Clinical Study Protocol	
Study Intervention	AZD7442
Study Code	D8850C00008
Version	2.0
Date	27Aug2021

A Phase II Double-blind, Placebo-controlled Study to Evaluate the Safety and Tolerability of AZD7442 in Chinese Adults

Sponsor Name: AstraZeneca AB

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Regulatory Agency Identifier Number(s): 2021L90010; 2021L90011

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: D8850C00008

Amendment Number: 1

Study Intervention: AZD7442, a combination product of 2 monoclonal antibodies (AZD8895 and AZD1061)

Study Phase: Phase II

Short Title: A Phase II Double-blind, Placebo-controlled Study of AZD7442 in Chinese Adults

Study Physician Name and Contact Information will be provided separately

National Coordinating Investigator Name and Contact Information:

PPD

Coordinating Principal Investigator Name and Contact Information:

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1 (CSP version 2.0)	27Aug2021
Original Protocol (CSP version 1.0)]	30Mar2021

AMENDMENT 1 27 AUGUST 2021

Overall Rationale for the Amendment

The primary rationale for this amendment is to revise the inclusion/exclusion criteria to allow enrolment of participants who have previously received a COVID-19 vaccine (excluded if vaccine was administered within 6 months prior to randomisation). Considering the increased COVID-19 vaccination roll-out in China, vaccinated participants will be eligible for the study and are expected to comprise a majority of participants (non-vaccinated participants are expected to be no more than 35% of the study population). According to China Guideline for Clinical Evaluation of COVID-19 Vaccines (Draft), 6 months protection should be provided (NMPA 2020). Therefore, for eligibility in the study, a minimum interval of 6 months between receipt of the COVID-19 vaccine and dosing with AZD7442 is considered adequate to minimise potential complication/interference in PK/PD and safety evaluation of AZD7442. Additional changes were made to incorporate leading site comments, including revisions to PK parameters (primarily formatting) and to add name and contact information for the Coordinating Principal Investigator.

Section number and name	Description of change [a]	Brief rationale for change
Cover page	Added the clinical trial approval number.	Added as approval number is available.
Cover page	Added the name and contact information of Coordinating Principal Investigator.	Updated based on discussion with leading site investigators.
1.1 (Synopsis)	For disclosure statement, updated “treatment study” to “parallel-group safety and tolerability study.”	Updated per sponsor standard wording and clarification.
1.3 (Schedule of Activities)/Table 1 (Schedule of Activities: Screening Period)	Added row to confirm vaccination status (vaccinated or non-vaccinated) for COVID-19 and vaccination dates (if applicable).	Per exclusion criterion 17, participants must not have received COVID-19 vaccine within 6 months prior to randomisation.

Section number and name	Description of change [a]	Brief rationale for change
1.2 (Schema)/Figure 2 (Study Flow Chart) 1.3 (Schedule of Activities)/Table 1 (Schedule of Activities: Screening Period) and Table 2 (Schedule of Activities: Intervention and Follow-up Periods)	Figure 2 (footnote b), Table 1 (footnote c), Table 2 (footnote k): Revised that SARS-CoV-2 qRT-PCR is required within 14 days prior to randomisation, and results from this test must be negative before randomisation. Figure 2 (footnote b), Table 1 (footnote c): Added that non-vaccinated participants with positive SARS-CoV-2 serology should not be randomised.	Footnotes revised to be consistent with the changes to criterion 4 in Section 5.1 (Inclusion Criteria) and criterion 5 in Section 5.2 (Exclusion Criteria).
1.3 (Schedule of Activities)/Table 2 (Schedule of Activities: Intervention and Follow-up Periods)	Table 2 (footnote h): Updated "end of infusion" to "end of infusion, **± 3 minutes**)" (bold indicates added text).	Revised to specify a 3-minute window for end of infusion.
1.3 (Schedule of Activities)/ Table 2 (Schedule of Activities: Intervention and Follow-up Periods)	Table 2 (footnote j): Changed "collected" to "analysed".	Reworded for clarification.
2.2 (Background)	Updated with information on new variants, latest information on pandemic in China as of 26 July 2021, and COVID-19 vaccination estimates in China as of July 2021. Updated information for preliminary data of AZD7442 neutralisation of SARS-CoV-2 variants of concern, variants of interest, and WHO variant alerts.	Updated to reflect most recent information.

Section number and name	Description of change [a]	Brief rationale for change
2.3.2 Benefit Assessment)	Added "In the STORM CHASER trial in adults who had been potentially exposed to a SARS-CoV-2 positive individual, AZD7442 reduced the risk of developing symptomatic COVID-19 by 33% (95% CI: -26, 65) compared to placebo, which was not statistically significant. In a pre-planned analysis of SARS-CoV-2 PCR positive (detectable virus) and PCR negative (no detectable virus) participants, AZD7442 reduced the risk of developing symptomatic COVID-19 by 73% (95% CI: 27, 90) compared with placebo, in participants who were PCR negative at time of dosing (AstraZeneca 2021a). In the PROVENT pre-exposure prophylaxis trial in adults who have increased risk for inadequate response to active immunisation (predicted poor responders to vaccines or intolerant of vaccine) or having increased risk for SARS-CoV-2 infection, AZD7442 reduced the risk of developing symptomatic COVID-19 by 77% (95% CI: 46, 90), compared to placebo (AstraZeneca 2021b)."	Provide updated efficacy data from AstraZeneca press releases for STORMCHASER and PROVENT global Phase 3 studies.
1.1 (Synopsis) 3 (Objectives and Endpoints)	For the primary objective revised to "6 months **after administration**" and for the first secondary objective, revised to "15 months **after administration**" (bold indicates added text).	Updated for clarity.
1.1 (Synopsis) 3 (Objectives and Endpoints) 4.3 (Justification for Dose) 8.5.1.2 (Pharmacokinetic Parameters)	Revised PK parameters, primarily to reformat subscript as regular text. Changes include: • "C_{max}" to "Cmax" • "$AUC_{0\text{-}180days}$" to "AUC(0-180days)" • "AUC_{last}" to "AUClast" • "AUC_{inf}" to "AUCinf" • "$t_{½\lambda z}$" to "t½λz" • "t_{last}" to "tlast" • "V_{ss}" to "Vss" • "$AUC_{0\text{-}60days}$" to "AUC(0-60days)" • "λz, N" to "λzN" • "%AUCextr" to "AUCextr"	Updated the format and definition of PK parameters based on new standard operating procedure.
1.1 (Synopsis) 3 (Objectives and Endpoints) 8.5.1.2 (Pharmacokinetic Parameters)	Added Vz as additional PK parameter in secondary endpoints and the corresponding definition.	Added, as Vz is applicable for IV cohort.

Section number and name	Description of change [a]	Brief rationale for change
3 (Objectives and Endpoints)	Revised SARS-CoV-2 serology exploratory efficacy endpoint from "Participants with post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 antibodies" to "Participants with post-treatment response (negative serology at baseline to positive at post-baseline [up to on-study COVID-19 vaccination, if applicable])"	Revised for clarification that serology data after on-study COVID-19 vaccination will be excluded as both SARS-CoV-2 infection and inactive COVID-19 vaccine can return positive serology result of nucleocapsid antibody.
1.1 Synopsis 4.1 (Overall Design) 6.3 (Measures to Minimise Bias: Randomisation and Blinding)	Revised that randomisation will also be stratified by vaccinated status (vaccinated or non-vaccinated) for COVID-19 at screening and added that non-vaccinated participants are expected to be no more than 35% of the study population.	Due to increased vaccination rates in China, the study design and inclusion/exclusion criteria were modified to allow vaccinated participants in the study. Randomisation will be stratified by vaccinated status as well as age to ensure 3:1 balanced representation of the 2 treatment arms in each of these strata.
4.2 (Scientific Rationale for Study Design)	Added rationale for including participants who have been previously vaccinated for COVID-19 in the study and rationale for requiring that such participants were vaccinated ≥ 6 months prior to randomisation. CCI [redacted]	Due to increasing vaccination rates in China, the study design and inclusion/exclusion criteria were modified to allow vaccinated participants in the study. CCI [redacted]
4.2 (Scientific Rationale for Study Design)	Next to last paragraph: CCI [redacted]	Revised for clarity per site comment.
4.3 (Justification for Dose)	Revised "…the bioavailability of 300 mg IM of AZD7442 (based on the 3-month AUC) was 64.1% and 63% for AZD8895 and AZD1061, respectively" to "…the bioavailability of 300 mg IM of AZD7442 (based on the 271-day AUC) was 68.54% and 65.79% for AZD8895 and AZD1061, respectively."	Updated bioavailability of the AZD7442 300-mg IM dose based on the FTIH Phase 1 interim CSR (D8850C00001).

Section number and name	Description of change [a]	Brief rationale for change
5.1 (Inclusion Criteria)/Criterion 4 5.2 (Exclusion Criteria)/Criterion 5	Inclusion 4: Removed inclusion requirement for negative SARS-CoV-2 serology test result within 14 days prior to randomisation. Exclusion 5: Removed exclusion requirement for positive SARS-CoV-2 serology test result within 14 days prior to randomisation. Added note to clarify that "Participants with any positive SARS-CoV-2 qRT-PCR result based on available data at screening will be excluded. Non-vaccinated participants with any positive SARS-CoV-2 serology result based on available data at screening will be excluded."	Modified the criteria to avoid excluding participants who test positive for SARS-CoV-2 serology due to having previously received COVID-19 vaccination.
5.1 (Inclusion Criteria)/Criterion 6	Revised "Male participants: Contraception for male participants is not required; however, to avoid the transfer of any fluids, all male participants must use..." to "Male participants: To avoid transfer of fluids to a sexual partner, all male participants must use..."	Removed "contraception for male participants is not required" to avoid confusion and to specify the exact purpose of contraception.
5.2 (Exclusion Criteria)/Criterion 6	Revised "on admission" to "randomisation".	Updated for clarity as term "admission" is not applicable in this study.
5.2 (Exclusion Criteria)/Criteria 16 and 17	Criterion 16: Revised from "Any prior receipt of an investigational or licensed vaccine or other mAb/biologic indicated for the prevention of SARS-CoV-2 or scheduled receipt" to "Any prior receipt of an investigational or licensed mAb/biologic indicated for the prevention of SARS-CoV-2 or COVID-19 or scheduled to receive any investigational or licensed mAb/biologic indicated for the prevention of SARS-CoV-2 or COVID-19." Criterion 17: Added exclusion for "Receipt of any COVID-19 vaccine within 6 months prior to randomisation or scheduled to receive any COVID-19 vaccine."	Revised to remove exclusion for prior receipt of COVID-19 vaccine. Considering increased roll-out of COVID-19 vaccine in China, only participants who have received COVID-19 vaccine within 6 months prior to randomisation will be excluded from the study. At least 6 months are required between receipt of the COVID-19 vaccine and dosing with AZD7442 to minimise potential complication/interference in PK/PD and safety evaluation of AZD7442.

