anaphylaxis and other serious hypersensitivity reactions, including confirmed diagnosis of immune complex disease

See Section 8.2.5 for safety monitoring on days of IMP administration.

Injection site reactions (IM administration) and infusion-related reactions (IV administration)

See Section 8.2.5 for safety monitoring on days of IMP administration)

Cardiac and Thromboembolic Events

The following cardiac and thromboembolic events will be designated as AESIs:

- Cardiac ischemic events (myocardial infarction and unstable angina)
- Cardiac failure events
- Cerebrovascular events (ischemic and hemorrhagic Stroke)
- Thromboembolic events (arterial, venous or unspecified/mixed, other)

Cardiac and thromboembolic events will be referred to a CV Events Adjudication Committee (see Section 9.7).

Multisystem Inflammatory Syndrome – Pediatric Participants

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

- 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 or more) 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.

8.3.5 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.

Diagnoses of suspected or confirmed COVID-19, confirmed asymptomatic SARS-CoV-2 infection, and/or recurrence of COVID-19 (or of SARS-CoV-2 reinfection) will be collected and recorded in the eCRF as an AE. Additionally, if a participant has prolonged COVID-19 for approximately 3 months, then an AE of post-acute COVID ("long COVID") will be recorded in the eCRF as an AE (In the case of post-COVID, symptoms may be of new onset following initial recovery from an acute COVID-19 episode, persist from the initial illness, or fluctuate/relapse over time; WHO 2021).

8.3.6 Adverse Events Based on Examinations and Tests

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

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

If deterioration in a laboratory value/vital sign/ECG 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.

8.3.7 Hy's Law

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

Aspartate aminotransferase 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 Hy's Law.

8.3.8 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the IMP 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 an 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 the AstraZeneca drug.

8.3.9 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any IMP.

8.3.9.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, the decision to continue or discontinue the IMP will be left to the participant and the Investigator. The IMP should only be administered during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

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 8.3.8) 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.

8.3.9.2 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.

8.3.10 Medication Error, Drug Abuse, and Misuse

8.3.10.1 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 **1 calendar 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 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 event of medication error, drug abuse, or misuse (see Section 8.3.8) and **within 30 days** for all other events.

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

8.3.10.2 Medication Error

For the purposes of this clinical study a medication error is defined as 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 full definition and examples of medication error can be found in Appendix B 4.

8.3.10.3 Drug Abuse

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.

8.3.10.4 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 authorised product information, or for unauthorised 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 IMP (or dosing frequency) greater than what is specified in this protocol will be considered an overdose (see Table 6).

- 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 in the course of 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 1 or 5 calendar days** for overdoses associated with an SAE (see section 8.3.8) 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/repatriated.

- 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 pharmacokinetic 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 Pharmacokinetics

- Serum samples will be collected for measurement of serum concentrations of AZD7442 (tixagevimab and cilgavimab) as specified in the SoA (Section 1.3).
- 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 analyse the PK of AZD7442. 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.

8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentration in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

Incurred sample reproducibility analysis, if any, will may be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

8.5.2 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.

8.5.2.1 Antidrug Antibody Assessments

Blood samples for determination of ADA in serum will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the methods and analyses performed will be described in a separate bioanalytical report.

Unscheduled samples for ADA analysis should be collected in response to suspected immune-related AEs.

The presence or absence of ADA will be determined in the serum samples using a validated bioanalytical method. A tiered testing scheme will be employed, with the first step being screening. Samples found positive in the screening step will be tested in the confirmatory step. Samples confirmed positive for ADA in the confirmatory step will undergo endpoint titer determination.

8.5.2.2 SARS-CoV-2 Serology Assessments

Serum samples will be collected to assess SARS-CoV-2 antigen-specific antibody levels. Baseline serostatus and the rate of SARS-CoV-2 infection in participants receiving AZD7442 will be determined by seroconversion (negative to positive) in a validated SARS-CoV-2 N protein antigen assay operated by an authorized laboratory.

8.5.2.3 Assessment of Mucosal Responses

Nasal lining fluid samples will be collected to evaluate PK or SARS-CoV-2 antigen-specific antibody responses in nasal secretions. Samples will also be collected at Illness Visits. Nasal lining fluid samples will be collected, when test supplies are available, by synthetic absorptive matrix sampling as outlined in the Laboratory Manual. AZD7442 nasal concentrations may be assessed using an appropriately qualified bioanalytical assay.

