Clinical Study Protocol

A Phase I Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability and Pharmacokinetics of AZD7442 in Healthy Adults

Parexel Study No.:	PXL252166
Sponsor Study Code:	D8850C00001
EudraCT No:	2020-003076-40
Investigational Medicinal Product(s):	AZD7442 (AZD8895 + AZD1061)
Therapeutic Indication:	Prophylaxis and treatment of SARS-CoV-2 infection
Pharmacological Class:	Combined monoclonal antibodies (mAbs)
Development Phase:	Phase I
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden
Study Centre:	Parexel Early Phase Clinical Unit (London) Level 7, Northwick Park Hospital PPD HA1 3UJ United Kingdom
Date of Protocol:	Final, 24 July 2020
Protocol Amendment No. 1:	Final, 07 August 2020
Protocol Amendment No. 2:	Final, 23 September 2020
Protocol Amendment No. 3:	Final, 08 December 2020
Protocol Amendment No. 4:	Final, 08 February 2021
Protocol Amendment No. 5:	Final, 16 April 2021
Protocol Amendment No. 6:	Final, 19 July 2021

This clinical study will be conducted according to the protocol and in compliance with the International Council for Harmonisation Tripartite guideline for Good Clinical Practice and with other applicable regulatory requirements.

Confidentiality Statement

This confidential document is the property of AstraZeneca. No unpublished information contained herein may be disclosed without prior written approval from AstraZeneca. Access to this document must be restricted to relevant parties.

PROTOCOL AMENDMENTS

Protocol Amendment No. 6, dated 19 July 2021

The revised CSP dated 16 April 2021 (Protocol Amendment No. 5) was amended to include administrative changes and an update to the SARS-CoV-2 serology and qRT-PCR footer in the screening Schedule of Assessment.

The following sections of the protocol have been changed:

- Investigators and study administrative structure: Sponsor's lead physician was updated from PPD. Details on an additional analytical laboratory (GCL-EU) were added.
- Table 3-1: Updated footnote 'b' (SARS-CoV-2 serology and qRT-PCR) to include the following: The COVID-19 tests at screening will be performed as part of the Clinical Unit's general screening. These COVID 19 screenings will occur after the subject has consented to the COVID-19 screening and before consent for the study is obtained.
- Section 12.1: Details of the Sponsor's lead physician were updated from PPD to PPD.
- Additional minor formatting and grammatical corrections were made.

Protocol Amendment No. 5, dated 16 April 2021

The revised CSP dated 08 February 2021 (Protocol Amendment No. 4) was amended to include a third and fourth interim analysis. The data from this analysis will be used in a regulatory submission.

The following sections of the protocol have been changed:

- Synopsis (Presentation and Analysis of Exploratory Data): Updated text to state that exploratory data may form part of the CSR.
- Synopsis (Interim Analysis): Added that a third and fourth interim analysis will be performed and specified what data will be used for each analysis.
- Investigators and Study Administrative Structure: Added Monogram Biosciences – LabCorp Specialty Testing Group for exploratory neutralising antibody analysis.
- Section 2.3: Updated exploratory outcome measure to state that exploratory data may form part of the CSR.
- Section 4.4: Added that a third and fourth interim analysis will be performed and specified what data will be used for each analysis.
- Section 6.6: Removed text stating that results for neutralising antibody assessments will be reported separately from the CSR.
- Section 11.2.6.2: Added how the results for nasal fluid PK will be analysed and presented.

Protocol Amendment No. 4, dated 08 February 2021

The revised CSP dated 08 December 2020 (Protocol Amendment No. 3) was amended to add the option for study participants to receive an approved vaccine for protection against SARS-CoV-2.

The following sections of the protocol have been changed:

- Synopsis (Study Design): Added that guidance for management of subjects who wish to receive an approved vaccine for protection against SARS-CoV-2 is provided.
- Section 3.1: Added that guidance for management of subjects who wish to receive an approved vaccine for protection against SARS-CoV-2 is provided.

  Added that an unscheduled unblinding visit will be included should a subject want to be unblinded for vaccination purposes outside the visit windows during the Follow-up Period.
- Figure 3-1: Added footnote that an unscheduled unblinding visit will be included should a subject want to be unblinded for vaccination purposes outside the visit windows.
- Table 3-3: Added footnote that an unscheduled unblinding visit will be included should a subject want to be unblinded for vaccination purposes outside the visit windows.
- Section 5.3.2: Methods for unblinding the study were updated to provide guidance in the event that a participant wishes to receive an approved vaccine to protect against infection with SARS-CoV-2 or wishes to withdraw completely from the study after unblinding.
- Section 5.5: Guidance was added regarding the procedure to be followed in the event that a participant becomes eligible for the COVID-19 vaccine against infection with SARS-CoV-2.
- Additional minor formatting and grammatical corrections were made.

Protocol Amendment No. 3, dated 08 December 2020

The revised CSP dated 23 September 2020 (Protocol Amendment No. 2) was amended to change the Principal Investigator from Dr Muna Albayaty to Dr Pablo Forte Soto.

Protocol Amendment No. 2, dated 23 September 2020

The revised Clinical Study Protocol (CSP) dated 07 August 2020 (Protocol Amendment No. 1) was amended to define Cohort 4 of the study for dosing of AZD7442 3000 mg intravenously (IV) with co-administration instead of sequential administration of the individual monoclonal antibodies (mAbs). Obtaining safety and pharmacokinetic (PK) data for mixed, IV co-administration of the mAbs will permit a simplified administration process and shorter IV infusion times for AZD7442.

The following sections of the protocol have been changed:

- Section 1.2 Rationale for Conducting This Study (text added).
- Section 2.2 Secondary Objectives (text added).
- Section 3.1 Overall Study Design and Flow Chart (text added).
- Figure 3-2 Overall Graphical Representation of the Study (figure updated; explanatory footnotes added).
- Table 3-2 Schedule of Assessments (Treatment Period) (footnotes updated; data of Day 2 moved from Table 3-3 to be displayed under Treatment Period rather than under Follow-up Period).
- Section 3.2.5 Dose Escalation Strategy (text added).
- Section 3.2.7.2 Data Reviewed by Dose Escalation Committee for Dose Escalation Decision (text added).
- Section 3.2.7.3 Dose Escalation Committee Decision on Next Dose (text added).
- Section 3.3.2 Degree of Uncertainty: Co-administration of Monoclonal Antibodies (new section added).
- Section 4.4 Interim Analysis (text added).
- Section 5.1.1 Procedures for Randomisation (text revised).
- Section 5.3.1 Methods for Ensuring Blinding (text added).
- Table 5-2 Identity of the Investigational Medicinal Product (text added).
- Section 5.4.3 Dose and Treatment Regimens (text added).
- Section 10 Evaluation and Calculation of Variables (text added).
- Section 11.2 Methods of Statistical Analysis (text added).
- Section 11.4 Determination of Sample Size (text added).

Furthermore, inconsistencies in the previous version of the protocol were clarified throughout the protocol. Text of the Protocol Synopsis was revised in alignment with corresponding sections within the protocol. The Tables of Contents were updated to show the heading and page number revisions.

Protocol Amendment No. 1, dated 07 August 2020

The following changes were made to the original CSP, dated 24 July 2020, to include changes requested by the Medicines and Healthcare Products Regulatory Agency (MHRA).

- Protocol Synopsis, Sections 3.1 and 11.4: Text regarding the potential for addition of a cohort with a higher dose of AZD7442 has been removed.
- Section 4.1.1: Inclusion Criterion 8 updated to state that females of childbearing potential who are sexually active with a non-sterilised male partner must have used a stable and highly effective method of contraception for at least 3 months prior to dosing with IMP and must agree to continue using such precautions until 360 days after the dose of IMP.