Section number and name	Description of change [a]	Brief rationale for change
5.4 (Screen Failures)	Revised from "Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Only one time rescreening is allowed in the study under exclusion criterion 3 (see criterion 3 of Section 5.2 for the details)" to "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."	Revised to not restrict rescreening to exclusion 3 and to allow a single rescreening if the eligibility criterion that resulted in a screen failure has changed in a manner that meets eligibility.
6.1.1 (Investigational Products)/Table 5 (Investigational Medicinal Products)	Updated the Sourcing and Packaging and Labelling for placebo to "Provided locally by the study site **or by the sponsor**" (bold indicates added text).	To clarify the sourcing and packaging for placebo might be done by sponsor if cannot be provided by site.
6.2.1 (Storage and Accountability)	Revised number 4 to "… are provided in the Investigational Medicinal Product Manual **or other equivalent documents**" (bold indicates added text).	Reworded as relevant information might be included in other documents and named differently.
6.2.2 (Preparation and Administration)	Changed from "…for both AZD8895 and AZD1061 infusion." to "…for both AZD8895 and AZD1061 infusion **and placebo infusion**" (bold indicated added text). In step 3: revised text to "**Use a coloured shading bag or** attach labels and cover to the IV bags in order to ensure blinding" (bold indicates added text). Revised "3.0 mL" to "3 mL" throughout and revised "6.0 mL" to "6 mL".	Reworded for clarification and updated specification in blinding step.
6.5.1 (COVID-19 Vaccines)	In third bullet, revised "…the number of months identified above for each dose represents…" to "…the number of months identified above for the dose represents…"	Updated for clarity as there is only one dose.
8.1.1 CCI [redacted])	Added Table 8 "COVID-19 Qualifying Symptoms"	Added the table to support evaluation and diagnosis for COVID-19 monitoring.
8.1.2 CCI [redacted] 8.5.2 (Pharmacodynamics)	Revised first sentence in Section 8.1.2 and first bullet in Section 8.5.2 to "…and **will be analysed** provided the analysis method is established and appropriate approval has been obtained" (bold indicates added text).	Reworded for clarity.

Section number and name	Description of change [a]	Brief rationale for change
8.2.1 (Physical Examinations)	Added cross-reference to Section 8.3.6.for AE reporting regarding physical examination. Revised "site-directed physical exam" to "symptom-directed physical examination".	Updated language for clarification and to avoid confusion regarding physical examination and AE reporting.
8.2.4 (Clinical Safety Laboratory Assessments)	Third paragraph: Revised to "…and samples for SARS-CoV-2 serology **(at screening)** and SARS-CoV-2 qRT-PCR will be performed at a local laboratory **at or near the investigational site**" (bold indicates added text).	Updated for clarity. SARS-CoV-2 serology test at screening is performed locally and if site does not have feasibility to perform the test, results from local laboratory at or near the investigational site are acceptable.
8.2.4 (Clinical Safety Laboratory Assessments)	Table 9 (Haematology, Serum Clinical Chemistry, Urinalysis, and Coagulation): Updated "Urea" to "Urea/blood urea nitrogen (BUN)". Table 11 (Viral Serology Testing): Revised "HIV antigen Antibody" to "HIV".	Updated based on local laboratory practice at sites in China.
8.3.6 (Adverse Events Based on Examinations and Tests)	Added "Abnormal results of examination and tests at screening (eg, haematology, clinical chemistry, urinalysis, ECG, physical examination, vital signs, etc.) are regarded as existing conditions before ICF and will not be recorded as AE. Relevant clinically significant abnormality of examination and tests during screening can be recorded as medical history according to investigator's medical judgment."	Added to clarify AE reporting requirement at screening as per clinical practice and discussion with site.
8.5 (Human Biological Samples)	Updated "Additional use includes but not limited to further characterisation of any ADAs…" to "Additional use includes further characterisation of any ADAs…"	Reworded to be more specific on additional use as per HGR requirement.
8.5.1.2 (Pharmacokinetic Parameters)	Revised first sentence to "Where possible, the PK parameters will be estimated for AZD7442 (each mAb: AZD8895 and AZD1061) **based** on serum concentrations" (bold indicates added text).	Editorial update.
8.5.1.2 (Pharmacokinetic Parameters)	Removed the sentence "Dose normalised Cmax, AUCinf, and AUClast will be calculated for each mAb: AZD8895 and AZD1061."	As there is only one dose evaluated in the study, dose normalised parameters are not needed.
8.5.1.2 (Pharmacokinetic Parameters)	Updated "actual elapsed times" to "actual times after dose".	Reworded to clarify and to avoid misunderstanding.

Section number and name	Description of change [a]	Brief rationale for change
1.1 (Synopsis), 9.2 (Sample Size Determination)	Moved the sentence "A dropout rate of 20% is assumed" to the end of the paragraph. Revised to 162 participants (previously 204 participants) in the AZD7442 group will provide a probability of at least 80% to observe at least one AE case.	Revised to clarify that sample size of 162 participants is before adjusting for the 20% dropout rate.
9.3 (Populations for Analyses)	Enrolled: Revised "Enrolled" analysis set to "All participants" analysis set. PK analysis set: Revised "evaluable" to "quantifiable" and "PK data" to "PK observation post-dose". PD analysis set: Revised "have evaluable SARS-CoV-2 neutralising responses" to "had at least one quantifiable titre observation post-dose".	Editorial changes for clarification.
9.4.3.1 (Primary Endpoint(s))	Revised "any AEs with outcome of death" to "any SAE with outcome of death"; revised "AEs leading to study withdrawal" to "other AE categories as appropriate". Revised text from "Summaries will be provided taking into consideration the relationship as assessed by the investigator, maximum intensity, seriousness, death, AEs leading to study withdrawal, and AESIs where appropriate.…An additional table will present the number and percentage of participants with the most common AEs. Most common AEs will be defined in the SAP" to "Summaries may be provided for AEs, SAEs, SAEs with outcome of death, AESIs, and other AE categories as appropriate. Additional summaries will be provided taking into consideration the relationship as assessed by the investigator as well as maximum intensity."	Editorial changes to simplify the section.
9.4.4 (Pharmacokinetic Analyses)	Removed "by dose regimen" in first sentence.	Removed for clarity as there is only one dose.
9.4.5 (Pharmacodynamic Analyses)	Revised "The serum neutralising responses…" to "All available data of serum neutralising responses…"	Revised to clarify that all available data of serum neutralising responses will be summarised.
Appendix E (Abbreviations)	Updated to include additional abbreviations.	Editorial updates in accordance with the updates in CSP body text.

Section number and name	Description of change [a]	Brief rationale for change
11 (References)	Updated Gonçalves et al 2020 to "CPT Pharmacometrics Syst Pharmacol. 2020;9(9):509-14." Added references for AstraZeneca STORM CHASER and PROVENT press releases. Added NHC 2021 and NMPC reference.	Update and add references in accordance with the updates in CSP body text.

[a] All changes are considered as non-substantial.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title

A Phase II Double-blind, Placebo-controlled Study to Evaluate the Safety and Tolerability of AZD7442 in Chinese Adults

Short Title

A Phase II Double-blind, Placebo-controlled Study of AZD7442 in Chinese Adults

Rationale

CCI [redacted] AZD7442 is currently being evaluated for administration to prevent and treat coronavirus disease 2019 (COVID-19) in global late stage studies. This Phase II study will gather additional safety and tolerability data of AZD7442 in the Chinese population.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of a single dose of 600 mg AZD7442 administered IV to Chinese participants (including those with stable medical conditions) ≥PPD of age at 6 months after administration	• AEs, SAEs, AESIs, safety laboratory parameters (haematology, clinical chemistry, coagulation, and urinalysis); 12-lead ECG; vital signs (blood pressure, pulse rate, body temperature, and respiratory rate)
Secondary	
• To evaluate the safety and tolerability of a single dose of 600 mg AZD7442 administered IV to Chinese participants (including those with stable medical conditions) ≥PPD of age at 15 months after administration	• AEs, SAEs, AESIs, safety laboratory parameters (haematology, clinical chemistry, coagulation, and urinalysis); 12-lead ECG; vital signs (blood pressure, pulse rate, body temperature, and respiratory rate)
• To evaluate the serum PK of AZD8895 and AZD1061 after a single dose of 600 mg AZD7442 administered IV	Where possible, PK parameters will be assessed for individual mAbs (AZD8895 and AZD1061): • Cmax, AUC(0-180days) • Additional PK parameters that may be determined when appropriate include: ° AUClast, AUCinf, t½λz, tlast, Vss, Vz, and CL

Objectives	Endpoints
• To evaluate the ADA responses to AZD7442 in serum	• Presence of ADA to AZD8895 and AZD1061 in serum Blood samples will be collected and stored for analysis of ADAs. Unscheduled samples for ADA analysis may be collected in response to suspected immune-related AEs.

ADA, antidrug antibody; AE, adverse event; AESI, adverse event of special interest; AUC(0-180days), area under the concentration-time curve from time zero to 180 days; AUCinf, area under the concentration-time curve from time zero to infinity; AUClast, area under the concentration-time curve from time zero to time of last measurable concentration; CL, clearance; Cmax, maximum concentration; ECG, electrocardiogram; IV, intravenous; mAb, monoclonal antibody; PK, pharmacokinetics; SAE, serious adverse event; t½λz, terminal elimination half-life, estimated as (ln2)/λz; tlast, time of last quantifiable concentration; Vss, volume of distribution at steady state; Vz, volume of distribution based on terminal phase.

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

Overall Design

This is a Phase II, randomised, double-blind, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of AZD7442 in Chinese adult participants ≥PPD of age, including healthy participants as well as participants with stable medical conditions. The study will be conducted in clinical study centres in mainland China.

Approximately 272 participants, who fulfil the study eligibility criteria will be randomised in a 3:1 ratio to receive a single dose of study intervention administered by intravenous (IV) infusion, either 600 mg AZD7442 (204 participants) or placebo (68 participants). Randomisation will be stratified by CCI [redacted] at screening. Considering the increased vaccination roll-out in China, non-vaccinated participants are expected to be no more than 35% of the study population.

Participants will then be monitored for approximately 15 months after dosing (through Day 451) for safety, including the recording of adverse events (AEs), AEs of special interest, and serious AEs, and the collection of blood samples for PK, PD, and antidrug antibodies.

Disclosure Statement

This is a parallel-group safety and tolerability study with 2 arms that is participant- and investigator-blinded.

Number of Participants

Approximately 272 participants will be randomised 3:1 to study intervention with 600 mg AZD7442 (n = 204) or placebo (n = 68) administered IV. If the true AE rate is 1% at the primary time point (ie, Month 6), 162 participants in the AZD7442 group will provide a

probability of at least 80% to observe at least one AE case. A dropout rate of 20% is assumed.

The 1% assumption is driven by the international convention where 1% is used as the lower limit of common AEs (between infrequent and frequent AEs) (CIOMS 1999). The randomisation ratio of 3:1 limits the number of participants in the placebo group so that adequate information can be obtained to objectively assess the safety of AZD7442 in the Chinese population.

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

Intervention Groups and Duration

The study is expected to be approximately 479 days in duration for each participant, consisting of a screening period of up to 28 days (Days -28 through -1), an intervention period of one day (Day 1 [randomisation and dosing]), and a safety follow-up period of 450 days (Days 2 through 451).

On Day 1, participants will receive a single dose of study intervention (AZD7442 or placebo) according to their randomised treatment assignment. The study intervention will be co-administered as a single IV infusion containing both mAbs (AZD8895 and AZD1061)/placebo.

Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will provide oversight, to ensure safe and ethical conduct of the study. The DSMB will have the responsibility of evaluating cumulative safety and other clinical trial data at regular intervals and making appropriate recommendations based on the available data.

Statistical Methods

Unless otherwise stated, the as-treated principle will be applied to study evaluations, which is participants who received study intervention other than the one assigned by randomisation will be analysed as belonging to the actual intervention received.

No statistical hypotheses will be evaluated based on formal statistical tests. Descriptive statistics will be presented for relevant data and parameters. See Section 9 of the protocol for further details.