8.5.2.4 Assessment of Cell-mediated Immune Responses

Cell-mediated immune responses (ie, B-cell and T-cell responses) will be assessed by characterizing PBMCs isolated from selected sites using methods that may include T-cell ELISpot assays to SARS-CoV2 antigens, flow cytometry after intracellular cytokine staining, single-cell RNA sequencing, B-cell and T-cell receptor sequencing, and other methodology as determined by the Sponsor, as technical and/or operational feasibility allows.

8.5.2.5 Additional Serum Immunogenicity

Additional serum samples will be collected for exploratory immunogenicity evaluation. Serologic assessment to seasonal coronavirus antigens may also be assessed quantitatively using a qualified multiplexed meso scale discovery (MSD) immunoassay. Exploratory sera samples may be utilized to investigate additional humoral and cellular immune responses, as well as potential correlates of protection as determined by the Sponsor based upon emerging safety, efficacy, and immunogenicity data.

8.5.3 Pharmacodynamics

8.5.3.1 SARS-CoV-2 Neutralizing Antibody Assessments

Serum samples to measure SARS-CoV-2 nAb levels will be collected from participants according to the time points specified in the SoA (see Section 1.3). Authorized laboratories may measure nAbs to SARS-CoV-2 using validated live virus neutralization assays or pseudo-neutralization assays.

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

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the study the participant consents to the mandatory research components of the study.

Samples for biomarker research are required and will be collected from participants, as specified in the SoAs (see Section 1.3). Nasopharyngeal swabs will be collected for virologic assessments. These biomarker measurements will support understanding of potential correlates of protection, duration of immune responses, and correlations between PD and immunogenicity. Details for sample collection, processing, and testing will be provided in the Laboratory Manual.

Any results from such analyses may be reported separately from the CSR.

8.6.1.1 Virologic Assessments

Nasopharyngeal swabs will be assessed by authorized RT-PCR assays for the detection of SARS-CoV-2 by local and central laboratories according to the time points specified in the SoA (Section 1.3). Instructions for obtaining and processing NP swab samples are provided in the Laboratory Manual.

The full-length S gene (AA 1-1274) from SARS-CoV-2-positive nasal samples may be amplified using a standard, single tube population-based RT-PCR method and sequenced by next-generation sequencing (NGS) at Illness Visits (Table 4). Amino acid variation across the full-length S protein sequence may be determined and reported separately from the CSR.

Amino acid changes identified by genotypic analyses of the S trimer protein ectodomain (AA 20-1213) can be evaluated by either a spike trimer binding affinity assay and/or a recombinant SARS-CoV-2 Spike-pseudovirus neutralization assay. Additional details on clinical virology analyses, including molecular surveillance of the S protein in global circulation will be provided in the Virology Analysis Plan.

Local and central assessments should be collected per the SoA (Section 1.3); where both local and central assessments are listed both are required and should be collected. Additionally, a validated multiplexed respiratory panel may be utilized to assess for the presence of other respiratory pathogens in NP swabs in a central laboratory operated on behalf of the Sponsor at Illness Visits.

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, PBMCs, or mucosal specimens to evaluate their association with observed clinical responses to AZD7442.

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

8.7 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable in this study.

8.8 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not collected or evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary objective of the study is to assess the safety and tolerability of AZD7442. No statistical hypotheses will be tested.

9.2 Sample Size Determination

Approximately 200 participants will be randomized to study intervention: 100 participants to Arm A (AZD7442 600 mg IM on Day 1 then 300 mg IM Q3M for 12 months) and 100 participants to Arm B (AZD7442 1200 mg IV on Day 1 then 600 mg IM Q6M for 12 months).

If the true AE rate is 3%, the probability of observing at least one AE in 100 participants is 95%. The number of participants in the study would also allow for assessment of immunogenicity based on ADA prevalence observed in PROVENT (D8850C00002; NCT04625725).

9.3 Populations for Analyses

The following populations are defined in Table 10.

Table 10 Populations for Analysis

Population/Analysis set	Description
Enrolled	All participants who sign the ICF.
Full analysis set	All randomized participants who receive at least one dose of IMP. Participants will be assigned according to their randomized treatment according to the intent-to-treat principle.
Safety analysis set	All participants who have received at least one dose of IMP. Participants will be assigned in this analysis set by the arm of treatment they actually received.
PK analysis set	All participants in the safety analysis set who received AZD7442 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 in the safety analysis set who have a non-missing baseline AZD7442 ADA result and at least one non-missing post-baseline AZD7442 ADA result.
nAb evaluable analysis set	All participants in the safety analysis set from whom blood samples are assumed not to be affected by factors such as protocol violations, and who had at least one quantifiable serum observation post dose. At any time during the study, participants will be excluded from this analysis set at the point at which they receive an alternative COVID-19 mAb.