- Section 4.2.1.2: Text added to clarify that the contraceptive requirements apply to woman of childbearing potential and their non-sterilised male partners. This is for consistency with wording used in Inclusion Criterion 8.
- Section 4.2.1.2: Text added stating that female participants should not donate ova for 360 days after the IMP dose.
- Section 4.2.1.3: Text is updated to state that female partner/spouse of the male participant should be stable on their chosen method of birth control for at least 3 months prior to dosing with IMP and must agree to continue using such precautions until 360 days after the dose of IMP.
- Section 11.3: Text added to confirm that planned protocol deviations are not acceptable and that those suspected or known to have the potential to significantly impact on a participant's safety, physical or mental integrity, or scientific value will be classified as a serious breach.

PROTOCOL SYNOPSIS

Title of the Study
A Phase I Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability and Pharmacokinetics of AZD7442 in Healthy Adults.

Principal Investigator (PI)
Dr Pablo Forte Soto (MD, MSc, PhD)

Study Centre
This study will be conducted at a single study centre.

Study Rationale and Justification of Study Design
AZD7442 monoclonal antibodies (mAbs) are being evaluated for administration to prevent or treat the Coronavirus Disease 2019 (COVID-19). This Phase I study will gather important information on the safety and tolerability of AZD7442, as well as relevant data on the pharmacokinetic (PK) profile and the generation of anti-drug antibodies (ADAs) to AZD7442. In addition, both sequential and co-administration of the mAbs will be investigated to gather important information on the PK, the IV administration process and infusion times.

Number of Participants Planned
It is planned to enrol at least 60 healthy participants across 5 dosing cohorts.

Study Objectives
The objectives of the study are:
Primary Objective:

- To evaluate the safety and tolerability of AZD7442 administered intravenously (IV) or intramuscularly (IM) to healthy adult participants 18 to 55 years of age.

Secondary Objectives:

- To evaluate the single dose PK of AZD7442 (when mAbs are administered sequentially [divided in separate infusion of each mAb component], and when mAbs are co-administered [both mAbs mixed into a single infusion]) in serum.
- To evaluate the ADA responses to the AZD7442 in serum.

Exploratory Objectives:

- To evaluate the single dose PK concentrations of AZD7442 in nasal fluid.
- To evaluate the functional inhibition of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by AZD7442 concentrations in serum.

Study Design
This is a Phase I, first time in human (FTIH), randomised, double-blind, placebo-controlled, dose escalation study evaluating the safety, tolerability, and PK of AZD7442 in healthy adult participants, 18 to 55 years of age. Approximately 60 healthy participants will be enrolled at one study centre and randomised 10:2 to either AZD7442 or placebo administered IV or IM, across 5 fixed-dose cohorts. For participants who will receive the investigational medicinal product (IMP) via IM injection (Cohort 1a), the IMP will be administered as sequential direct gluteal IM administrations starting with AZD8895/placebo and followed by AZD1061/placebo. For participants who will receive

the IMP via IV infusion in the first 3 cohorts to be dosed via IV infusion (Cohorts 1b, 2, and 3), the IMP will be administered in two sequential IV infusions at a maximal infusion rate of 20 mg/minute, starting with AZD8895/placebo and followed by AZD1061/placebo. For participants who will receive the IMP via IV infusion in Cohort 4, the IMP will be co-administered as a single IV infusion containing both mAbs/placebo at a maximal infusion rate of 50 mg/minute. Additional cohorts may be added with lower or intermediate doses of AZD7442 if the Dose Escalation Committee (DEC) determines they are warranted.

After the screening period, each eligible participant will be admitted to early phase clinical unit (EPCU) on Day -1 (1 day prior to dosing) and discharged on Day 2 (1 day after dosing, after the 24-hour procedures are completed). Participants will then be monitored for approximately one year after dosing (Day 361) for safety, including recording of adverse events (AEs) and serious adverse events (SAEs), and collection of blood samples for PK and ADAs. Sentinel dosing will be applied for all dosing cohorts to ensure participant safety, as follows: Two participants of each cohort will be dosed at a ratio of 1:1 (AZD7442:placebo) and will then undergo a safety monitoring period for at least 24 hours before dosing the rest of the participants of that cohort. Escalation from one dose level to the next dose level, and from the last cohort with sequential IV infusions of the mAbs (Cohort 3) to the first cohort with a co-administered infusion of the mAbs (Cohort 4), will be based on review of all available safety data up to and including Day 8. In addition, any available PK data will also be reviewed.

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. Reporting of SARS-CoV-2 positive results during the study conduct will be reported as AEs and measures will be applied at the discretion of the PI to minimise further SARS-CoV-2 exposure as much as possible. Guidance for management of subjects who wish to receive an approved vaccine for protection against SARS-CoV-2 is provided.

Expected Duration of the Study
The study is expected to be approximately 389 days in duration for each participant, consisting of a Screening Period of up to 27 days (Day -28 through Day -2), a Treatment Period of 2 days (Day -1 to Day 1) and a 360-day safety Follow-up Period (Day 2 through Day 361).

Target Study Population
This study will be conducted in healthy male and female participants, 18 to 55 years of age.

Investigational Medicinal Product

Supplier:	AZD7442 (AZD8895 + AZD1061): AstraZeneca. Placebo/Diluent: 0.9% Sodium Chloride (Ph.Eur., British Pharmacopoeia): Parexel.
Formulation:	Each vial of AZD8895 and AZD1061 is formulated as a sterile, white to off-white, lyophilised powder, in a glass vial, 150 mg. After reconstitution in sterile water for injection/infusion; each vial yields CCI mg/mL of active ingredient (AZD8895 or AZD1061), CCI mM L-histidine/L-histidine hydrochloride, CCI mM sucrose, and CCI (w/v) polysorbate 80, at pH 6.0.
Strength/concentration:	Supplied as powder for solution for injection/infusion. After reconstitution, each vial will contain CCI AZD8895 or CCI mg/mL AZD1061, with a unit dose strength of 150 mg AZD8895 or 150 mg AZD1061.
Dose:	AZD7442 doses (combined doses of AZD8895 and AZD1061 each represents half of the total dose) to be administered sequentially are 300 mg IM (direct gluteal IM injections) (Cohort 1a), 300 mg IV (Cohort 1b), 1000 mg IV (Cohort 2), and 3000 mg IV (Cohort 3) at 20 mg/minute for the IV infusions, and the AZD7442 dose to be co-administered is 3000 mg IV at 50 mg/minute (Cohort 4) for the IV infusion.
Route of administration:	IV infusion or IM injection.
Specific device for drug administration, if applicable:	IV bags, lines, and catheters for IV infusion as well as the syringes and needles for injection will be provided by Parexel.
Regimen:	Single, separate, sequential doses as IV infusions will be administered at maximal infusion rate of 20 mg/minute or direct IM injections of each mAbs. A co-administered dose of both mAbs mixed in a single IV infusion will be administered at a maximal infusion rate of 50 mg/minute.
Special handling requirements:	Will be provided in a separate document.
Availability of the investigational medicinal product (IMP):	Will be shipped when approvals are in place.

IM: intramuscular; mAbs: monoclonal antibodies: IV: intravenous.
Dosing instructions and dispensing details will be provided in the pharmacy manual.

Outcome Measures

Safety and Tolerability Endpoints:

Safety and tolerability variables will include:

- AEs, SAEs, concomitant medication, safety laboratory parameters (haematology, clinical chemistry, coagulation, and urinalysis); 12-lead safety electrocardiogram (ECG); vital signs (blood pressure [BP], pulse rate, oral temperature, and respiratory rate), and physical examination.
- Injection site reactions with IM administration will be monitored (including assessment of size, redness/erythema, swelling, itching/pruritis, pain or tenderness, induration, discolouration) and will be documented as an AE and a photograph taken, at the discretion of the PI, with visible measuring tape.