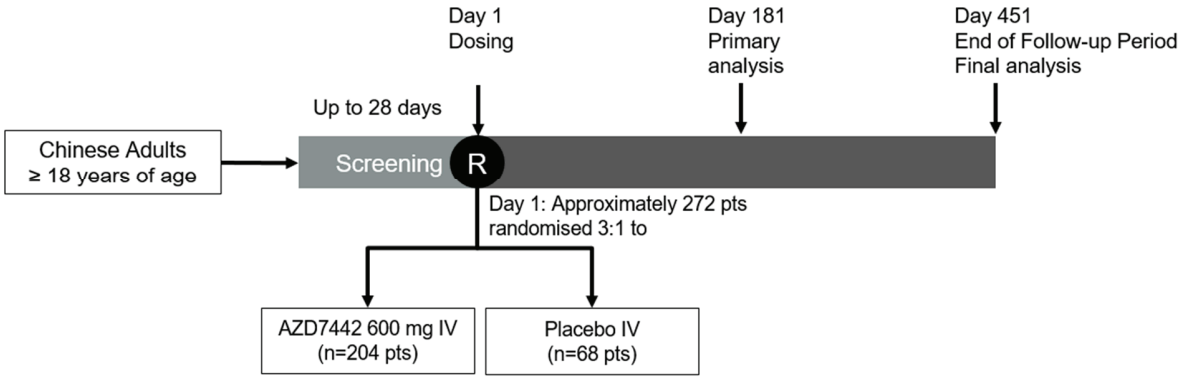
The primary database lock (DBL) will occur after all treated participants have completed follow-up through Day 181 to conduct the primary analysis. No early stopping decision will

be made for futility or superiority at the primary analysis. A final DBL will occur when all participants have completed the study (ie, completed follow-up through Day 451) to conduct the final analysis. As safety evaluation is the primary objective and no multiplicity control is applied, ad-hoc interim analyses may be performed for additional evaluation of a potential signal in the safety profile.

1.2 Schema

The overall study design is presented in Figure 1. The study flow chart is presented in Figure 2.

Figure 1 Study Design



IV, intravenous; pt, participant; R, randomisation.

Figure 2 Study Flow Chart

[a] Visit 1 may be conducted over one or more days during the screening period.
[b] Participants must be tested for SARS-CoV-2 infection by qRT-PCR within 14 days prior to randomisation, and results must be negative before randomisation. Additionally, non-vaccinated participants with positive SARS-CoV-2 serology should not be randomised.
[c] On-site visits during follow-up occur from Day 8 (Visit 3) through Day 361 (Visit 9). On Day 451, participants will be contacted by phone for safety follow-up.

IV, intravenous; qRT-PCR, quantitative reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

1.3 Schedule of Activities

The Schedule of Activities (SoA) for the study is presented in the following tables:

- Screening period: Table 1
- Intervention and follow-up periods: Table 2

Table 1 Schedule of Activities: Screening Period

Study period	Screening	Details in section of CSP
Visit	**Visit 1**	
Procedure	**Day -28 to Day -1**	
Written informed consent/assignment of enrolment code	X	5.1, Appendix A 3
Medical history and demographics	X	5.1, 5.2
Full physical examination, height, weight, and BMI	X	5.1, 8.2.1
12-Lead ECG	X	5.1, 8.2.3
Vital signs [a]	X	5.1, 8.2.2
Serum chemistry	X	5.1, 5.2, 8.2.4
Haematology	X	5.1, 5.2, 8.2.4
Coagulation	X	5.1, 5.2, 8.2.4
FSH (suspected postmenopausal women < 50 years only)	X	5.1, 5.2, 8.2.4
Urinalysis	X	5.1, 5.2, 8.2.4
Pregnancy test (serum β-hCG); FOCBP only [b]	X	5.1, 5.2, 8.2.4, 8.3.9, 8.3.9.1
HIV, hepatitis B, hepatitis C testing	X	5.2, 8.2.4
History of drug and alcohol abuse	X	5.2
Assessment of AEs/SAEs	X	5.2, 8.3
Concomitant therapies	X	5.2, 6.5
Confirm vaccination status (vaccinated or non-vaccinated) for COVID-19 and vaccination dates (if applicable)	X	5.2
SARS-CoV-2 serology and qRT-PCR [c]	X	5.1, 5.2, 8.2.4
Monitoring for COVID-19 symptoms and exposure history [d]	X	5.1, 8.1.1
Verify eligibility criteria	X	5.1, 5.2

[a] The following variables will be collected after the participants have rested in the supine position for at least 5 minutes: Systolic BP, diastolic BP, pulse rate, body temperature, and respiratory rate.

[b] Pregnancy test must be negative at screening.

[c] Participants must be tested for SARS-CoV-2 infection by qRT-PCR within 14 days prior to randomisation, and results must be negative before randomisation. Additionally, non-vaccinated participants with positive SARS-CoV-2 serology should not be randomised.

[d] A negative SARS-CoV-2 qRT-PCR retest result is required if participant has symptoms of infection or if participant has any known/suspected exposure after the initial test.

AE, adverse event; β-hCG, beta human chorionic gonadotropin; BMI, body mass index; BP, blood pressure; COVID-19, corona virus disease 2019; CSP, clinical study protocol; ECG, electrocardiogram; FOCBP, females of childbearing potential; FSH, follicle stimulating hormone; HIV, human immunodeficiency virus; qRT-PCR, quantitative reverse transcriptase polymerase chain reaction; SAE, serious adverse event.

Table 2 Schedule of Activities: Intervention and Follow-up Periods

Study period	**Intervention**		**Follow-up**											**Details in section of CSP**
Study visit	**V2**		**V3**	**V4**	**V5**	**V6**	**TPV [a]**	**V7**	**TPV [a]**	**V8**	**TPV [a]**	**V9/EDV**	**TPV [a]**	
Study day	**D1 pre-dose**	**D1 post-dose**	**D8**	**D31**	**D61**	**D91**	**D121 D151**	**D181**	**D211 D241**	**D271**	**D301 D331**	**D361**	**D451**	
Procedure / visit window			**-1d**	**-2d**	**± 5d**	**± 5d**	**± 10d**	**± 5d**	**± 10d**	**± 10d**	**± 10d**	**± 10d**	**± 10d**	
Medical history	X [b]													5.1, 5.2
Brief physical examination	X [b]													8.2.1
Full physical examination			X	X				X				X		8.2.1
Weight	X											X		8.2.1
12-lead ECG [c]				X				X				X		8.2.3
Vital signs	X [d]	X [d]	X [e]	X [e]	X [e]	X [e]		X [e]		X [e]		X [e]		8.2.2
Serum chemistry	X		X	X				X				X		8.2.4
Haematology	X		X	X				X				X		8.2.4
Coagulation	X		X	X				X				X		8.2.4
Urinalysis	X		X	X				X				X		8.2.4
Pregnancy test (urine hCG); FOCBP only	X [f]			X	X	X		X		X		X		8.2.4, 8.3.9.1
PK serum sample	X [g]	X [h]	X [i]	X [i]	X [i]	X [i]		X [i]		X [i]		X [i]		8.5.1
ADA serum sample	X [g]			X		X		X				X		8.5.3
Neutralising antibody serum sample [j]	X [g]		X	X	X	X		X		X		X		8.5.2

Table 2 Schedule of Activities: Intervention and Follow-up Periods

Study period	**Intervention**		**Follow-up**											**Details in section of CSP**
Study visit	**V2**		**V3**	**V4**	**V5**	**V6**	**TPV [a]**	**V7**	**TPV [a]**	**V8**	**TPV [a]**	**V9/EDV**	**TPV [a]**	
Study day	**D1 pre-dose**	**D1 post-dose**	**D8**	**D31**	**D61**	**D91**	**D121 D151**	**D181**	**D211 D241**	**D271**	**D301 D331**	**D361**	**D451**	
Procedure / visit window			**-1d**	**-2d**	**± 5d**	**± 5d**	**± 10d**	**± 5d**	**± 10d**	**± 10d**	**± 10d**	**± 10d**	**± 10d**	
Serum sample for SARS-CoV-2 serology central testing [j]	X [g]							X				X		8.1.2
Assessment of AEs/SAEs	X (ongoing observation and questioning)												X	8.3
Concomitant therapies	X (ongoing observation and questioning)												X	6.5
Monitoring for COVID-19 symptoms and exposure history	X [k]		X (ongoing observation and questioning) [l]											8.1.1
SARS-CoV-2 qRT-PCR [k, l]	If clinically indicated													8.1.1, 8.2.4
Verify eligibility criteria	X													5.1, 5.2
Randomisation [k]	X													4.1, 6.3
Study intervention administration	**X**													6.1.1, 6.2.2

[a] Telephone contact for safety monitoring.
[b] Update screening medical history and physical examination (any new findings since screening).
[c] ECGs will be obtained after at least 5 minutes supine rest.

[d] On Day 1, vital signs (systolic BP, diastolic BP, pulse rate, body temperature, and respiratory rate) will be monitored before and after administration of study intervention. Time points will include pre-dose (up to 120 minutes prior to start of infusion), completion of infusion (0-~ 5 minutes), 30 (± 5) minutes, 60 (± 5) minutes, 90 (± 5) minutes, and 120 (± 5) minutes post completion of infusion.

[e] Any abnormal vital signs must be repeated after the participant has been at rest for at least 5 minutes.

[f] Pregnancy test must be negative prior to randomisation.

[g] Pre-dose sample (up to 90 minutes prior to start of infusion).

[h] PK serum sample should be collected when the infusion is complete (end of infusion, ± 3 minutes). The actual end time of infusion completion (duration of infusion) should be recorded.

[i] PK serum samples will not be collected once a participant is unblinded and found to be on placebo arm.

[j] Serum sample for neutralising antibody and serum sample for SARs-CoV-2 serology will only be analysed if the analysis method is established and appropriate approval has been obtained.

[k] Participants must be tested for SARS-CoV-2 infection by qRT-PCR within 14 days prior to randomisation, and results must be negative before randomisation. A negative SARS-CoV-2 qRT-PCR and serology retest result is required if participant has symptoms of infection or if participant has any known/suspected exposure after the initial test.

[l] After Day 1, if participant has symptoms of infection or if participant has any known/suspected exposure, SARS-CoV-2 qRT-PCR should be performed at the discretion of the investigator.

AE, adverse event; ADA, antidrug antibodies; BP, blood pressure; COVID-19, coronavirus disease 2019; CSP, clinical study protocol; D/d, day; ECG, electrocardiogram; EDV, early discontinuation visit; FOCBP, females of childbearing potential; hCG, human chorionic gonadotropin; PK, pharmacokinetic(s); qRT-PCR, quantitative reverse transcriptase polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TPV, telephone visit; V, visit.

1.3.1 Order of Assessments

It is important that PK sampling occurs as closely as possible to the scheduled time. To achieve this, other assessments scheduled at the same time will be initiated prior to/following the PK time point. The sequence at a particular time point is:

1 12-lead safety ECGs
2 Vital signs (systolic and diastolic blood pressure, pulse rate, body temperature, and respiratory rate)
3 PK and safety blood samples (will be collected at the specified time point)
4 Other procedures

2 INTRODUCTION

AZD7442 is a combination of 2 recombinant human IgG1 kappa mAbs, AZD8895 and AZD1061, directed against the RBD of the spike protein of SARS-CoV-2. AZD7442 is being developed for the prophylaxis and treatment of COVID-19.

2.1 Study Rationale

AZD7442 is currently being evaluated for administration to prevent and treat COVID-19 in global late-stage studies. This Phase II study will gather additional safety and tolerability data of AZD7442 in the Chinese population.

2.2 Background

SARS-CoV-2 is a newly emerged CoV responsible for the current COVID-19 global pandemic. The SARS-CoV-2 spike protein contains the virus's RBD, which enables the virus to bind to receptors on human cells. Unlike the majority of CoVs that cause mild disease in humans and animals, SARS-CoV-2 can replicate in the lower respiratory tract to cause acute respiratory distress syndrome and fatal pneumonia. 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). With a basic R_0 value estimated between 2.43 to 3.10, SARS-CoV-2 is highly transmissible from person to person, which has contributed to its rapid dissemination worldwide (D'Arienzo and Coniglio 2020). As of 15 August 2021, there have been approximately 206 million confirmed cases of COVID-19, including approximately 4.4 million deaths, reported to the World Health Organisation (WHO 2021).