ADA, antidrug antibody; COVID-19, coronavirus disease 2019; ICF, informed consent form; IMP, investigational medicinal product; nAb, neutralizing antibody; PK, pharmacokinetic.

9.4 Statistical Analyses

Results will generally be summarized by treatment arm using descriptive statistics. Categorical variables will be summarized using frequency and percentages, where the denominator for calculation is the underlying analysis set population, unless otherwise stated. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate.

The final data readout will occur once all participants have completed the follow-up period (at Month 24) or withdrawn due to premature termination of the study.

9.4.1 Primary Endpoints

9.4.1.1 Safety

The safety of AZD7442 will primarily be assessed by the incidence and exposure adjusted incidence of AEs, SAEs, and AESIs.

Adverse event severity will be graded according to Appendix B and coded using the most recent version of the Medical Dictionary for Regulatory Activities. Adverse events will be presented 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 will include exposure adjusted rates. An overview of AEs will be presented for each 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.

9.4.1.2 Antidrug Antibodies

The incidence of ADA to AZD7442 will be assessed and summarized by number and percentage of participants who are ADA positive. The ADA titer will be summarized with descriptive statistics.

9.4.2 Secondary Endpoints

9.4.2.1 Pharmacokinetic

Individual AZD7442 (tixagevimab and cilgavimab) serum concentration data will be listed and tabulated, along with descriptive statistics. Appropriate PK parameters may be calculated.

9.4.2.2 Neutralizing Antibodies

Descriptive statistics for GMTs and GMFR in SARS-CoV-2 nAbs will include number of participants, geometric mean, GSD, 95% CI, minimum, and maximum.

The GMT will be calculated as the antilogarithm of Σ(log2 transformed titer/n), ie, as the antilogarithm transformation of the mean of the log-transformed titer, where n is the number of participants with titer information. The GSD for GMT will be calculated as the antilogarithm transformation of the standard deviation of the log-transformed titer. The 95% CI will be calculated as the antilogarithm transformation of the upper and lower limits for a two-sided CI for the mean of the log-transformed titers.

The fold rise is calculated as the ratio of the postdose titer level to the predose titer level. GMFR will be calculated as antilogarithm of Σ (log2 transformed (postdose titer/predose titer)/n). The GSD and 95% CIs for GMFR will be calculated similarly to those for GMT.

9.4.3 Exploratory Endpoints

9.4.3.1 SARS-CoV-2 RT-PCR-positive Symptomatic Illness

The incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness will be summarized with descriptive statistics.

9.4.3.2 SARS-CoV-2 RT-PCR-positive Severe or Critical Symptomatic Illness

The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness will be summarized with descriptive statistics.

9.4.3.3 Biomarkers of AZD7442

Exploratory biomarkers thought to play a role in COVID-19 severity or outcomes will be summarized with descriptive statistics and may be reported outside of the CSR.

9.5 Interim Analyses

Interim analyses may be conducted to support regulatory requirements or at the discretion of the Sponsor, and will be specified in the statistical analysis plan if applicable.

9.6 Data Safety Monitoring Board

An independent DSMB will provide oversight, to ensure safe and ethical conduct of the study (see Appendix A 5.1).

The DSMB will make any necessary recommendations to the Sponsor based on their evaluations of emerging data. The frequency of Data Review Meetings will be held in line with the DSMB Charter. The DSMB will also review study progress and monitor for evidence of harm resulting from AZD7442. If required, the DSMB will recommend temporarily stopping or termination of the study.

For details on the DSMB, see Appendix A 5.1. 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 International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure (IB), and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (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 contract research organization (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 Code of Federal Regulations (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 Serious Adverse Events

- Prompt notification by the Investigator to the Sponsor of a serious adverse event (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, IRBs/IECs, 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 an 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 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. Pediatric participants will

be required to provide their assent, and participants or their legally authorized representative (defined as a parent or legal guardian for pediatric participants) 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 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 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 Clinical Study Protocol (CSP) and letters to investigators.