Immunogenicity Endpoints

- Venous blood samples will be collected and stored for analysis of ADAs. Unscheduled samples for ADA analysis should be collected in response to suspected immune-related AEs.

Serum Pharmacokinetic Endpoints:

Where possible, PK parameters will be assessed for individual mAbs (AZD8895 and AZD1061):

- PK parameters:
  - After IV infusion: Cmax, Tmax, t½λz, AUClast, AUCinf, Vss, Vz, and CL.
  - After IM injection: Cmax, Tmax, t½λz, AUClast, AUCinf, extravascular systemic clearance (CL/F), bioavailability (F), and extravascular terminal phase volume of distribution (Vz/F).

Additional PK parameters may be determined where appropriate.

Exploratory Endpoints:

- Single dose AZD8895 and AZD1061 PK concentrations in nasal fluid.
- Assessment of SARS-CoV-2 neutralising activity of AZD7442.

Statistical Methods

Analysis Sets

The safety analysis set will include all participants who were randomised and received any amount of AZD7442. The PK analysis set will consist of all participants in the safety analysis set who received AZD7442 and who have evaluable serum PK data, with no important protocol deviations thought to impact on the analysis of the PK data. The Randomised Set will consist of all participants randomised into the study.

Presentation and Analysis of Safety and Tolerability Data:

The safety of AZD7442 will primarily be assessed and measured by the occurrences of all AEs and SAEs, as well as by review of safety clinical laboratory data and summary of clinical laboratory measurements (ie, serum chemistry, haematology, coagulation and urinalysis).

All AEs and SAEs will be summarised by system organ class, preferred term (using the latest available version of the Medical Dictionary for Regulatory Activities [MedDRA]), and by severity and relationship to IMP.

Presentation and Analysis of Serum Pharmacokinetic Data:

The serum AZD7442 mAbs (AZD8895 and AZD1061) concentrations and PK parameters will be listed and presented in tabular and graphical form as appropriate. For AZD7442 mAbs (AZD8895 and AZD1061), the serum concentrations for each scheduled time point will be summarised by treatment group using appropriate descriptive statistics, based on the PK analysis set. PK parameters will be derived using noncompartmental methods. All PK parameters will be summarised by treatment group using appropriate descriptive statistics, based on the PK analysis set.

Presentation and Analysis of Anti-drug Antibody Data:
The incidence of ADAs to AZD7442 will be summarised by number and percentage of participants who are ADA positive. The ADA titer will be listed by participant at different time points. The impact of ADA on PK, and association with AEs and SAEs may be assessed.

Presentation and Analysis of Exploratory Data:
Results of nasal fluid PK analysis and the evaluation of the functional inhibition of SARS-CoV-2 by AZD7442 concentrations in serum may form part of the study's report.

Interim Analysis:
There will be four unblinded interim analyses. The first will assess data from Cohort 1a and Cohort 1b once all participants in those two cohorts have completed their Day 8 visit. The second will assess cumulative data from all cohorts once all participants in Cohort 4 have completed their Day 8 visit. The third interim analysis will assess all available data from all cohorts once all participants in Cohort 4 have completed their Day 151 visit. The fourth interim analysis will assess data from all cohorts once all participants have completed their Day 211 visit and participants in Cohort 1a and Cohort 1b have completed their Day 271 visit. The results of these analyses will be used to assist AstraZeneca's internal operational planning. The primary analysis will be conducted when all treated participants for each planned analysis have completed follow-up through Day 31. All available data at the time of data cut-off will be included in the interim analyses. The unblinded safety, PK, ADA data (ADA data if available), neutralising antibody and nasal fluid data will be used to determine whether to initiate a Phase 2/3 prophylaxis study in broader populations. AstraZeneca personnel, associated personnel at the contract research organisation conducting the study and the testing laboratories will be unblinded as needed to perform the analysis and planning. Unblinded data may be shared with regulatory agencies and other parties for the development programs, as needed, in regulatory applications and other development-required correspondence. It is anticipated that study site personnel and participants will remain blinded.
The results will be based on clean data and nominal times will be used for the derivation of the serum PK parameters.
A subset of the outputs that will be required for the interim analyses will be identified in the tables, listings, and figures shells of this study and the results will be provided only on whichever data is available.

Determination of Sample Size
Approximately 60 healthy adult participants will be randomised to AZD7442 or placebo across 5 fixed-dose cohorts in a sequential order (for details refer study design). Because all analyses will be descriptive in nature and no hypothesis is being tested statistically, no formal sample size calculations were performed, however, the sample size is considered sufficient for an early assessment of safety, tolerability, immunogenicity, and PK. Additional cohorts may be added with lower or intermediate doses of AZD7442 if the DEC determines they are warranted:

- Cohort 1a (12 participants): 300 mg AZD7442 (150 mg AZD8895 and 150 mg AZD1061) (n=9) or placebo (n=1), administered IM,
  - Sentinel dosing: 300 mg AZD7442 (150 mg AZD8895 and 150 mg AZD1061) (n=1) or placebo (n=1), administered IM.

- Cohort 1b (12 participants): 300 mg AZD7442 (150 mg AZD8895 and 150 mg AZD1061) (n=9) or placebo (n=1), administered IV,
  - Sentinel dosing: 300 mg AZD7442 (150 mg AZD8895 and 150 mg AZD1061) (n=1) or placebo (n=1), administered IV.
- Cohort 2 (12 participants): 1000 mg AZD7442 (500 mg AZD8895 and 500 mg AZD1061) (n=9) or placebo (n=1), administered IV,
  - Sentinel dosing: 1000 mg AZD7442 (500 mg AZD8895 and 500 mg AZD1061) (n=1) or placebo (n=1), administered IV.
- Cohort 3 (12 participants): 3000 mg AZD7442 (1500 mg AZD8895 and 1500 mg AZD1061) (n=9) or placebo (n=1), administered IV,
  - Sentinel dosing: 3000 mg AZD7442 (1500 mg AZD8895 and 1500 mg AZD1061) (n=1) or placebo (n=1), administered IV.
- Cohort 4 (12 participants): 3000 mg AZD7442 (1500 mg AZD8895 and 1500 mg AZD1061 mixed in single infusion) (n=9) or placebo (n=1), administered IV,
  - Sentinel dosing: 3000 mg AZD7442 (1500 mg AZD8895 and 1500 mg AZD1061 mixed in single infusion) (n=1) or placebo (n=1), administered IV.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Please note that definitions of abbreviations for pharmacokinetic variables are presented in Section 10.2 of this protocol.

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.3.1.1)
ACE	Angiotensin converting enzyme
ADA	Anti-drug antibody
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
aPPT	Activated partial thrombin time
AST	Aspartate aminotransferase
AUC	Area under the curve
AUCinf	Area under the serum concentration versus time curve extrapolated to infinity
AUClast	Area under the serum concentration versus time curve from time zero to time of last measurable concentration
AV	Atrioventricular
AZRand	AstraZeneca randomisation system
β-hCG	Beta human chorionic gonadotropin
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CI	Confidence interval
CFR	Code of Federal Regulations
ClinBase™	Parexel's electronic source data capturing and information management system
COVID-19	Coronavirus disease-2019
(e)CRF	(electronic)Case report form
CL	Systemic clearance
CL/F	Apparent total clearance
Cmax	Maximum serum concentration
CRO	Contract research organisation
CRP	C-reactive protein
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Coefficient of variation
DAE	Adverse event leading to the discontinuation of IMP
DCF	Data clarification form
DEC	Dose Escalation Committee