Several variants have been identified, such as B.1.1.7 (Alpha), B.1.351 (Beta), B.1.617.2 (Delta), and P.1 (Gamma), which are classified as variants of concern (WHO 2021, US CDC 2021). These variants contain multiple spike protein mutations and mutations in other genomic regions. While it is known and expected that viruses constantly change through mutation leading to the emergence of new variants, preliminary analysis in the UK suggests that variant B.1.1.7 is significantly more transmissible than previously circulating variants, with an estimated potential to increase the R_0 by 0.4 or greater with an estimated increased transmissibility of up to 70% (WHO 2021, ECDC 2020). Variant B.1.1.7 has been detected in 190 countries including China (WHO 2021).

To date, the COVID-19 pandemic is under control in China with approximately 767 cases between 09 to15 August 2021, which includes imported cases and clusters of new cases in several cities (WHO 2021). With the emergence of new variants, there are risks to the new imported cases spreading due to their high transmissibility. Strict preventative measures to control local transmission and transmission from imported cases are in place to prevent spreading. However, the strict preventative measures require constant vigilance and expend

significant resources throughout China. The China border is currently open to allow international travel with restrictions (eg, China residency or work permits), and it is anticipated that, eventually, such restrictions will be lifted. Thus, efficacious and safe options for prophylaxis and treatment of COVID-19 are needed to mitigate the risks of uncontrolled spreading and future outbreaks due to international travel.

To bring this COVID-19 pandemic to an end, vaccines are developed and provided for people worldwide. Overall, more than 1.5 billion vaccines have been administered in China by July 2021 (NHC 2021).

Effective interventions to treat and prevent COVID-19 remain few in number and clinical experience is limited. Current clinical management is primarily limited to supportive care. Under these clinical circumstances, there is a high need for drugs that can be used from before or during the SARS-CoV-2 infection to prevent severe illness. High-risk populations (pre-exposure prevention) and people who may have been in close contact with those confirmed to have SARS-CoV-2 infection may benefit from prophylactics due to the rapid onset of preventive effect by eradicating the viral load earlier than accomplished by the innate and acquired immune responses.

AZD7442 is a combination of 2 mAbs (AZD8895 and AZD1061), with distinct binding sites, directed CCI [redacted]. The use of 2 mAbs provides redundancy in protection in case of virus mutation and escape. Preliminary data have been generated demonstrating that AZD7442 neutralises SARS-CoV-2 variants of concern (Alpha, B.1.1.7; Beta, B.1.351; Gamma, P.1; and Delta, B.1.617.2), variants of interest (Eta, B.1.525; Iota, B.1.526; Kappa, B.1.617.1; and Lambda, C.37), and several WHO variant alerts for further monitoring (Epsilon, B.1.427 / B.1.429; Zeta, P.2; R.1; and B.1.1.519) in live virus and/or pseudovirus neutralisation assays. AZD8895 and AZD1061 mAbs have been engineered with triple amino acid substitutions (YTE) in the Fc region to prolong the half-life, which is expected to provide protection from COVID-19 for a duration of at least 5 months. An additional triple amino acid substitution (TM) in the Fc region was engineered for both AZD8895 and AZD1061 to reduce Fc-mediated effector function, which is expected to reduce theoretical risk of antibody-dependent enhancement of disease.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD7442 is provided in the Investigator's Brochure.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of AZD7442 may be found in the Investigator's Brochure.

2.3.1 Risk Assessment

There are no identified risks associated with AZD7442. No observations are considered to represent expected adverse reactions that would form part of an emerging safety profile.

As of the data cut-off date of 27 November 2020 (Investigator's Brochure edition 4.0), a total of 60 healthy adult participants from the UK had been randomised into 5 cohorts and received a single dose of AZD7442 (10 participants per cohort) or placebo (2 participants per cohort) in the FTIH Phase I dose-escalation study (D8850C00001): 300 mg IM (mAbs administered as separate injections), 300 mg IV, 1000 mg IV, and 3000 mg IV (mAbs administered as separate infusions), and 3000 mg IV (mAbs co-administered in a single infusion).

- There were no deaths, SAEs, or discontinuations of the study intervention due to AEs in any participant.
- All AEs reported were mild in intensity, with the exception of the following events of moderate intensity: urinary tract infection (1 participant; 300 mg IM); headache and malaise (1 participant each; 300 mg IV), dysmenorrhea, headache, and toothache (1 participant each; 1000 mg IV), headache, back pain, and arthralgia (1 participant each; 3000 mg IV).
- There were no haematology, clinical chemistry, or vital signs findings of concern in any participant.
- No safety signals in this healthy adult population were observed. These results demonstrated an acceptable safety profile for AZD7442, including no observed infusion-related reactions (IV cohorts), injection site reactions (IM cohort), or hypersensitivity reactions, and support the use of AZD7442 in further clinical studies.

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

Potential risks are associated with the administration of any Ig, including polyclonal Ig preparations and mAbs.

The important potential risks associated with the administration of Ig, include, but are not limited to, anaphylaxis and other serious hypersensitivity reactions including immune complex disease.

Other potential risks include, but are not limited to, injection site reactions, infusion-related reactions, and ADE disease.

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

exist:

- ADE, which involves increased binding efficiency of virus-antibody complexes to Fc receptor bearing cells and which triggers virus entry. The mAbs in AZD7442 have been designed with a modification to prevent binding to cellular Fc receptors, so the risk of ADE occurring via this mechanism should range from very low to none.
- Vaccine-associated enhanced respiratory disease, which is a distinct clinical syndrome that occurred in young children in the 1960s when whole inactivated virus vaccines for measles and RSV were tested.

Immunising with limiting doses of RSV antigen, especially with conformationally incorrect antigens, can result in 2 major types of immunological phenomena:

- A relatively high ratio of antibody that binds, but does not neutralise, the virus could potentially result in immunogenic cell death and complement activation (leading to inflammation and airway obstruction)
- Immunisation with whole inactivated virus vaccines can result in allergic inflammation characterised by, eg, increased mucus production, airway hyperresponsiveness, and attenuated cytolytic T cell activity (T helper 2 cell immune response). This mechanism, induced by vaccines, should not be provoked by mAbs.

2.3.2 Benefit Assessment

Recipients of AZD7442 do not have any guaranteed benefit; however, AZD7442 may be efficacious and offer participants protection from COVID-19.

In the STORM CHASER trial in adults who had been potentially exposed to a SARS-CoV-2 positive individual, AZD7442 reduced the risk of developing symptomatic COVID-19 by 33% (95% CI: -26, 65) compared to placebo, which was not statistically significant. In a pre-planned analysis of SARS-CoV-2 PCR positive (detectable virus) and PCR negative (no detectable virus) participants, AZD7442 reduced the risk of developing symptomatic COVID-19 by 73% (95% CI: 27, 90) compared with placebo, in participants who were PCR negative at time of dosing (AstraZeneca 2021a).

In the PROVENT pre-exposure prophylaxis trial in adults who have increased risk for inadequate response to active immunisation (predicted poor responders to vaccines or intolerant of vaccine) or having increased risk for SARS-CoV-2 infection, AZD7442 reduced the risk of developing symptomatic COVID-19 by 77% (95% CI: 46, 90), compared to placebo (AstraZeneca 2021b).

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimise 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 at risk of COVID-19.

3 OBJECTIVES AND ENDPOINTS

The objectives and endpoints for the study are presented in Table 3.

Table 3 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of a single dose of 600 mg AZD7442 administered IV to Chinese participants (including those with stable medical conditions) ≥PPD of age at 6 months after administration	• AEs, SAEs, AESIs, safety laboratory parameters (haematology, clinical chemistry, coagulation, and urinalysis); 12-lead ECG; vital signs (blood pressure, pulse rate, body temperature, and respiratory rate)
Secondary	
• To evaluate the safety and tolerability of a single dose of 600 mg AZD7442 administered IV to Chinese participants (including those with stable medical conditions) ≥PPD of age at 15 months after administration	• AEs, SAEs, AESIs, safety laboratory parameters (haematology, clinical chemistry, coagulation, and urinalysis); 12-lead ECG; vital signs (blood pressure, pulse rate, body temperature, and respiratory rate)
• To evaluate the serum PK of AZD8895 and AZD1061 after a single dose of 600 mg AZD7442 administered IV	Where possible, PK parameters will be assessed for individual mAbs (AZD8895 and AZD1061): • Cmax, AUC(0-180days) • Additional PK parameters that may be determined when appropriate include: ° AUClast, AUCinf, t½λz, tlast, Vss, Vz, and CL
• To evaluate the ADA responses to AZD7442 in serum	• Presence of ADA to AZD8895 and AZD1061 in serum Blood samples will be collected and stored for analysis of ADAs. Unscheduled samples for ADA analysis may be collected in response to suspected immune-related AEs.
Exploratory [a]	
• CCI	• CCI
• CCI	• CCI
• CCI	• CCI • CCI

[a] Results may be reported separately from the clinical study report.

ADA, antidrug antibody; AE, adverse event; AESI, adverse event of special interest; AUC(0-180days), area under the concentration-time curve from time zero to 180 days; AUCinf, area under the concentration-time curve from time zero to infinity; AUClast, area under the concentration-time curve from time zero to time of last measurable concentration; CL, clearance; COVID-19, coronavirus disease 2019; Cmax, maximum concentration; ECG, electrocardiogram; IV, intravenous; mAb, monoclonal antibody; PK, pharmacokinetics; qRT-PCR, quantitative reverse transcriptase polymerase chain reaction; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; t½λz, terminal elimination half-life, estimated as (ln2)/λz; tlast, time of last quantifiable concentration; Vss, volume of distribution at steady state; Vz, volume of distribution based on terminal phase.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase II, randomised, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK, and PD of AZD7442 in Chinese adult participants ≥PPD of age, including healthy participants as well as participants with stable medical conditions. The study will be conducted in clinical study centres in mainland China.

The study is expected to be approximately 479 days in duration for each participant, consisting of a screening period of up to 28 days (Days -28 through -1), an intervention period of one day (Day 1 [randomisation and dosing]), and a safety follow-up period of 450 days (Days 2 through 451). The overall study design is presented in Figure 1. The study flow chart is presented in Figure 2.

Approximately 272 participants who fulfil the study eligibility criteria (Sections 5.1 and 5.2) will be randomised in a 3:1 ratio to receive a single dose of study intervention administered IV, either 600 mg AZD7442 (204 participants) or placebo (68 participants). Randomisation will be stratified by CCI [redacted] at screening. Considering the increased vaccination roll-out in China, non-vaccinated participants are expected to be no more than 35% of the study population.

The study intervention will be co-administered as a single IV infusion containing both mAbs (AZD8895 and AZD1061)/placebo (see Sections 6.1.1 and 6.2 for additional details). Participants will then be monitored for approximately 15 months after dosing (through Day 451) for safety, including the recording of AEs, AESIs, and SAEs, and the collection of blood samples for PK, PD, and ADAs.

There will be 2 DBLs during the study (see Section 9 for additional details):

- The primary DBL will occur after all treated participants have completed follow-up through Day 181 for the primary analysis.

- The final DBL will occur after all treated participants have completed the study, ie, have completed follow-up through Day 451 for the final analysis.

As no multiplicity control is applied, ad-hoc interim analyses may be performed, if warranted, for additional evaluation of a potential signal in the safety profile.

As the study will very likely take place during the COVID-19 pandemic, measures will be put in place to ensure minimal SARS-CoV-2 exposure for site staff as well as study participants. Exclusion and withdrawal criteria are in place to ensure site staff and study participant safety, and participants will be monitored for COVID-19 symptoms during the study and tested for SARS-CoV-2 if warranted based on the investigator's judgment. SARS-CoV-2 positive results during the study will be reported as AEs and measures will be applied at the discretion of the investigator to minimise further SARS-CoV-2 exposure as much as possible. SARS-CoV-2 infection (based on qRT-PCR and serology) will also be assessed as exploratory endpoints (Section 8.1).