A 5.1 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (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. To minimize the potential introduction of bias, DSMB members will not have direct contact with the study site personnel or participants. The frequency of Data Review Meetings will be held in line with the DSMB Charter. Ad hoc meetings will be implemented if required. The DSMB will review safety data on a regular basis as set out in the DSMB Charter. Participant enrollment can continue during DSMB review of safety data. The available safety data for the participants will be evaluated by the DSMB. Safety summaries will be prepared prior to each Data Review 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.

A 5.2 Cardiovascular Event Adjudication Committee

See Section 9.7.

A 6 Dissemination of Clinical Study Data

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 the 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 electronic case report form (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 relevant study plans.

- 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 review and targeted source data verification to ensure 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 CRO(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 adverse event (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

A serious adverse event (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 **SAEs**. 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 intravenous 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

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

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 Appendix B 2. 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 Appendix B 2.

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.

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

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.

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** intercepted before the 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, eg, 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 Interactive Response Technology [IRT]/ Randomization and Trial Supply Management [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
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AstraZeneca product

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 authorised product information, or for unauthorised 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
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- 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 life cycle.

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, and the action is documented, and the 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 alanine aminotransferase (ALT) from a central laboratory **and/or** elevated total bilirubin (TBL) from a local laboratory.

The Investigator will also review adverse event (AE) 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 investigational medicinal product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting serious adverse events (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 ALT) ≥ 3 × upper limit of normal (ULN) **together with** 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

Aspartate aminotransferase 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 electronic case report form (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 Clinical Study Protocol (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 one day of PHL criteria being met, the Investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For participants who met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition.
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participant's 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.
  - 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.

[#]**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.

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 Lead 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 PHL 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 PHL, (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	Gamma glutamyl transpeptidase (GGT) Lactate dehydrogenase (LDH) Prothrombin time International normalized ratio (INR)
Viral hepatitis	Immunoglobulin (Ig)M anti-hepatitis A virus (anti-HAV) Hepatitis B surface antigen (HBsAg) IgM and IgG hepatitis B core antibody (anti-HBc) Hepatitis B virus (HBV) DNA [a] IgG anti-hepatitis C virus (anti-HCV) HCV RNA [b] IgM anti-hepatitis E virus (anti-HEV) HEV RNA
Other viral infections	IgM and IgG anti-cytomegalovirus (anti-CMV) IgM and IgG anti-herpes simplex virus (anti-HSV) IgM and IgG anti- Epstein-Barr virus (anti-EBV)
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-liver/kidney microsomal antibody (anti-LKM) Anti-smooth muscle antibody (ASMA)
Metabolic diseases	Alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin 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.

Appendix E Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following notification from the Sponsor and instructions on how to perform these procedures will be provided at the time of implementation.

Please note that during civil crisis, natural disaster, or public health crisis, some study assessments and procedures may not be conducted due to international or local policies or guidelines, hospital or clinic restrictions and other measures implemented to ensure the participant's safety. If in doubt, please contact the AstraZeneca Study Physician.

E 1 Rescreening of Participants to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened participants. The Investigator should confirm this with the designated study physician prior to any rescreening while study mitigation procedures are in effect.

In addition, during study disruption there may be a delay between confirming eligibility of a participant and either enrollment into the study or commencing of dosing with IP. If this delay is outside the screening window specified in Section 1.3 the participant will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a participant in addition to that detailed in Section 5.4. The procedures detailed in Section 1.3 must be undertaken to confirm eligibility using the same randomization number as for the participant.

E 2 Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified HCP from the study site or TPV service will visit the participant's home or other remote location as per local SOPs, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP.

E 3 Telemedicine Visit or Remote Contact to Replace On-site Visit (where applicable)

In this appendix, the term telemedicine or remote contact visit refers to contact with the participants using telecommunications technology including virtual or video visits (telemedicine visits) or remote contacts via phone calls, text, email, or mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit or remote contact if allowed by local/regional guidelines. Having a telemedicine or remote contact with the participants will allow at a minimum,, monitoring of adverse events, concomitant medication, and if applicable, any visual inspection of post-dose injection site reactions to be reported and documented. If possible, safety procedures and blood sample collection will be performed according to the SoA.

E 4 At-home or Remote Location IP Administration Instructions

If a site visit is not possible, at-home or remote location administration of IP may be performed by a qualified HCP, provided this is acceptable within local regulation/guidance. The option of at-home or remote location IP administration ensures participant's safety in cases of a pandemic where participants may be at increased risk by traveling to the site/clinic. This will also minimize interruption of IP administration during other study disruptions, eg, site closures due to natural disaster.