Abbreviation or special term	Explanation
DES	Data Entry Site – where serious adverse event reports from AstraZeneca Clinical studies are entered onto the AstraZeneca Patient Safety database by Tata Consultancy Services
dECG	Digital electrocardiogram
DGR	Dangerous Goods Regulations
DILI	Drug-Induced Liver Injury
DMP	Data management plan
DNA	Deoxyribonucleic acid
DVS	Data validation specification
EC	Ethics Committee
ECG	Electrocardiogram
EClysis©	User-interactive, modular computer-based system for dECG data processing, analysis and measurement of ECG intervals and wave amplitudes, exports and reports, used by the AstraZeneca ECG Centre
ELF	Endothelial lining fluid
EMA	European Medicines Agency
EPCU	Early phase clinical unit
EU	European Union
FAAN	Fellow of the American Academy of Nursing
FcRn	Neonatal Fc receptor
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
FTIH	First time in Human
GCP	Good Clinical Practice
GGT	Gamma glutamyl transpeptidase (transferase)
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Hb	Haemoglobin
HBsAg	Hepatitis B surface antigen
HCT	Haematocrit
HED	Human equivalent dose
HIV	Human immunodeficiency virus
IATA	International Airline Transportation Association
IB	Investigator's brochure
I Bundle branch block	Incomplete bundle branch block
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

Abbreviation or special term	Explanation
IgG1	Immunoglobulin G1
INR	International normalised ratio
IM	Intramuscular
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISRB	Independent Safety Review Board
IUD	Intrauterine device
IUS	Intrauterine contraceptive system
IV	Intravenous
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
mAbs	Monoclonal antibodies
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
MHRA	Medicines and Healthcare Products Regulatory Agency
n	Number of participants
NIAID	National Institute of Allergy and Infectious Diseases
NA	Not applicable
ND	Not determined
NOAEL	No-observed-adverse-effect level
NR	No result
OSAE	Other significant adverse event
OTC	Over-the-counter
PD	Pharmacodynamics
PDF	Portable Document Format
PDS	Protocol deviation specification (document)
pECG	Paper print-out ECG
Ph.Eur.	European Pharmacopoeia
PHL	Potential Hy's Law
PI	Principal Investigator
PK	Pharmacokinetics
PPE	Personal protective equipment
PR(PQ)	ECG interval measured from the onset of the P wave to the onset of the QRS complex

Abbreviation or special term	Explanation
PT	Preferred term
QRS	ECG interval measured from the onset of the QRS complex to the J point
qRT-PCR	quantitative real-time polymerase chain reaction
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
R&D	Research and Development
RBC	Red blood cell
RBD	Receptor binding domain
RR	The time between corresponding points on two consecutive R waves on ECG
RSV	Respiratory syncytial virus
SAD	Single ascending dose
SAE	Serious adverse event (see definition in Section 6.3.1.2).
SAP	Statistical Analysis Plan
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SoA	Schedule of assessments
SOC	System Organ Class
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TBL	Total bilirubin level
TCA	Tricyclic anti-depressant
TCS	Tata Consultancy Services – an AstraZeneca partner who conduct data entry onto Sapphire
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TSH	Thyroid-stimulating hormone
TM	Triple mutation
Tmax	Time to reach maximum serum concentration
t½λz	Terminal elimination half-life
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
Vss	Volume of distribution at steady state
Vz/F	Apparent volume of distribution at terminal phase
Vz	Volume of distribution at terminal phase

Abbreviation or special term	Explanation
WAD	Window Allowance Document
WBC	White blood cell
WHO	World Health Organisation

INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden
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A list and contact details of Investigators and other key study team members are provided in the Project Plan in the electronic Investigator's Site File. A list of all participating Investigators will be provided in the Clinical Study Report (CSR).

1. INTRODUCTION

1.1. Disease Background

Coronaviruses are a family of large, single-strand, positive-sense RNA viruses which reside in multiple animal reservoirs, including bats. Coronaviruses are primarily respiratory viruses, and most typically cause common-cold like symptoms on an annual basis [1]. However, more pathogenic coronaviruses have the capacity to cross from animal hosts to humans, with varying degrees of human to human transfer, and can cause serious human disease [2]. The previous SARS outbreak began in China (2002 through 2003) and spread to 37 countries, with roughly 8,300 cases, 775 deaths, and a case fatality rate of ~10%. The MERS outbreak that has been ongoing since 2012 is even more deadly; while only 2,519 laboratory-confirmed cases have been reported this has included 866 associated deaths with a resulting case fatality rate of 34.3% [3].

Severe acute respiratory coronavirus 2 is a novel coronavirus that appears to have first emerged in China in November 2019 causing cases of atypical pneumonia. Since then, the COVID-19 pandemic has caused major disruption to healthcare systems with significant socioeconomic impacts. As of 20 July 2020, the virus had spread to all corners of the globe, involving 188 countries/regions with over 14.7 million confirmed cases reported and more than 610,000 associated deaths [4, 5]. As a response to the ongoing pandemic, AstraZeneca is developing mAbs to the SARS-CoV-2 spike protein. The SARS-Cov-2 spike protein contains the virus's receptor binding domain, which enables the virus to bind to receptors on human cells. By targeting this region of the virus's spike protein, antibodies can block the virus's attachment to human cells, and, therefore, is expected to block infection. Two IgG_1 antibodies that have been identified to have potent neutralising activity are being combined and will be evaluated for efficacy in both prophylactic and therapeutic settings. Amino acid substitutions have been introduced into the antibodies to both extend their half-lives, which should prolong their potential prophylactic benefit, and decrease Fc effector function in order to decrease the potential risk of antibody-dependent enhancement of disease. For detail please refer to the IB [6].

1.2. Rationale for Conducting This Study

AZD7442 is being evaluated for administration to prevent and/or treat COVID-19. This Phase I study, however, will gather important information on the safety and tolerability of AZD7442 as well as relevant data on the PK profile and the generation of ADAs to the mAbs.

As of Protocol Amendment no. 2, both sequential and co-administration of the mAbs will be investigated to gather important information on the PK, the IV administration process and infusion times.

1.3. Background to COVID-19

The regulatory authorities have issued new guidelines that aim to provide recommendations for actions for conduct of clinical studies of medical products during COVID-19 pandemic [7]. Since the pandemic situation is evolving, guidelines, recommendations, national laws and local restrictions may change at a rapid pace. Given the circumstances of a potentially relapsing pandemic or epidemic situation with regard to the spread of COVID-19 in the future, special attention will be given to protect participants participating in the study and site staff involved in the investigations against infection with SARS-CoV-2 as requested by the newly issued MHRA guidelines. In order to adhere to the newly issued MHRA Guidance on the Management of Clinical Trials during the COVID-19 pandemic an assessment of risk of the IMP and the study design has been done and concluded that AZD7442 is not expected to negatively interfere with healthy participants' response to COVID-19.

The participants enrolled in this study can be SARS-CoV-2 naive but should not be positive for SARS-CoV-2 mucosal swabs RT-PCR before allocation in the study.

The EPCU will consider including additional precautionary and safety measures in this study, such as social distancing to reduce the risk of SARS-CoV-2 infection, COVID-19, testing for presence of viral particles and antibodies and the use of PPE for both staff and volunteers guided by local requirements and current government advice. Information on COVID-19 considerations, testing and precautionary unit measures are described in a Unit specific consent form which is approved by the Generic Ethics Committee. The trial participants will be consented to Unit specific consent form in addition to the Study Specific consent form.

Participants will undergo COVID-19 testing at screening, prior to randomisation and can be performed as per PI’s discretion during the study, including the Follow-up Period. A participant with current confirmed COVID-19 infection will not be included in the study. Confirmed and suspected SARS-CoV-2 infection and COVID-19 will be recorded in the AEs fields.