4.2 Scientific Rationale for Study Design

This is a Phase II, randomised, double-blind, placebo-controlled study. Randomisation and blinding will minimise potential bias.

The potential target population for the development of AZD7442 is the general population and specifically healthcare workers, or individuals at increased risk of COVID-19 or those who are expected to have a severe outcome and need immediate protection. In this Phase II study, Chinese participants from mainland China ≥PPD of age who are healthy or who have stable medical conditions (eg, those who could potentially have an impaired response to a vaccine such as participants with immunosuppression) will be included. As older participants are considered to be at increased risk for inadequate response to active immunisation on the basis of age (immunosenescence), randomisation will be stratified by CCI [redacted]. Furthermore, considering the increased COVID-19 vaccination roll-out in China, vaccinated participants will be eligible for the study and are expected to comprise a majority of participants (non-vaccinated participants are expected to be no more than 35% of the study population). According to China Guideline for Clinical Evaluation of COVID-19 Vaccines (Draft), 6 months protection should be provided (NMPA 2020). Therefore, for eligibility in the study, a minimum interval of 6 months between receipt of the COVID-19 vaccine and dosing with AZD7442 is considered adequate to minimise potential complication/interference in PK/PD and safety evaluation of AZD7442. CCI [redacted] at screening to ensure 3:1 balanced representation of the 2 treatment arms in each of the strata. This Phase II study will provide additional safety and tolerability data as well as PK and PD data in the Chinese population.

The primary study endpoints are standard endpoints for safety assessment, including AEs,

SAEs, and safety clinical laboratory measurements. The secondary study endpoints are those required to characterise the PK and ADAs through 360 days after administration (Day 1 through Day 361). The 15-month follow-up period will allow for follow-up of dosed participants through approximately 5 half-lives, which is expected to provide sufficient safety follow-up. Collection of blood samples for ADA through Day 361 will also maximise the probability of detecting ADA to AZD7442. The PK endpoints will describe the disposition of AZD7442 in participants after IV administration. Antidrug antibody responses will be measured to ensure that they are at acceptable levels and do not affect safety or PK. TCCI [redacted] however, based on the limited sample size and current COVID-19 status in China, no trend in occurrence of infection is expected to be observed.

4.3 Justification for Dose

This study will be conducted with a 600 mg IV dose of AZD7442. This is the highest dose that is to be evaluated in the planned Phase I study (D8850C00007) in healthy Chinese participants. As the primary objective of the Phase II study is to evaluate the safety of AZD7442, the 600 mg IV dose will have the highest exposure. Additionally, based on the linear PK assumption, 600 mg IV is expected to have a higher exposure and can provide efficacy that is not less than 300 mg IV or 600 mg IM in the treatment of SARS-CoV-2 infection.

The dose regimens 300 mg IM and 300, 1000, and 3000 mg IV have been evaluated in the ongoing FTIH study (D8850C00001). Tolerability has been confirmed for the dose range from 300 mg IM to 3000 mg IV. The NOAELs of 600 mg/kg IV or 150 mg/kg IM single dose were well tolerated in the cynomolgus monkey toxicity study. The safety margin (monkey/human) between 300 mg IM dose in the FTIH study and NOAEL 150 mg/kg IM is 33-fold and 62-fold for AUC(0-60days) and Cmax, respectively. When comparing between the clinical 300 mg IV dose in the FTIH study and the NOAEL of 600 mg/kg IV dose, a much larger exposure safety margin (monkey/human) was obtained, that being 67-fold and 150-fold for AUC(0-60days) and Cmax, respectively. For the clinical dose of 1000 mg IV, the safety margin (monkey/human) is 22-fold and 49-fold for AUC(0-60days) and Cmax, respectively. For the highest 3000 mg IV dose tested in the FTIH study, the safety margin (monkey/human) is 7.5-fold and 16-fold for AUC(0-60days) and Cmax, respectively. The FTIH study revealed that Cmax and partial AUC increased linearly in the dose range between 300 mg to 3000 mg IV and the bioavailability of 300 mg IM of AZD7442 (based on the 271-day AUC) was 68.54% and 65.79% for AZD8895 and AZD1061, respectively. Based on this information, the 600 mg IV dose in humans is expected to be safe since a sufficient exposure margin has covered this dose.

Human efficacious doses were projected based on in vitro functional potency data that account for potential synergistic effect of the two-mAb combination. The AZD7442 dose levels of 300 mg IM, 300 mg IV, 1000 mg IV and 3000 mg IV that are tested in the FTIH study ensure exposure in serum and in the ELF of the lungs to be above the IC_{80} of 40 ng/mL for a duration of at least 5 months post-dose.

To further support the selection of the study doses, a viral dynamic model was developed, which allows understanding of the PD effects of AZD7442 on the replication of SARS-CoV-2 and the resulting immune response (Gonçalves et al 2020, Goyal et al 2020, Kim KS et al 2020, Kim SE et al 2020, Liu et al 2020). The viral dynamic model indicates that virus entry inhibition greater than approximately 80% is sufficient to prevent infection. Assuming a partition ratio of 1% for lung ELF-to-serum and an IC_{80} of 40 ng/mL, a 300 mg IM dose would provide prophylactic coverage for 6 to 9 months, and this dose and higher doses would also be effective to treat active SARS-CoV-2 infection with a significant reduction in peak viral load and complete suppression of the viral load earlier than accomplished by the innate and acquired immune response only.

Considering the demonstrated safety in the FTIH study and the predicted efficacy, the dose level of 600 mg IV AZD7442 is expected to show good safety and efficacy profiles in the Chinese population and have the potential to be applied in clinics.

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 (Section 1.3).

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

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment 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:

Age

1 Chinese adults ≥ PPD of age, at the time of signing the informed consent.

Informed Consent

2 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.

Type of Participant and Disease Characteristics

3 Healthy participants or participants with stable medical conditions.

(a) Participants who are healthy by medical history, physical examination, and baseline safety laboratory tests, as judged by the investigator.

OR

(b) Participants with stable disease/condition, as judged by the investigator, who may benefit from passive immunisation with antibodies. "Stable" is defined below as:

- No hospitalisation or emergency visit for worsening of disease/condition within the 12 months prior to enrolment.
- No acute change in the participant's condition at the time of study enrolment, and, as judged by the investigator, no exacerbation in disease/condition and no significant change in therapy expected during at least the first 6 months of the study.
- Participation in the clinical study not expected to pose a significant risk to the participant, as judged by the investigator.
- Diseases/conditions include elderly (≥ PPD of age), obese (BMI ≥ PPD kg/m^2), chronic obstructive pulmonary disease, congestive heart failure (NYHA classification ≤ class II), chronic kidney disease, chronic liver disease, immunocompromised state requiring maintenance use of corticosteroids and/or other immunosuppressive medicines, intolerant of vaccines, or another disease as judged by the investigator.

4 Negative results of SARS-CoV-2 qRT-PCR test within 14 days prior to randomisation.
NOTE: A negative SARS-CoV-2 qRT-PCR retest result is required if participant has symptoms of infection or has any known/suspected exposure after the initial test.

5 Able to complete the follow-up period through Day 451 as required by the CSP.

Reproduction

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

6 Contraceptive use by men or women:

(a) Male participants: To avoid transfer of fluids to a sexual partner, all male participants must use a condom from Day 1 and agree to continue through 365 days following administration of the study intervention.

(b) Female participants: Female participants of childbearing potential must use one highly effective form of birth control. Women of childbearing potential who are sexually active with a non-sterilised male partner must agree to use one highly effective method of birth control, as defined below, from Day 1 and agree to continue

through 365 days following administration of the study intervention. Cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Female condom and male condom should not be used together. All women of childbearing potential must have a negative serum pregnancy test result at Visit 1 and throughout the study as indicated per the SoA (Section 1.3).

- Women not of childbearing potential are defined as women who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomisation without an alternative medical cause. The following age-specific requirements apply:
  - Women < PPD of age would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle stimulating hormone levels in the postmenopausal range.
  - Women ≥ PPD of age would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. Examples of highly effective birth control methods are listed in Table 4.

Table 4 Highly Effective Methods of Contraception

Barrier method	Hormonal method

• Intrauterine device
• Intrauterine hormone-releasing system [a]
• Bilateral tubal occlusion
• Vasectomised partner [b]
• Sexual abstinence [c]
	• Combined (estrogen- and progestogen-containing hormonal contraception) associated with inhibition of ovulation
	  ° Oral (combined pill)
	  ° Intravaginal
	  ° Injectable
	  ° Transdermal (patch)
	• Progestogen-only hormonal contraception associated with inhibition of ovulation
	  ° Oral
	  ° Injectable
	  ° Implantable

[a] This is also considered a hormonal method.
[b] Provided that partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomised partner has received medical assessment of the surgical success.

[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study and if it is the preferred and usual lifestyle of the participant.

5.2 Exclusion Criteria

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

Medical Conditions

1 Known history of allergy or reaction to any component of the study intervention formulation.

2 Previous hypersensitivity, infusion-related reactions, or severe adverse reaction following administration of an mAb.

3 Significant infection or other acute illness, including fever > 100 °F (> 37.8 °C) on the day prior to or day of randomisation. Participants excluded for transient acute illness may be dosed if illness resolves within the 28-day screening period. Otherwise, the participant will be reported as a screen failure. Upon obtaining an informed consent again, the participant may be rescreened just once (Section 5.4).

4 History of infection with severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS).

5 History of laboratory-confirmed SARS-CoV-2 infection. NOTE: Participants with any positive SARS-CoV-2 qRT-PCR result based on available data at screening will be excluded. Non-vaccinated participants with any positive SARS-CoV-2 serology result based on available data at screening will be excluded.

6 Any clinical signs and symptoms consistent with COVID-19, eg, fever, dry cough, dyspnoea, sore throat, fatigue, or confirmed infection by appropriate laboratory test within the last 4 weeks prior to screening or randomisation.

7 History of malignancy.

(a) Participants who have had basal cell carcinoma, localized squamous cell carcinoma of the skin, or in situ carcinoma of the cervix are eligible provided that the participant is in remission and curative therapy was completed at least 12 months prior to enrolment.

(b) Participants who have had other malignancies are eligible provided that the participant is in remission and curative therapy was completed at least 5 years prior to enrolment.

8 History of clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture.

9 Current active liver disease.
Chronic stable hepatitis B and C (including positive testing for hepatitis B surface antigen

or hepatitis C antibody), or other stable chronic liver disease are acceptable if the participant otherwise meets eligibility criteria. Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice, or cirrhosis.

10 History of HIV or positive HIV at screening.

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

12 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.

Significant Laboratory Abnormalities

13 Any of the following laboratory abnormalities at screening:

(a) AST or ALT > 2.0 × ULN, ALP > 1.5 × ULN, or TBL > 1.5 × ULN (unless due to Gilbert's syndrome)

(b) Serum creatinine > 176 μmol/L (2 mg/dL)

(c) Haemoglobin < 10 g/dL (100 g/L)

(d) Platelet count < $100 \times 10^3/\mu L$ ($100 \times 10^9/L$)

(e) White blood cell count < $3.5 \times 10^3/\mu L$ ($3.5 \times 10^9/L$) or neutrophil count < $1.5 \times 10^3/\mu L$ ($1.5 \times 10^9/L$)

(f) Any other laboratory value in the screening panel that, in the opinion of the investigator, is clinically significant or might confound analysis of study results

Prior/Concomitant Therapy

14 Any newly initiated drug therapy within 7 days or 5 drug half-lives (whichever is longer) prior to screening.

15 Receipt of Ig or blood products within 6 months prior to screening.

16 Any prior receipt of an investigational or licensed mAb/biologic indicated for the prevention of SARS-CoV-2 or COVID-19 or scheduled to receive any investigational or licensed mAb/biologic indicated for the prevention of SARS-CoV-2 or COVID-19.