E 4.1 At-home or Remote Location IP Administration by a Qualified HCP or TPV Service

A qualified HCP from the study site or TPV service should administer the IP at the participant's home or other remote location according to the CSP. All necessary supplies and instructions for administration and documentation of IP administration will be provided. Additional information related to the visit can be obtained via a telemedicine visit, remote contact, or home visit.

E 5 Data Capture During Telemedicine or Home/Remote Visits

Data collected during modified telemedicine/remote contact or home / remote visits will be captured by the qualified HCP from the study site or TPV service.

Appendix F Abbreviations

Abbreviation or special term	Explanation
ACE2	angiotensin-converting enzyme 2
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase/transaminase
AST	aspartate aminotransferase/transaminase
AUC	area under the concentration-time curve
β-hCG	beta-human chorionic gonadotropin
CD4	cluster of differentiation 4
CI	confidence interval
C_{max}	maximum concentration
CoV	Coronavirus
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	cardiovascular
DNA	deoxyribonucleic acid
DP	drug product
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic Case Report Form
EoT	End of Treatment
FSH	follicle-stimulating hormone
FTIH	first-time-in-human
GCP	good clinical practice
GMFR	geometric mean fold rise
GMT	geometric mean titer
GSD	geometric standard deviation
HCP	health care professional
HIV	human immunodeficiency virus

Abbreviation or special term	Explanation
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IL-D*x*	Illness Visit Day *x*
IM	intramuscular
IMP	investigational medicinal product
IRT	interactive response technology
IV	intravenous
mAb	monoclonal antibody
MERS	Middle East Respiratory Syndrome
nAb	neutralizing antibody
NP	nasopharyngeal
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
Q3M	Every 3 months
Q6M	Every 6 months
Q12M	Every 12 months
RBD	receptor binding domain
RNA	ribonucleic acid
RTM	remote telemedicine
RT-PCR	reverse transcriptase polymerase chain reaction
RTSM	randomization and trial supply management
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome-coronavirus 2
SMQ	Standardized Medical Dictionary for Regulatory Activities Queries
SoA	Schedule of Activities
TBL	total bilirubin
TM	telemedicine
TPV	third-party vendor
ULN	upper limit of normal
VLP	virus-like particles
WHO	World Health Organization

Appendix G Protocol Amendment History

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

Version 3.0, 09 December 2022

Key amendment and rationale for change:

Due to the changing nature of the ongoing pandemic, the need for interim analyses, per regulatory/health authority requests, is changing, therefore, the CSP has been amended to allow flexibility around interim analyses.

Other changes have been made to provide clarifications and to maintain consistency within the AZD7442 development program.

Synopsis, Figure 1 (Study Design), Section 9.5 (Interim Analyses): Text has been amended to allow for flexibility around the conduct of interim analyses: *Interim analyses may be conducted to support regulatory requirements or at the discretion of the Sponsor, and will be specified in the statistical analysis plan if applicable.*

Synopsis, Section 9.4.2.1 (Pharmacokinetics): The specification to calculate PK parameters at the primary and final analysis has been removed. The text has been updated to clarify that appropriate PK parameters *may* be calculated.

Section 1.3 (Schedule of Activities): To provide flexibility on targeted physical examinations and a reminder of items to be covered during the monthly contact, footnotes have been added to Tables, 1, 2, 3 and 4.

Section 7.3 (Lost to Follow-up): To provide clarity on when a participant should be considered lost to follow-up, text has been added to confirm that after repeated efforts to contact a participant, those who do not return for their next visit may be considered lost to follow-up.

Section 8.2.1 (Physical Examinations), Tables 1, 2, 3 and 4 (Schedule of Activities): Following feedback from study sites, clarification to the targeted physical examination description has been added.

Section 8.3.4 (Adverse Events of Special Interest): Section has been updated to provide clarification to investigators in the reporting of cardiac and thromboembolic events as AESIs. Clarification has been added to specify which events can be included when reporting cardiac and thromboembolic events as AESIs.

Section 9.3 (Populations for Analyses): The FAS description was incorrectly defined in the original protocol, therefore, to maintain consistency within the AZD7442 development program it has been corrected: All randomized participants who receive at least one dose of IMP. Participants will be assigned according to their randomized treatment *according to the intent-to-treat principle*.

The study includes repeat dosing and, therefore, visit level exclusions are more appropriate, to reflect this the PK analysis set was changed so that participants with protocol violations concerning PK sampling are not excluded.

Corrected typos have not been listed above.