2. STUDY OBJECTIVES

2.1. Primary Objective

Table 2-1 Primary Objective and Outcome Measures

Primary Objective	Outcome Measures
• To evaluate the safety and tolerability of AZD7442 administered IV or IM to healthy adult participants 18 to 55 years of age.	• AEs, SAEs, safety laboratory parameters (haematology, clinical chemistry, coagulation, and urinalysis); 12-lead safety ECG; vital signs (BP, pulse rate, oral temperature, and respiratory rate), and physical examination. • Injection site reactions will be monitored for the IM injection cohort (including assessment of size, redness/erythema, swelling, itching/pruritis, pain or tenderness, induration, discolouration) and will be recorded as an AE and a photograph taken, at the discretion of the PI, with visible measuring tape.

AEs: adverse events; BP: blood pressure; ECG: electrocardiogram; IM: intramuscular; IV: intravenous; SAEs: serious adverse events.

2.2. Secondary Objectives

Table 2-2 Secondary Objectives and Outcome Measures

Secondary Objective	Outcome Measures
• To evaluate the single dose PK of AZD7442 (when mAbs are administered sequentially [divided in separate infusion of each mAb component], and when mAbs are co-administered [both mAbs mixed into a single infusion]) in serum.	• After IV infusion: Cmax, Tmax, t½λz, AUClast, AUCinf, Vss, Vz, and CL. • After IM injection: Cmax, Tmax, t½λz, AUClast, AUCinf, extravascular CL/F, F, and extravascular Vz/F.
• To evaluate the ADA responses to AZD7442 in serum.	• Incidence of ADA to AZD7442 in serum over time.

ADA: anti-drug antibody; AUCinf: Area under the serum concentration versus time curve extrapolated to infinity; AUClast: Area under the serum concentration versus time curve from time zero to time of last measurable concentration ; CL: systemic clearance; CL/F: apparent total clearance; Cmax: maximum serum concentration; IM: intramuscular; IV: intravenous; PK: pharmacokinetics; t½λz: terminal elimination half-life; Tmax: time to reach maximum serum concentration; SAEs: serious adverse events; Vss: volume of distribution at steady state; Vz: volume of distribution at terminal phase; Vz/F: apparent volume of distribution at terminal phase.

2.3. Exploratory Objectives

Table 2-3 Exploratory Objectives and Outcome Measures

Exploratory Objective(s)	Outcome Measures
• To evaluate the single dose PK concentrations of AZD7442 in nasal fluid.	• Nasal fluid and blood samples to be collected, however, results may form part of the study's report.
• To evaluate the functional inhibition of SARS-CoV-2 by AZD7442 concentrations in serum.	

PK: pharmacokinetics; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Refer to Section 6.3 for safety variables and Section 10.2 for PK parameters.

3. STUDY DESIGN

3.1. Overall Study Design and Flow Chart

This is a Phase I, FTIH, randomised, double-blind, placebo-controlled, dose escalation study evaluating the safety, tolerability, and PK of AZD7442 in healthy adult participants, 18 to 55 years of age. Approximately 60 healthy participants will be enrolled at one study centre and randomised 10:2 to either AZD7442 or placebo administered IV or IM, across 5 fixed-dose cohorts. For participants who will receive the IMP via IM injection (Cohort 1a), the IMP will be administered as sequential direct gluteal IM administrations starting with AZD8895/placebo and followed by AZD1061/placebo. For participants who will receive IMP via IV infusion in the first 3 cohorts to be dosed via IV infusion (Cohorts 1b, 2, and 3), the IMP will be administered in two sequential IV infusions at a maximal infusion rate of 20 mg/minute, starting with AZD8895/placebo and followed by AZD1061/placebo. For participants who will receive the IMP via IV infusion in Cohort 4, the IMP will be co-administered as a single IV infusion containing both mAbs at a maximal infusion rate of 50 mg/minute. Additional cohorts may be added with lower or intermediate doses of AZD7442 if the DEC determines they are warranted.

All participants will be admitted to a Phase I unit on their respective Day -1 (1 day prior to dosing; SARS-CoV-2 qRT-PCR results must be available before dosing on Day 1) and discharged on Day 2 (1 day after dosing, after the 24-hour procedures are completed). Participants will then be followed up until and including Day 361 for safety, including recording of AEs and SAEs, and collection of blood samples for PK and ADAs. Sentinel dosing (see Section 3.3.1) will be applied for all dosing cohorts to ensure participant safety. Two participants of each cohort will be dosed at a ratio of 1:1 (AZD7442:placebo) and will then undergo a safety monitoring period for at least 24 hours before dosing the rest of the participants of that cohort. Escalation from one dose level to the next dose level, and from the last cohort with sequential IV infusions of the mAbs (Cohort 3) to the first cohort with a co-administered infusion of the mAbs (Cohort 4), will be based on review of all available safety data up to and including Day 8. In addition, any available PK data will also be reviewed.

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. Reporting of SARS-CoV-2 positive results during the study conduct will be reported as AEs and measures will be applied at the discretion of the PI to minimise further SARS-CoV-2 exposure as much as possible. Guidance for management of subjects who wish to receive an approved vaccine for protection against SARS-CoV-2 is provided.

Details on IMP administration are provided in Section 5.4.3.

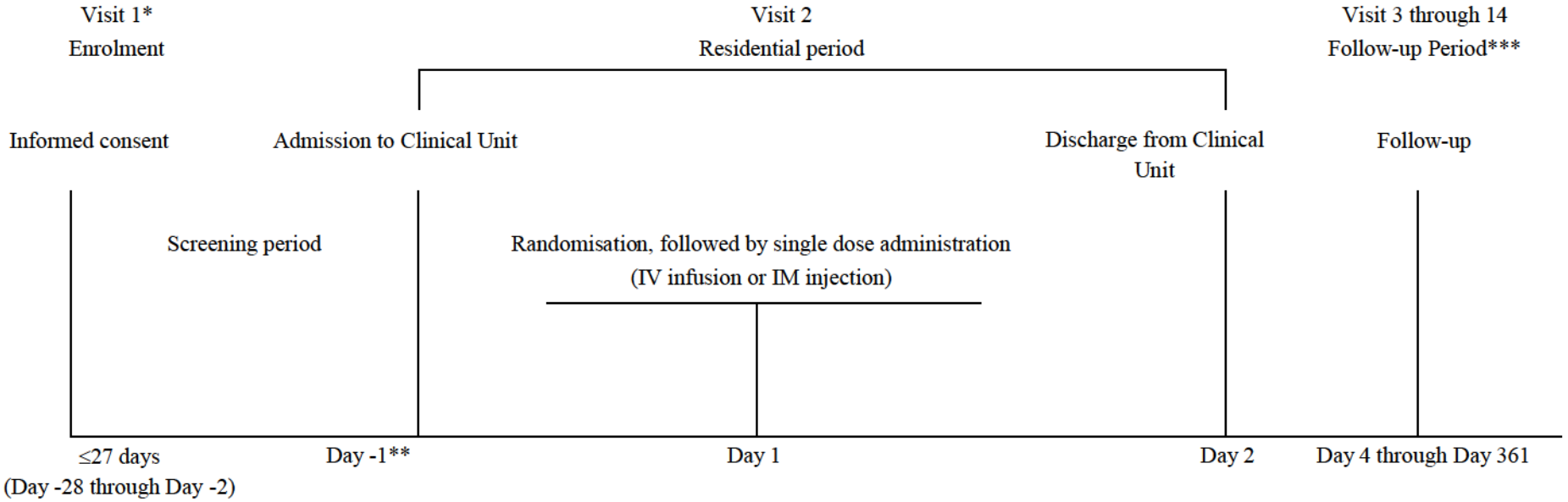
The study will comprise of:

- A Screening Period of up to 27 days (Day -28 through Day -2);
- A Treatment Period during which participants will be resident at the Clinical Unit from Day -1, 1 day before IMP administration (on Day 1) until at least 24 hours after IMP administration, will be discharged on Day 2 after all safety evaluations have been completed, and
- A Follow-up Period lasting 360 days (through to Day 361) after the IMP dose. Should a subject want to be unblinded for vaccination purposes outside the visit windows during the Follow-up Period, an unscheduled unblinding visit will be included).