17 Receipt of any COVID-19 vaccine within 6 months prior to randomisation or scheduled to receive any COVID-19 vaccine.

Prior/Concurrent Clinical Study Experience

18 Receipt of any investigational product within 90 days or 5 antibody half-lives (whichever is longer) prior to Day 1, or expected receipt of investigational product during the follow-up period, or concurrent participation in another interventional study.

Other Exclusions

19 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

20 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.

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

5.3 Lifestyle Considerations

- 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 5 half-lives after dose of study intervention; ie, 15 months.

5.3.1 Meals and Dietary Restrictions

- There are no meal and dietary restrictions.

5.3.2 Caffeine, Alcohol, and Tobacco

- There are no caffeine, alcohol, and tobacco restrictions.

5.3.3 Activity

- Participants should rest comfortably during the IV infusion and for 1 hour after the end of the infusion.
- Participants should abstain from strenuous activity for 72 hours prior to dosing and 24 hours after dosing.

5.3.4 Reproduction/Contraception Requirements

Male Participants:

- To avoid transfer of fluids to a sexual partner, all male participants must use a condom starting from Day 1 and through 365 days following administration of the study intervention (Section 5.1).
- Male participants should refrain from fathering a child during the study and for 365 days following the administration of study intervention. Contraception for female partners of childbearing may be considered, but is not required for this protocol.
- Male participants should not donate sperm from Day 1 and through 365 days following administration of the study intervention.

Female Participants:

- Female participants must follow the contraception requirements outlined in Section 5.1.
- Female participants must abstain from breastfeeding during the study.
- Female participants should not donate ova from Day 1 and through 365 days following administration of the study intervention.

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 study intervention. 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. Rescreened participants should be assigned the same participant number as for the initial screening (Appendix A 3).

6 STUDY INTERVENTION

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

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

The study intervention (AZD7442 and placebo) is described in Table 5.

Table 5 Investigational Medicinal Products

Intervention name	AZD7442 (AZD8895 + AZD1061)	Placebo
Type	Biological	Drug
Dose formulation	AZD7442 is comprised of the 2 mAbs, and will be supplied as separate vials of AZD8895 and AZD1061 as sterile, clear to opalescent, colourless to yellow solutions. The solutions contain 100 mg/mL of active ingredient (AZD8895 or AZD1061) in 20 mM L-histidine /L-histidine hydrochloride, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0. The label-claim volume is 1.5 mL and each vial contains 150 mg (nominal) of active ingredient.	Sterile solution of 0.9% (w/v) sodium chloride for injection
Unit dose strength(s)	150 mg (nominal) AZD8895 or AZD1061 per vial	Not applicable
Dosage level(s)	AZD7442 doses (combined doses of AZD8895 and AZD1061) to be administered: 600 mg IV co-administration (300 mg AZD8895 and 300 mg AZD1061)	Dosing to match AZD7442 (AZD8895 and AZD1061)
Route of administration	IV infusion	IV infusion
Use	Experimental	Placebo
Sourcing	Provided centrally by the sponsor	Provided locally by the study site or by the sponsor
Packaging and labelling	Each vial will be labelled in accordance with GMP Annex 13 and per regulatory requirement in China.	0.9% (w/v) sodium chloride for injection sourced by the study site or by the sponsor.

GMP, Good Manufacturing Practice; w/v, weight per volume; IV, intravenous; mAb, monoclonal antibody.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Storage and Accountability

1 The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

2 Only participants randomised in the study may receive study intervention and only authorised site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

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

4 Further guidance and information for the final disposition of unused study interventions are provided in the Investigational Medicinal Product Manual or other equivalent documents.

6.2.2 Preparation and Administration

All products must be stored at 2 °C to 8 °C and used within the assigned expiry date on the label.

The dose of AZD7442 for administration must be prepared using aseptic technique. The total time from needle puncture of the vial to the start of administration must not exceed:

- 24 hours at 2 °C to 8 °C
- 4 hours at room temperature

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

The study intervention does not contain preservatives and any unused portion must be discarded.

Use a single 50 to 100 mL 0.9% (w/v) sodium chloride IV bag for both AZD8895 and AZD1061 infusion and placebo infusion. Use a soft IV bag made of polyolefin (PO), polyvinylchloride (PVC), or polyethylene (PE).

Steps 1, 2, and 3 will be performed by an unblinded qualified professional:

Step 1:

Retrieval of AZD7442 vials or placebo

(a) For AZD7442, remove the required number of vials (AZD8895 and AZD1061) for administration, as shown below in Table 6.

Table 6 Required Vials of AZD7442 (AZD8895 and AZD1061)

Dose level	Number of required AZD8895 vials	Volume of AZD8895	Number of required AZD1061 vials	Volume of AZD1061
600 mg AZD7442 (300 mg AZD8895 and 300 mg AZD1061)	2	3 mL	2	3 mL

(b) For placebo, remove the 0.9% (w/v) sodium chloride solution from storage.

Step 2:

Accurately withdraw the required volume for the infusion and add to the IV bag as required (see below):

(a) AZD7442: Remove 3 mL of AZD8895 from 2 AZD8895 vials and transfer to an IV bag. Then, remove 3 mL of AZD1061 from 2 AZD1061 vials and transfer to the same IV bag. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

(b) Placebo: Remove 6 mL of 0.9% (w/v) sodium chloride and transfer to an IV bag.

Step 3:

Use a coloured shading bag or attach labels and cover to the IV bags in order to ensure blinding.

A blinded qualified professional must perform Steps 4 and 5:

Step 4:

Administer the entire contents of the IV bag using IV administration sets containing low protein binding 0.2-µm or 0.22-µm filters made of polyethersulfone (PES). The target infusion time is 30 minutes and the target infusion rate is 20 mg/minute, which translates to IV pump programmable rates of approximately:

- 100 mL/hr for a 50 mL IV bag
- 200 mL/hr for a 100 mL IV bag

Step 5:

Flush the IV line according to local practices to ensure the full dose is administered. Infusion time does not include the final flush time. Flush the catheter with 0.9% (w/v) sodium chloride

at the end of the infusion.

6.3 Measures to Minimise Bias: Randomisation and Blinding

All participants who fulfil eligibility criteria will be centrally assigned to randomised study intervention using an IRT/RTSM. Before the study is initiated, the log-in information and directions for the IRT/RTSM will be provided to each site. Refer to the IRT/RTSM user manual that will be provided to each centre.

Randomisation will be stratified by CCI [redacted] at screening. Considering the increased vaccination roll-out in China, non-vaccinated participants are expected to be no more than 35% of the study population.

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

Investigators and participants will remain blinded to each assigned study intervention throughout the course of the study. To maintain blinding, the IRT/RTSM will provide to the unblinded pharmacists the kit identification number to be allocated to the participant at the dispensing visit.

Unblinded site personnel will endeavor to ensure that there are no differences in time taken to dispense following randomisation. Unblinded site personnel also will be instructed to avoid discussing the colour, or packaging of the study intervention with investigators and the participant (or legally authorised representative).

Code break services provided by IRT/RTSM will be available to the investigator and Patient Safety department at AstraZeneca for individual blind breaking.

The randomisation code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomisation. The investigator documents and reports the action to AstraZeneca, without revealing the study intervention given to the participant to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to a study intervention and that potentially require expedited reporting to regulatory authorities. Randomisation codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

The IRT/RTSM will be programmed with blind-breaking instructions. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the

immediate management of the participant's condition (eg, antidote available), the investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind.

6.4 Study Intervention Compliance

Participants will be dosed at the site and will receive study intervention directly from the investigator or designee, under medical supervision. The date, and time if applicable, of the dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5 Concomitant Therapy

Any medication or vaccine (including OTC or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment 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.

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.

Permitted, restricted, and prohibited medications are summarised in Table 7.

Table 7 Summary of Medications and Treatments Permitted, Prohibited, and Restricted During the Study

Use category	Type of medication/treatment	Timeline/instructions
Permitted	Contraceptives or a single use of acetaminophen, aspirin, antihistamine, or combination OTC product that contains acetaminophen with an antihistamine, or OTC nonsteroidal anti-inflammatory agent	At a dose equal to or lower than that recommended on the package (at the discretion of the investigator)
	Vitamins and other nutritional supplements	Not newly introduced, ie, have been taken for at least 30 days prior to screening
Prohibited	Not applicable	Not applicable
Restricted	COVID-19 vaccines	See Section 6.5.1 for details
	Any other drug therapy	Newly initiated drugs within 7 days or 5 half-lives (whichever is longer) prior to screening is not allowed until the completion of the study, unless, in the opinion of the investigator, the medication will not interfere with the study. Note: participants with stable chronic conditions may continue taking their maintenance medications provided they have taken them for at least 30 days prior to screening and at a stable dose for at least 7 days or 5 half-lives (whichever is longer).

COVID-19, coronavirus disease 2019; OTC, over-the-counter.

6.5.1 COVID-19 Vaccines

- When a participant becomes eligible for the nationally deployed COVID-19 vaccine and it is locally available, they will be able to be unblinded on request, after a fully informed, objective discussion based on all available up-to-date information, and remain in the study.
  - Unblinded participants who received placebo should be advised that no study-associated contraindication to receiving a vaccine exists.
  - Unblinded participants who received AZD7442 should be advised that the 600 mg dose may provide 6 to 9 months of protection, but that this has not yet been demonstrated. In these participants, there would be little or no urgency for receiving a vaccine. In addition, in the presence of adequate neutralising antibody titres, an appropriate and effective response to the vaccine could be impaired. Such participants should be advised to consider waiting an appropriate length of time (as suggested above for the dose) before receiving an anti-SARS-CoV-2 vaccine. For AZD7442, the number of months identified above for the dose represents the approximate number of elimination half-lives of the mAbs, after which the potential

for the mAbs to protect against COVID-19 should be reduced, and after which their potential interference with a vaccine may be reduced.

- For participants who have received study intervention (blinded) and develop symptomatic COVID-19 at some point in the study:
  - There is no reason to believe that administration of a vaccine during acute COVID-19 will ameliorate the illness.
  - In almost all placebo recipients, and in most mAb recipients, an infection-induced immune response will occur, and this response should be protective. At this time, there is no reason to believe that the protection afforded by natural infection is less frequent or less robust than the protection provided by a vaccine, so the benefit of vaccination may be limited.
  - The risk of receiving a vaccine after resolution of the illness should be low.

6.6 Dose Modification

The study intervention will be administered as described in Sections 6.1.1 and 6.2.2. Dose modification is not permitted. Re-administration of a dose is not permitted.

6.7 Intervention After the End of the Study

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

At any time, participants are free to discontinue study intervention or withdraw from the study, without prejudice to further treatment.

7.1 Discontinuation of Study Intervention

Each participant randomised in this study will receive a single dose of study intervention on Day 1 as detailed in Sections 6.1.1 and 6.2.2.

If the infusion of study intervention is interrupted and not resumed (ie, it is discontinued), the participant should remain in the study to be evaluated for the full study period (up to and including Day 451, 450 days after study intervention dosing) with all laboratory and clinical evaluations collected as defined in this CSP, unless the participant withdraws consent to participate in the study. Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention 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 may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an early study intervention discontinuation visit should be conducted, as shown in the SoA (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 study intervention 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 he/she still agrees for existing samples to be used in line with the original consent. If he/she 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, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
  - Unscheduled Visits: An unscheduled visit may occur in-between scheduled visits, eg, to follow up on potential safety events.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- 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 utilised 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).

8.1 Efficacy Assessments

8.1.1 CCI

CCI will be performed as specified in the SoA (Section 1.3). Additionally, a participant should be instructed to contact the study site CCI . CCI should be performed at the discretion of the investigator. CCI

Table 8 COVID-19 Qualifying Symptoms

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

Adapted from US CDC 2021.
COVID-19, coronavirus disease 2019; US CDC, United States Centers for Disease Control and Prevention.