Version 2.0, 08 July 2022

Key amendment and rationale for change:

To support the use of AZD7442 in the ongoing COVID-19 pandemic, there is an urgent requirement for safety, PK, and PD data on repeat dosing with AZD7442. To provide the necessary data an additional data cut is required. To provide data, at this data cut, at approximately 29 days post the second and third doses in Arm A and after the second dose in Arm B additional visits have been added. These visits include assessments for safety monitoring, PK, PD, and ADA. In addition, to support this additional data collection, the IL-D28 and IL-D90 visits have been changed to In-patient visits and a sample for SARS-CoV-2 RT-PCR sequencing respiratory panel will be collected. To support the additional data cut, an interim analysis has been added to occur after at least approximately 75 participants in Arm A, based on study conduct feasibility, have completed the Week 17 (Month 4) visit. To ensure the availability of safety, PK and PD data, the possibility to include an additional interim analysis, once all participants have completed the Week 30 (Month 7) visit, has also been included.

Study mitigation language has been added to provide sites with measures that may be implemented during study disruptions due to cases of civil crisis, natural disaster, or public health crisis to ensure that the clinical trial can continue whilst minimizing risk to the participant, maintaining compliance with GCP, and minimizing risks to the study integrity.

To maintain compliance with the schedule of activities, flexibility has been added so that sites or study participants unable to perform RTM visits can perform the visit in-person. Furthermore, to reduce participant burden, the 18 and 21 month follow-up visits have been amended so that they can be performed as an RTM visit or by telephone.

To monitor long COVID-19, participants with long COVID-19 will be monitored every 3 months until their symptoms resolve.

To remove the risk of alternative COVID-19 mAb treatment affecting nAb assessments the nAb evaluable analysis set has been amended to exclude participants from the applicable analysis at the time they receive an alternative mAb.

Section 1.1 (Synopsis), Section 1.2 (Schema), and Section 9.5 (Interim Analyses): To support the requirement for an additional data cut a description of the interim analyses have been added.

Section 1.3 (Schedule of Activities) Table 1 and Table 2: To Arm A (Table 1), Day 121 and Day 212 visits has been added. To Arm B (Table 2) a Day 212 visit has been added. These new visits include AE and concomitant medication monitoring, targeted physical exam, pregnancy test, vital signs, PK, PD, and ADA assessments. Where applicable, all visits have been updated to allow optional In-person visits when a RTM visit is not possible.

Section 1.3 (Schedule of Activities) Table 3: In Table 3, the 18 month visit has been changed to allow either RTM or telephone contact, and all assessments requiring onsite contact have been removed leaving concomitant medication and AE assessments. The 21 month visit has been changed to either a RTM or telephone visit.

Section 1.3 (Schedule of Activities) Table 4 and Section 8.1.1 (Monitoring COVID-19 Symptoms: In Table 4 visits IL-D28 and IL-D90 changed to site visits and the RTM option removed. To these visits an assessment for symptoms and SARS-CoV-2 RT-PCR sequencing respiratory panel has been included. For participants with Long COVID-19, a 3 monthly symptom assessment has been included. This symptom assessment will continue until the participant's symptoms have resolved or until the end of study.

Section 1.3 (Schedule of Activities) Table 1 and Table 2: Updated to allow In-person visits where RTM visits are not possible. In addition, to increase flexibility for participants, Table 1 and Table 2 have been updated to include, in agreement with the Sponsor, home or mobile visits if required and if operationally feasible.

Section 4.1.1 (Study Conduct Mitigation During Study Disruptions due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis) [New Section] and Appendix E [New Appendix]: New wording added which gives guidance on how the study could continue in the event of a serious disruption with details of mitigation that could be employed to ensure study continuity.

Section 5.2 (Exclusion Criteria): To confirm that participants with prior COVID-19 infection should not be excluded from the study: 'Prior COVID-19 infection is not an exclusion' has been added to exclusion criterion 1.

Section 5.3 (Lifestyle Considerations and Restrictions) and Section 6.5 (Concomitant Therapy) Table 7: Clarification to include contraceptive methods as a permitted therapy.

Section 9.3 (Population for Analyses): The nAb evaluable analysis set has been updated to exclude participants from the analysis if they receive an alternative mAb during the study.

Appendix A7 (Data Quality Assurance): For process clarification, source data verification changed to targeted source data verification.

Due to the addition of appendices numbering has been updated throughout.

Corrected typos have not been listed above.

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Initial version

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