The study design is deemed appropriate for conduct in healthy volunteers during the COVID-19 pandemic ongoing at the time of writing this CSP.

The study flow-chart is presented in Figure 3-1 and the overall graphical representation of the study scheme is illustrated in Figure 3-2. The SoA displaying assessments/tasks and time points is presented in Table 3-1, Table 3-2, and Table 3-3.

Figure 3-1 Study Flow Chart



* Visit 1 may be conducted over one or more days during the Screening Period

** Participants may be admitted to the Clinical Unit on Day -2 to allow for SARS-CoV-2 qRT-PCR results to be available before dosing on Day 1.

*** An unscheduled unblinding visit will be included should a subject want to be unblinded for vaccination purposes outside the visit windows.

IM: intramuscular; IV: intravenous; qRT-PCR: quantitative real-time polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Figure 3-2 Overall Graphical Representation of the Study

AZD7442 will be administered sequentially in Cohorts 1a, 1b, 2, and 3 (AZD8895/placebo followed by AZD1061/placebo).

IM: intramuscular; IV: intravenous; n: number of participants.

See Section 11.4 and Section 3.3.1 for further details on determination of sample size and sentinel dosing, respectively.

Table 3-1 Schedule of Assessments (Screening)

Screening Procedures	
Study Period	**Screening**
Procedure / Study	**Day -28 to Day -2**
Written informed consent/assignment of Run-in number	X
Medical history and demographics	X
Full physical examination, height, weight and BMI	X
12-Lead ECG	X
Vital signs	X
Serum chemistry	X
Haematology	X
Coagulation	X
Follicle stimulating hormone (postmenopausal women only)	X
Urinalysis	X
Pregnancy test (serum β-hCG) [a]	X
HIV, hepatitis B, hepatitis C testing	X
Urine drug and alcohol screen	X
Assessment of AEs/SAEs	X (SAEs only)
Concomitant medications	X
Verify eligibility criteria	X
SARS-CoV-2 serology and qRT-PCR [b]	X

a. Female participants only. Pregnancy test must be negative at screening.
b. SARS-CoV-2 serology can be done at screening visit. Confirmatory qRT-PCR can be done at the discretion of the PI depending on the serology results at screening. A qRT-PCR must be done at admission and result shown to be negative prior to randomisation of participants. The COVID-19 tests at screening will be performed as part of the Clinical Unit's general screening. These COVID-19 screenings will occur after the subject has consented to the COVID-19 screening and before consent for the study is obtained.

AE: adverse event; β-hCG: beta human chorionic gonadotropin; ECG = electrocardiogram; HIV = human immunodeficiency virus; PI: principal investigator; qRT-PCR: quantitative real-time polymerase chain reaction; SAE: serious adverse event.

Table 3-2 Schedule of Assessments (Treatment Period)

Treatment Period Study Procedures					
Procedure	**Treatment Period**				
	Day -1 [a]	**Dosing (Day 1)**			**Day 2**
	Admission	**Dosing**	**End of Dosing**	**8 hours post-dose**	**Discharge**
Medical History	X [b]				
Physical examination	X [b] (brief)				
Weight	X				
12-Lead ECG [c]		X	X	X	X
Vital signs	X	X [d]	X [d]	X	X
Serum chemistry	X				
Haematology	X				
Coagulation	X				
Urinalysis	X				
Pregnancy test (urine hCG)	X [e]				
Urine drug and alcohol screen	X				
PK serum sample		X [f]	X [g]	X	X
PK nasal fluid sample		X			
ADA serum sample		X			
Neutralising antibody serum sample	X				
Assessment of SAEs and AEs	X (ongoing observation and questioning)				
Concomitant medications	X (ongoing observation and questioning)				
Verify eligibility criteria	X	X			
Admission to the Clinical Unit	X [h]				
Randomisation after admission to infusion unit		X			
Screen Failure		X			
Participant identification card		X			
Investigational medicinal product administration		**X**			
Injection site reaction monitoring (local tolerability) [i]		X	X	X	X

a. Participants may be admitted to the Clinical Unit on Day -2 to allow for SARS-CoV-2 qRT-PCR results to be available before dosing on Day 1. For these participants, admission assessments may be performed on Day -1.
b. Update screening medical history and physical examination (any new findings since screening).
c. ECG will be obtained after at least five minutes supine rest (pre-dose) in all cohorts. In the IV cohorts time points will include pre-dose on Day 1, at completion of infusion, 60 minutes after completion of infusion, 4 and 8 hours (± 10 minutes) post start of IMP administration. For the IM cohort ECGs will be obtained at pre-dose on Day 1, and at 1, 4, and 8 hours after the start of IMP administration. On Day 2, resting ECG will be performed before discharge for all cohorts.

d. Vital signs will be monitored before and after IM and IV administration of IMP. A pre-dose BP, pulse rate, temperature and respiratory rate readings will be obtained in all cohorts. For IV cohorts, vital signs should be monitored at the start of infusion and every 30 minutes (± 5 minutes) during infusion, at completion of infusion (± 5 minutes), 30 (± 5), and 60 (± 5) minutes after completion of infusion. For the IM cohort, vital signs should be monitored at 30 (± 5) minutes and 60 (± 5) minutes post-dose.
e. Female participants only. Pregnancy test must be negative prior to dosing.
f. Pre-dose sample for both IM and IV dosing cohorts. For IV cohorts an additional sample is to be collected when the infusion is 50% complete (for each mAb when IV administration is sequential in Cohorts 1b, 2 and 3, and once during the co-administered single infusion in Cohort 4).
g. For IV cohorts only (end of infusion for each mAb in Cohorts 1b, 2 and 3, and for the co-administered infusion in Cohort 4).
h. Participants may be admitted to the Clinical Unit 2 days prior to dosing (Day -2) to allow for SARS-CoV-2 qRT-PCR results to be available before dosing on Day 1. For these participants, admission samples may be collected on Day -1.
i. Local tolerability check: for participants in Cohort 1a (intramuscular administration only). Assessments at pre-dose, immediately after dosing, 0.5, 1, 8, and 24 hours post-dose.

AE: adverse event; ADA: anti-drug antibodies; ECG: electrocardiogram; hCG: human chorionic gonadotropin; IMP: investigational medicinal product; IV: intravenous; IM: intramuscular; mAb: antibody; PK: pharmacokinetic; qRT-PCR: quantitative real-time polymerase chain reaction; SAE: serious adverse event; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

NOTE: With the exception of vital signs and safety ECGs [c,d], all Day 1 assessments are to have their start time (nominal time) match the time of "end of infusion". Post-dose assessments on Day 2 are to have their start time (nominal time) match the time point of Day 1 "start of infusion".