8.1.2 CCI [redacted]

Serum samples will be collected to assess CCI [redacted] from all participants at time points specified in the SoA (Section 1.3) and will be analysed provided the analysis method is established and appropriate approval has been obtained. CCI [redacted] in participants receiving AZD7442 versus placebo will be CCI [redacted] operated by an authorised laboratory.

8.2 Safety Assessments

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

8.2.1 Physical Examinations

Physical examination will be performed at time points specified in the SoA (Section 1.3). For AE reporting regarding physical examination, see Section 8.3.6.

- A complete physical examination will include assessments of the following: height and BMI (screening only); weight; general appearance; respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, muscular-skeletal (including spine and extremities), and neurological systems.
- A brief physical examination will include, at a minimum, assessments of the general appearance, skin, lungs, cardiovascular system, and abdomen (liver and spleen). Symptom-directed physical examination should be performed to assess symptoms reported by participant.

8.2.2 Vital Signs

Vital signs will be performed at time points specified in the SoA (Section 1.3).

The following variables will be collected after the participant has rested in the supine position for at least 5 minutes:

- Systolic blood pressure (mm Hg)
- Diastolic blood pressure (mm Hg)
- Pulse rate (beats per minute)
- Body temperature
- Respiratory rate (breaths per minute)

8.2.3 Electrocardiograms

An ECG will be performed at time points specified in the SoA (Section 1.3). A 12-lead ECG will be obtained after at least 5 minutes supine rest.

Results for PR interval, QRS duration, QT interval, QTcF interval, RR interval, and heart rate will be recorded in eCRF. In addition, the investigators will judge the overall interpretations as normal, abnormal together with their reasons, and this evaluation will be reported in eCRF. If abnormal, it will be further documented as to whether or not the abnormality is clinically significant by the investigators. For all abnormalities (regardless of clinical significance) the specific type and nature of the abnormality will be documented in eCRF. Clinically significant findings should also be documented on the AE page of the CRF if applicable.

The investigators may add extra 12-lead resting ECG assessments if there are any abnormal findings or if the investigators consider them to be required for any other safety reason. These assessments should be entered as unscheduled assessments.

ECG results will be stored at the site with their photocopy dated and signed/sealed by the investigators.

8.2.4 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology, urinalysis, coagulation, pregnancy testing, viral serology, and SARS-CoV-2 testing will be taken at the visits indicated in the SoA (Section 1.3).

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

Blood and urine samples for determination of clinical chemistry, haematology, urinalysis, coagulation, viral serology, pregnancy testing (serum beta-hCG at screening), and reproductive status (serum for FSH at screening) will be performed at a central laboratory. Instructions for the collection and handling of the samples will be provided in the study-specific Laboratory Manual. If supplies or test kits are not available, the testing may be performed at a local laboratory. Urine samples for pregnancy testing (urine hCG) and samples for SARS-CoV-2 serology (at screening) and SARS-CoV-2 qRT-PCR will be performed at a local laboratory at or near the investigational site. Samples tested locally will be collected and handled per routine practice and laboratory methods at the site.

The following laboratory variables will be measured:

- Haematology, serum clinical chemistry, urinalysis, and coagulation: Table 9
- Pregnancy testing: Table 10
- Viral serology: Table 11
- SARS-CoV-2 testing: Table 12

Table 9 Haematology, Serum Clinical Chemistry, Urinalysis, and Coagulation

Haematology	
White blood cell (WBC) count	Neutrophils absolute count
Red blood cell (RBC) count	Lymphocytes absolute count
Haemoglobin (Hb)	Monocytes absolute count
Haematocrit (HCT)	Eosinophils absolute count
Mean corpuscular volume (MCV)	Basophils absolute count
Mean corpuscular haemoglobin (MCH)	Platelets
Mean corpuscular haemoglobin concentration (MCHC)	Reticulocytes absolute count
Serum clinical chemistry	
Sodium	C-reactive protein (CRP)
Potassium	Alkaline phosphatase (ALP)
Urea/blood urea nitrogen (BUN)	Alanine aminotransferase (ALT)
Creatinine	Aspartate aminotransferase (AST)
Albumin	Gamma glutamyl transpeptidase (GGT)
Calcium	Total bilirubin
Phosphate	Conjugated bilirubin
Glucose	Creatine kinase
Urinalysis	
Glucose	Protein
Blood	Microscopy (if positive for protein or blood): RBC, WBC, Casts (cellular, granular, hyaline)
Coagulation	
International normalised ratio (INR)	Prothrombin time
Activated partial thrombin time (aPTT)	

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

Table 10 Pregnancy Testing (Females Only)

Pregnancy Test (FOCBP only): • Serum β-hCG (screening; central laboratory) • Urine hCG (pre- and post-dose; local laboratory)	Reproductive status test (suspected postmenopausal women < PPD only): • FSH (using serum at screening; central laboratory)

β-hCG, beta human chorionic gonadotropin; FOCBP, females of childbearing potential; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin.

Table 11 Viral Serology Testing

Hepatitis B surface antigen	HIV
Hepatitis C virus antibody	

HIV, human immunodeficiency virus.

Table 12 SARS-CoV-2 Testing

SARS-CoV-2 qRT-PCR; local laboratory	SARS-CoV-2 serology; local laboratory (screening) [a]

[a] SARS-CoV-2 serology test at screening will be analysed in a local laboratory. Subsequent SARS-CoV-2 serology tests after screening will be analysed in a central laboratory (see Section 8.1.2).

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; qRT-PCR, quantitative reverse transcriptase polymerase chain reaction.

8.2.5 Monitoring of Administration of Study Intervention

Participants will be monitored during and after administration of study intervention. Vital signs will be measured before and after administration of study intervention according to time points specified in the SoA (Section 1.3).

As with any biologic product, hypersensitivity reactions (including anaphylaxis) 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 recognise and treat anaphylaxis.

Any AEs should be reported as described in Section 8.3.

8.3 Adverse Events and Serious Adverse Events

The principal 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 authorised 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 and SAEs will be recorded from the time of signature of the ICF through the last participant contact.

If the investigator becomes aware of an SAE with a suspected causal relationship to the study

intervention 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:

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the study intervention (yes or no)
- Action taken with regard to study intervention
- AE caused participant's withdrawal from study (yes or no)
- Outcome

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

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

8.3.3 Causality Collection

The investigator should assess causal relationship between study intervention 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 study intervention?'

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 are events of scientific and medical interest, specific to the further understanding of the study intervention 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 Investigator's Brochure for additional information on AESIs.

The AESIs for AZD7442 include:

- Anaphylaxis and other serious hypersensitivity reactions, including immune complex disease
- Infusion-related reactions

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 had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.6 Adverse Events Based on Examinations and Tests

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

Abnormal results of examination and tests at screening (eg, haematology, clinical chemistry, urinalysis, ECG, physical examination, vital signs, etc.) are regarded as existing conditions before ICF and will not be recorded as AE. Relevant clinically significant abnormality of examination and tests during screening can be recorded as medical history according to investigator's medical judgment.

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

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin 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 screening assessment may be reported as an AE.

8.3.7 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN may need to be reported as SAEs. 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 must be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives within 1 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 1 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 1 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.

The reference document for definition of expectedness/listedness is the Investigator's Brochure for the AstraZeneca drug.

8.3.9 Pregnancy

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

8.3.9.1 Maternal Exposure

The study intervention should not be given to pregnant women.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention 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) 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

Male participants should refrain from fathering a child during the study and for 365 days following the administration of study intervention.

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. The pregnancy will also be followed up, and the outcome of the pregnancy (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly) should, if possible, be obtained and documented.

8.3.10 Medication Error

If a medication error 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 completed within **1** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.8) and **within 30 days** for all other medication errors.

The definition of a medication error can be found in Appendix B 4.

8.4 Overdose

For this study, any dose of study intervention greater than the assigned dosage will be considered an overdose.

- 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 to properly address potential questions from regulatory agencies or for a maximum of 2 years following the date of issue of the final CSR (whichever is earlier) in line with consent and local requirements, after which they will be destroyed.

- The PK samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier).
  - The PK samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- ADA sample aliquots and PD (as neutralising activity in serum) samples will be retained at AstraZeneca or its designee to properly address potential questions from regulatory agencies or for a maximum of 2 years following the date of issue of the final CSR (whichever is earlier) in line with consent and local requirements, after which they will be destroyed. Additional use includes further characterisation of any ADAs, confirmation and/or requalification of the assay, as well as additional assay development work based on regulatory requirement or feedback. The results from additional analysis may be reported separately from the CSR.

8.5.1 Pharmacokinetics

- Blood samples will be collected for measurement of serum concentrations of AZD7442 (AZD8895 and AZD1061) at time points specified in the SoA (Section 1.3).
- Serum samples will be used to analyse the PK of AZD7442.
- Samples will be collected, labelled, 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.

Drug concentration information that would unblind the study will not be reported to

investigative sites or blinded personnel until the study has been unblinded.

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

8.5.1.2 Pharmacokinetic Parameters

Where possible, the PK parameters will be estimated for AZD7442 (each mAb: AZD8895 and AZD1061) based on serum concentrations.

Cmax	Maximum concentration
AUC(0-180days)	Area under the concentration-curve from time zero to 180 days
AUClast	Area under the concentration-curve from time zero to the time of last quantifiable concentration
AUCinf	Area under the concentration-time curve from time zero extrapolated to infinity
t½λz	Terminal elimination half-life, estimated as (ln2)/λz
tlast	Time of last quantifiable concentration
Vss	Volume of distribution at steady state
Vz	Volume of distribution based on terminal phase
CL	Clearance

The following parameters will be calculated for PK diagnostic purposes and will also be summarised.

λz lower	Lower (earlier) t used for λz determination
λz upper	Upper (later) t used for λz determination
λzN	Number of data points included in the log-linear regression analysis
λz span ratio	Time period over which λz was determined as ratio of t½λz
Rsq_adj	Statistical measure of fit for the regression used for λz determination adjusted for the number of used data points (n obs)
λz	Terminal elimination rate constant
AUCextr	Extrapolated area under the curve from tlast to infinity, expressed as percentage of AUCinf

Additional serum PK parameters may be determined where appropriate.

The bioanalytical analysis of the serum concentration for AZD7442 mAbs (AZD8895 and AZD1061) will be performed at bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method.

The PK data analysis will, where data allow, be carried out using actual time after dose

determined from the PK sampling and dosing times recorded in the database. If actual times are missing, nominal times may be used.

8.5.2 Pharmacodynamics

- Blood samples for the determination of PD as [redacted] will be collected at time points specified in the SoA (Section 1.3) and will be analysed provided the analysis method is established and appropriate approval has been obtained.
- Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

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

8.5.3 Immunogenicity Assessments

Blood samples for determination of ADA in serum will be collected as specified in the SoA (Section 1.3) and 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 used will be described in a separate report.

ADA samples may also be further tested for characterisation of the ADA response.

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

8.6 Human Biological Sample Biomarkers

Not applicable.

8.7 Optional Genomics Initiative Sample

Not applicable.

8.8 Medical Resource Utilisation and Health Economics

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

No statistical hypotheses will be evaluated based on formal statistical tests. Descriptive statistics will be presented for relevant data and parameters.

9.2 Sample Size Determination

Approximately 272 participants will be randomised 3:1 to study intervention with 600 mg

AZD7442 (n = 204) or placebo (n = 68) administered IV. If the true AE rate is 1% at the primary time point (ie, Month 6), 162 participants in the AZD7442 group will provide a probability of at least 80% to observe at least one AE case. A dropout rate of 20% is assumed.

The 1% assumption is driven by the international convention where 1% is used as the lower limit of common AEs (between infrequent and frequent AEs) (CIOMS 1999). The randomisation ratio of 3:1 limits the number of participants in the placebo group so that adequate information can be obtained to objectively assess the safety of AZD7442 in the Chinese population.

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

9.3 Populations for Analyses

The populations for analysis are defined in Table 13.

Table 13 Populations for Analysis

Population/analysis set	Description
All participants	All participants who signed the ICF.
Randomised	All participants who were randomised in the study.
Full	All randomised participants who received any amount of AZD7442 or placebo, irrespective of their protocol adherence and continued participation in the study. Participants will be analysed according to their randomised treatment, irrespective of whether or not they have prematurely discontinued, according to the intent-to-treat principle. Participants who withdraw consent to participate in the study will be included up to the date of their study termination.
Safety	All participants who received any amount of AZD7442 or placebo. Erroneously treated participants (eg, those randomised to intervention A but actually given intervention B) will be analysed according to the intervention they actually receive.
PK	All participants in the safety analysis set who received AZD7442 and had at least one quantifiable serum PK observation post-dose, with no important protocol deviations thought to impact the analysis of the PK data.
ADA	All participants who received any amount of AZD7442 or placebo and had a non-missing baseline ADA result and at least one non-missing post-baseline ADA result.
PD	All participants in the safety analysis set who received AZD7442 or placebo and had at least one quantifiable titre observation post-dose, with no important protocol deviations thought to impact the analysis of the PD data.

ADA, antidrug antibody; ICF, informed consent form; PD, pharmacodynamics; PK, pharmacokinetic; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Participant disposition will be reported using the all participants analysis set. Pharmacokinetics will be assessed using the PK analysis set. Pharmacodynamics will be assessed using the PD analysis set. CCI [redacted] Immunogenicity will be assessed using the ADA analysis set. All remaining evaluations including safety analysis will use the safety analysis set, unless otherwise stated.

9.4 Statistical Analyses

The primary DBL will occur after all treated participants have completed follow-up through Day 181 to conduct the primary analysis. All available data at the time of DBL will be included in the primary analysis. No early stopping decision will be made for futility or

superiority at the primary analysis.

All participants in the study will be assessed for safety and tolerability, PK, and PD for approximately 15 months following the dose of study intervention (through Day 451). A final DBL will occur when all participants have completed the study.

The SAP will be finalised within 90 days of the First Subject In or the first DSMB meeting, whichever comes first, and prior to the primary DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints.

9.4.1 General Considerations

The study will initially be double-blind until the primary analysis (ie, blind for participants, investigators/site staff, and sponsor/designated clinical research organisation). To maintain the integrity of the study to allow rigorous evaluation of study objectives through the end of the study, investigators and participants will remain blinded to the intervention assignment until the end of the study. The sponsor may be unblinded after the primary DBL as needed to perform the analysis and planning.

Unless otherwise stated, the as-treated principle will be applied to study evaluations, which is participants who received study intervention other than the one assigned by randomisation will be analysed as belonging to the actual intervention received.

Categorical variables will be summarised using frequency and percentages, where the denominator for calculation is the underlying analysis set population, unless otherwise stated.

Continuous variables will be summarised with descriptive statistics of number of available observations, mean, standard deviation, median, minimum, maximum, and quartiles as appropriate.

9.4.2 Efficacy

The efficacy objective and endpoints are considered exploratory, and no hypothesis testing will be evaluated. Efficacy data will be presented based on the full analysis set. The results may be reported separately from the CSR. Details will be described in the SAP.

9.4.3 Safety

Safety data will be summarised by intervention group on the safety analysis set, unless otherwise specified. In general, the baseline value for summaries is the last non-missing value prior to administration of the first dose of study intervention. Details will be described in the SAP.

9.4.3.1 Primary Endpoint(s)

The safety of AZD7442 will primarily be assessed by AEs.

Adverse events will be presented for each intervention group by system organ class and/or preferred term covering the number and percentage of participants reporting at least one event and number of events where appropriate.

An overview of AEs will be presented for each intervention group showing the number and percentage of participants with any AE, any SAE, any SAE with outcome of death, and other AE categories as appropriate.

Summaries may be provided for AEs, SAEs, SAEs with outcome of death, AESIs, and other AE categories as appropriate. Additional summaries will be provided taking into consideration the relationship as assessed by the investigator as well as maximum intensity. The AE severity will be graded according to Appendix B and coded using the most recent version of the Medical Dictionary for Regulatory Activities.

An AE listing for the safety analysis set will cover details for each individual AE. Full details of AE analyses will be provided in the SAP.

9.4.3.2 Other Safety Endpoint(s)

Other safety endpoints include:

- Laboratory parameters (haematology, clinical chemistry, coagulation, and urinalysis)
- Vital signs (blood pressure, pulse rate, body temperature, and respiratory rate)
- 12-lead safety ECG
- Physical examination

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.

All parameters from laboratory, ECG, and vital signs will be summarised by intervention group with descriptive statistics based on data type (continuous, categorical, etc).

For each scheduled post-baseline visit, descriptive statistics parameters will be presented for observed values and change from baseline as appropriate. Shift tables presenting number and percentage of participants in the respective category may be provided.

Full details of safety endpoint analysis will be provided in the SAP.

9.4.4 Pharmacokinetic Analyses

The AZD7442 mAbs (AZD8895 and AZD1061) concentrations measured from serum at each

time point will be summarised based on the PK analysis set, using the appropriate descriptive statistics. Individual and mean of serum concentrations over time will be plotted, on both linear and semi-logarithmic scale.

The PK parameters will be derived using noncompartmental methods and will be summarised based on the PK analysis set, using the appropriate descriptive statistics.

Potential correlation between PK exposure and safety response may be explored. Population PK analysis may be performed and reported in a separate report.

9.4.5 Pharmacodynamic Analyses

All available data of serum neutralising responses against SARS-CoV-2 will be listed and presented in tabular and graphical form as appropriate. The serum neutralising responses against SARS-CoV-2 will be summarised by intervention group using geometric mean titre and geometric mean fold rise from baseline, based on the PD analysis set.

Results of the evaluation of the functional inhibition of SARS-CoV-2 by AZD7442 concentrations in serum may be reported separately from the CSR.

9.4.6 Immunogenicity Analyses

A summary of the number and percentage of participants who developed detectable ADA to AZD7442 (ADA results to AZD8895 and AZD1061 will be reported separately) by ADA categories will be presented by intervention group based on the ADA evaluable analysis set. The ADA titre will be presented for samples confirmed positive for the presence of ADA to AZD7442. Samples confirmed positive for ADA may be further tested, including possible assessments of neutralising antibodies.

The potential effects of immunogenicity on PK or safety of AZD7442 may be evaluated, if appropriate.

9.5 Interim Analyses

As no multiplicity control is applied, ad-hoc interim analyses may be performed, if warranted, for additional evaluation of a potential signal in the safety profile.

9.6 Data Safety Monitoring Board

An independent DSMB will provide oversight, to ensure safe and ethical conduct of the study. The DSMB will have the responsibility of evaluating cumulative safety and other clinical trial data at regular intervals and making appropriate recommendations based on the available data. During the study, the benefit/risk assessment will be continuously monitored by the DSMB to ensure that the balance remains favourable. If required, the DSMB will recommend temporarily stopping or termination of the study. There is no formal efficacy review by the

DSMB with the potential for early stopping due to efficacy planned for this study.

For details on the DSMB, refer to Appendix A 5.

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 Organisations 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, 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 authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a contract research organisation (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 utilising 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 Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

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 authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorised representative 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 centre.
- 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 authorised 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 authorised representative.

Participants who are rescreened are required to sign a new ICF.

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 authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees Structure

An independent Data 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. Summaries of unblinded data will be reviewed by the DSMB during the study on a regular basis. To minimise the potential introduction of bias, DSMB members will not have direct contact with the study site personnel or participants. The data for review will be outlined in the DSMB Charter and will be agreed in advance by the DSMB members.

The DSMB will review safety data on a regular basis as set out in the DSMB Charter, including, but not limited to, reviewing the safety data from all participants during the study.

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.

As no efficacy endpoints will be evaluated as study objectives, the primary/interim analysis will be conducted by AstraZeneca Clinical Study Team or delegates and the primary/interim results will be reviewed by the DSMB.

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 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 an 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 Monitoring Plan and Protocol Deviations Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised 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 Source Data Agreement and Clinical Study Agreement.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open 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 multicentre 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 unfavourable 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 fulfils one or more of the following criteria:

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

Adverse events for **malignant tumours** reported during a study should generally be assessed as **serious AEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious AE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, 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).

Hospitalisation

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). 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, hospitalisation, disability or incapacity but may jeopardise 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 anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- 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 an 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 an SAE when it satisfies the criteria shown in Appendix B 2.

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 aetiology 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 recognised 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

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

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

Medication error includes situations where an error.

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognised 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]/Randomisation 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.

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

The investigator keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst 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 lifecycle 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 lifecycle.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are 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 analysed, 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 organisation(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 study site is notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING 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 them occurs, are capable of causing permanent disability or 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 Hy's Law (HL) criteria are met. Hy's Law 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

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

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

D 3 Identification of Potential Hy's Law Cases

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

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

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 Section D 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results).

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 that 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 participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Complete follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the study physician. This includes deciding which 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 an 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 Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

D 6 Laboratory Tests

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

Hy's Law Lab Kit for Central Laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HBsAg IgM and IgG anti-HBc HBV DNA [a] IgG anti-HCV HCV RNA [b] IgM anti-HEV HEV RNA
Other viral infections	IgM and IgG anti-CMV IgM and IgG anti-HSV IgM and IgG anti-EBV
Autoimmune hepatitis	Antinuclear antibody Anti-liver/kidney microsomal antibody Anti-smooth muscle antibody
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

CMV, cytomegalovirus; EBV, Epstein-Barr virus; GGT, gamma-glutamyl transferase; HAV, hepatitis A virus; HBc, hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HSV, herpes simplex virus; IgG, immunoglobulin G; IgM, immunoglobulin M; INR, international normalized ratio; LDH, lactate dehydrogenase.

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Appendix E Abbreviations

Abbreviation or special term	Explanation
ADA	antidrug antibody
ADE	antibody-dependent enhancement
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC(0-60days)	area under the concentration-time curve from time 0 to 60 days
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CI	confidence interval
Cmax	maximum concentration
CoV	coronavirus
COVID-19	coronavirus disease 2019
CSP	clinical study protocol
CSR	clinical study report
DBL	database lock
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form
ELF	endothelial lining fluid
Fc	fragment crystallisable
FTIH	first time in human
HIV	human immunodeficiency virus
IC_{80}	80% maximal inhibitory concentration
ICF	informed consent form
Ig	immunoglobulin
IM	intramuscular(ly)
IRT	interactive response technology
IV	intravenous(ly)
LLN	lower limit normal
mAb	monoclonal antibody

Abbreviation or special term	Explanation
MERS	Middle East Respiratory Syndrome
NHC	National Health Commission
NMPA	National Medical Products Administration
NOAEL	no observed adverse effect level
OTC	over-the-counter
PC	polycarbonate
PD	pharmacodynamics(s)
PE	polyethylene
PES	polyethersulfone
PK	pharmacokinetic(s)
PO	polyolefin
PP	polypropylene
PREGOUT	pregnancy outcome
PREGREP	pregnancy report
PVC	polyvinylchloride
qRT-PCR	quantitative reverse transcriptase polymerase chain reaction
QTcF	corrected QT interval by Fredericia
R_0	reproduction number
RBD	receptor binding domain
RSV	respiratory syncytial virus
RTSM	Randomisation and Trial Supply Management
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	Schedule of Activities
TBL	total bilirubin
TM	immunoglobulin constant heavy chain substitutions to modify effector function (L234F/L235E/P331S)
ULN	upper limit of normal
UK	United Kingdom
US	United States
w/v	weight per volume
YTE	immunoglobulin constant heavy chain substitutions to modify the half-life of the antibody (M252Y/S254T/T256E)

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