Table 3-3 Schedule of Assessments (Follow-up)

Follow-up Procedures											
Procedure	**Post-dose Follow-up Day ± Assessment Window [c]**										
	4	**6**	**8 -1**	**15 ±1**	**31 -2**	**61 ±5**	**91 ±5**	**151 ±5**	**211 ±5**	**271 ±10**	**361 ±10**
Vital signs [a]	X		X		X		X	X	X	X	X
12-Lead safety ECG			X		X						X
Serum chemistry	X		X		X						X
Haematology	X		X		X						X
Coagulation	X		X		X						X
Urinalysis	X		X		X						X
PK serum sample	X	X	X	X	X	X	X	X	X	X	X
PK nasal fluid sample			X		X		X	X			
ADA serum sample			X	X	X		X	X	X		X
Neutralising antibody serum sample			X		X	X	X	X	X	X	X
Assessment of AEs and SAEs [b]	X (ongoing observation and questioning)										
Concomitant medications	X (ongoing observation and questioning)										
Full physical examination			X		X						X
Weight											X
Study completion information											X

Follow-up Procedures											
Procedure	**Post-dose Follow-up Day ± Assessment Window [c]**										
	4	**6**	**8 -1**	**15 ±1**	**31 -2**	**61 ±5**	**91 ±5**	**151 ±5**	**211 ±5**	**271 ±10**	**361 ±10**
Pregnancy test (urine hCG)					X	X	X	X	X	X	X
AstraZeneca Thank you Card											X

a. Any abnormal vital signs must be repeated after the participant has been at rest for at least five minutes. As part of COVID-19 monitoring daily oral temperature measurements during in-house stay and at every outpatient visit will be implemented.
b. SARS-CoV-2 qRT-PCR or serology to be performed at the discretion of the PI.
c. An unscheduled unblinding visit will be included should a subject want to be unblinded for vaccination purposes outside the visit windows.

ADA: anti-drug antibodies; AE: adverse event; ECG: electrocardiogram; β-hCG: beta-human chorionic gonadotropin; PK: pharmacokinetic; qRT-PCR: quantitative real-time polymerase chain reaction; SAE: serious adverse event; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

NOTE: All post-dose assessments from, and including, Day 2 are to have their start time (nominal time) match the time point of Day 1 "start of infusion".

3.1.1. Order of Assessments

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

1 12-Lead Safety ECGs.
2 Vital signs (systolic and diastolic BP and pulse rate, oral temperature and respiratory rate).
3 PK blood and nasal fluid sampling (will be collected at the specified time point).
4 Safety blood and urine sampling.
5 Other procedures.

Details of acceptable tolerance windows for safety and PK assessments will be included in a WAD which will be agreed upon and signed off before the start of the study.

3.1.2. End of Study

The end of study is defined as the last participant's last visit to the Clinical Unit.

3.1.3. Expected Duration of the Study

Each participant will be involved in the study for up to 389 days (an up to 27-day Screening Period [Day -28 through Day -2]; a 2-day Treatment Period [Day -1 and Day 1] and a 360-day Follow-up Period [Day 2 through Day 361]).

Table 3-4 Expected Duration of Each Study Part

	All Participants
Screening	Period of 27 days. Day -28 through Day -2. Two days before dosing (Day 1).
Treatment Period	A single Treatment Period during which participants will be resident at the Clinical Unit from 1 day before dosing (Day -1) until at least 24 hours after dosing (Day 2) and will be discharged on Day 2 after the 24-hour assessments are completed. Participants may be admitted to the Clinical Unit on Day -2 to allow for SARS-CoV-2 qRT-PCR results to be available before dosing on Day 1.
Washout Period	Not applicable.
Follow-up	A 360-day safety Follow-up Period (up to and including Day 361).
Total Duration	Up to 389 days.

qRT-PCR: quantitative real-time polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

3.2. Rationales for Study Design and Dose Selection

3.2.1. Rationale for Study Design

AZD7442 is being evaluated for administration to prevent and for treatment of COVID-19. This Phase I study will gather important information on the safety and tolerability of AZD7442, as well as relevant data on the PK profile and the generation of ADAs.

3.2.2. Rationale for Endpoints

The primary study endpoints are standard endpoints for safety assessment, including AEs, SAEs, and safety clinical laboratory measurements. Use of the safety endpoints is justified by their ability to characterise the safety and tolerability profile of AZD7442 in healthy adults prior to administration to broader populations in later Phase 2/3 studies.

The secondary study endpoints are those required to define the PK and incidence of ADAs through 360 days after administration (Day 1 through Day 361). The 360-day Follow-up Period will allow follow-up of dosed participants through approximately five half-lives, which is expected to provide sufficient safety follow-up and will also maximise the probability of detecting ADA to AZD7442. The PK endpoints will describe the disposition of AZD7442 in healthy adults after IV or IM administration. Anti-drug antibody responses and incidence will be measured to ensure that they are at acceptable levels and do not affect safety or PK. In an exploratory assessment, the functional activity of AZD7442 will also be assessed by the ability to neutralise SARS-CoV-2 infection in a microneutralisation assay.

3.2.3. Dose Rationale

Dose levels of AZD7442 in FTIH study were selected based on all available pharmacology and PK data, which were used to predict HED. Human PK parameters for AZD7442 were predicted based on observed nirsevimab (MEDI8897) human PK data. Nirsevimab is an anti-RSV IgG1 with YTE substitution to prolong half-life. AZD7442 is an anti-COVID-19 IgG1 with both YTE and TM substitutions. Similar PK for AZD7442 and nirsevimab was observed in human FcRn transgenic mice. The similarity of PK for AZD7442 and MEDI8897 will be confirmed in the monkey study.

Human efficacious doses were projected based on in vitro functional potency data that accounts for potential synergistic effect of two-mAb combination. These dose levels were selected to ensure exposure in serum and the ELF of the lungs to be above the IC_{80} for AZD7442 to be approximately CCI 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 pharmacodynamic effects of AZD7442 on the growth of a SARS-CoV-2 infection and the resulting immune response. For prophylaxis, 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} for AZD7442 to be approximately CCI, a minimum effective IM dose of

CCI is required for prophylaxis to provide protection from SARS-CoV-2 infection for 5 months. If the partition ratio is 0.1%, a conservative assumption, then a minimum effective dose of CCI IM may be needed for prophylaxis. With 76% IM bioavailability assumed, IV doses would be proportionally lower. For participants with active infection, the model indicates that virus entry inhibition greater than approximately 92% is sufficient to rapidly suppress the viral load to less than one copy per swab, which is a numerical cut-off criteria that is regarded as clinically meaningful effect that will accompany complete natural infection clearance. With an entry inhibition IC_{80} for AZD7442 to be approximately CCI and a lung ELF to serum partition range of 1% to 0.1%, the minimum effective dose then ranges from 300 mg IM to 3000 mg IM. This aligns with the dose required to achieve the target reduction of 92% in virus entry inhibition. With 76% IM bioavailability assumed, IV doses would be proportionally lower.

Pending completion of ongoing toxicology studies, the assumption is the dose tested in monkey toxicology study (CCI per Ab for IM and CCI per Ab for IV) is the NOAEL. Safety margins are predicted using expected exposures at monkey NOAEL divided by expected exposures at human doses in the Phase 1 study. Sufficient safety margins are maintained for starting and top dose levels in the Phase 1 study. At the starting dose of CCI per Ab IM, Cmax-based safety margin is 30, AUC-based and HED-based safety margin is 10. At the starting dose of 150 mg per Ab IV, Cmax-based safety margin is 120, AUC-based and HED-based safety margin is 40. At the top dose of 1500 mg per Ab IV, Cmax-based safety margin is 12, AUC-based and HED-based safety margin is four.

3.2.4. Rationale for Study Population

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. Thus, this study is being conducted in healthy adults 18 to 55 years of age. The PK of AZD7442 in healthy adults, aged 18 to 55 years is expected to be most representative of that in the potential target populations, making the healthy population appropriate for dose selection. In addition, initially evaluating AZD7442 in healthy volunteers allows safety data to be gathered with the lowest risk of observing confounding events related to pre-existing underlying illnesses or prior COVID-19 exposure.

3.2.5. Dose Escalation Strategy

A study specific DEC will be responsible for dose escalation decisions, and for the decision to permit IV co-administration of the mAbs mixed in a single infusion, after review of up to and including Day 8 safety data from Cohort 1b and onwards. An expected minimum of 8 participants' worth of safety data will be required to evaluate the dose escalation. This committee includes the AstraZeneca Lead Physician, the AstraZeneca Patient Safety Physician, and the PI for the study. Ad hoc members may be added or consulted on an as-needed basis. The DEC will review blinded data, including all AEs and laboratory parameters, after all participants in each dose cohort (unless withdrawn or lost

to follow-up) have been followed through to the Day 8 visit. Blinded updated safety data from lower dosing cohorts will also be reviewed for the dose escalation decisions. Blinded updated safety data from the 3000 mg IV sequentially dosed cohort will be reviewed prior to a decision to permit IV co-administration of the 2 mAbs that comprise AZD7442. This committee may also review blinded data at other time points in response to AEs assessed as medically relevant by the Lead Physician or PI. The DEC may also request to review unblinded data if this is considered necessary to fully evaluate a potential safety signal. The 7-day Follow-up Period should provide adequate safety information for dose escalation, and the transition from sequential administration to co-administration of the mAbs, because 1) AZD7442 does not have human host tissue targets and 2) there are no specific safety concerns in light of the tissue cross-reactivity data.

3.2.6. Stopping Criteria for Dose Escalation

If rules specified in this chapter are fulfilled, dosing will be stopped. (Please refer also to DEC section for further information.)

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

Each participant in this study will receive a single dose of IMP (divided into two separate doses for each mAb component). An individual participant will not receive IMP if any of the following occur in the participant in question:

- Withdrawal of consent after signing informed consent.
- Participant meets one or more of the exclusion criteria or fails to meet all inclusion criteria for study participation.
- A severe or potentially life-threatening serious systemic, allergic, or local reaction with onset after dosing has been initiated. If such a reaction is observed during IMP administration, the infusion will be immediately stopped, no further IMP will be administered, and the Lead Physician must be contacted immediately.

Each participant who has received IMP will be followed for the full study period unless consent is withdrawn specifically from further study participation, or the participant is lost to follow-up. Participants who have not received IMP, regardless of reason, will not be followed. Unless consent for follow-up is withdrawn, participants discontinued after receiving a partial dose of IMP will be followed for the full study period (up to and including Day 361, 360 days after IMP dosing) with all laboratory and clinical evaluations collected as defined in this CSP.

3.2.6.2. Stopping Rules for a Whole Cohort, Dose Escalation, Progression to Next Study Part and Termination of Study

Stopping rules as detailed below (general, cardiovascular, laboratory, and AZD7442 specific) are applicable for each of the following situation:

- Stopping dosing for a whole cohort.
- Stopping dose escalation.
- Final stop of study.

General Criteria

The study will be put on temporary hold (defined as treatment stopped for enrolled participants; and stop of enrolment of participants into the study) pending further safety data analysis if any of the following criteria occur in participants receiving AZD7442:

- A "serious" adverse reaction (ie, a SAE [including death]) considered at least possibly related to the IMP administration) in any one participant;
- "Severe" non-serious adverse reactions (ie, severe non-serious AEs considered as, at least, possibly related to the IMP administration) in two or more participants in the same cohort, independent of within or not within the same SOC.

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

The DEC will carefully review the totality of data, taking into account moderate non-serious AEs at least possibly related to the IMP administration, the number of participants in which they occur, and concurrency of more than one within the same participant.

Cardiovascular Criteria

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

Laboratory Findings

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

Study Specific Stopping Criteria Related to AZD7442

1 Anaphylactic reaction (per NIAID and the FAAN definition [8]) considered related to the IMP in any participant.

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

3.2.7. Dose Escalation Committee

3.2.7.1. Composition of Dose Escalation Committee

The DEC will consist of the following core members:

- Principal Investigator (Chair, voting member).
- AstraZeneca Lead Physician (voting member).

- AstraZeneca Patient Safety Physician (voting member).

The DEC may also request to have attendance of or off-line support and input from the following functions as required:

- AstraZeneca Clinical Pharmacokineticist.
- AstraZeneca Team Pharmacometrician.
- Covance Pharmacokineticist.
- AstraZeneca Statistician.
- AstraZeneca and/or Parexel and/or external Medical Specialists as needed. AstraZeneca Clinical Scientist and Safety Scientist may provide inputs as necessary.

Written statements and conclusions by the DEC will be in place before allowing trial progression at the noted times as per CSP. This includes documentation of appropriate quality control checks on the data reviewed.

3.2.7.2. Data Reviewed by Dose Escalation Committee for Dose Escalation Decision

The DEC will decide on progression to the next CSP-specified dose levels throughout the study, and for the decision to permit IV co-administration of the mAbs mixed in a single infusion, considering at each decision point the degree of uncertainty (Section 3.3).

At every DEC, cumulative data for all cohorts will be reviewed. The following data will be reviewed for each individual cohort:

- Safety and tolerability data for up to 24 hours post-dose for the sentinel participants and at least 7 days' worth of post-dose safety data for each cohort for dosing escalation between cohorts.

Evaluable participants are defined as participants on AZD7442/placebo, who have completed all safety follow-ups, as detailed above. A minimum number of evaluable participants of eight on AZD7442 will be considered appropriate for DEC decision; no replacement participants are planned.

Appropriate safety data collection of up to and including Day 8 safety data in a given dosing cohort should be complete to proceed to the next dose cohort.

3.2.7.3. Dose Escalation Committee Decision on Next Dose

The DEC will make the decision whether to escalate to the next dose level, or to permit IV co-administration of the mAbs, or expand the size of the last dosed cohort, or stop the study after reviewing all the pertinent safety and any other relevant data.

If consensus among the voting DEC members cannot be reached then the PI, who has the ultimate responsibility for the safety of the participants, will make the final decision on the

next dose level, next cohort, or whether to stop the study. In order to escalate to a next dose level or cohort a unanimous DEC decision is needed.

The decisions of the DEC on the next dose level or cohort will be documented and provided to all the appropriate parties involved with the study, including the Pharmacist to enable IMP preparation for the next scheduled dosing day.

- A dose in which the safety stopping criteria have been met (please refer to Section 3.2.6, Stopping Rules) will not be repeated and further dose escalation **must not** occur.
  - In this case, the DEC will review the totality of data and restart of dosing is possible without a substantial amendment (eg, in the case of a laboratory error) if DEC review concludes that the relevant stopping criterion was not fulfilled.
  - A lower dose level expected to be tolerable and not to meet the stopping criteria, would be acceptable in this case.
  - If the safety stopping criteria are met and the DEC decides that there are reasons that the dose level should be repeated or further dose escalation is warranted a summary of the data and justification (protocol amendment) will be submitted to the AstraZeneca Safety Review Committee, the ISRB, the Regulatory Authority and EC for their approval before further dosing.
- In some circumstances, consideration can be given to test fractionated or split doses.

3.2.7.4. Blinding at Dose Escalation Committee Meeting

Initially, the data will be reviewed blinded, but if the PI or the DEC consider it necessary due to a safety concern, either individual participants or the entire cohort may be unblinded to using code break envelopes to enable decision-making. The code will be broken according to local SOPs.

3.2.7.5. Assessments Adaptation

Following review of data from a cohort of participants, the timing of assessments and/or blood samples may be adjusted for subsequent cohorts.

Additional assessment or sampling times may be added if indicated by the data; however, the maximum blood volume taken from each participant will not exceed 240.2 mL for participants in the IV group and 230.2 mL for participants in the IM group.

3.3. Degree of Uncertainty

At the time of this CSP, no clinical studies have yet been conducted with AZD7442. Overall, it is considered that the AZD7442 non-clinical data available to date and clinical data from similar compounds, along with the sentinel dosing strategy and appropriate clinical monitoring applied in the study, provide confidence that the risk to subjects will be minimised. The non-clinical toxicology studies are ongoing.

3.3.1. Sentinel Dosing

Dosing for all cohorts will be initiated with two participants in a sentinel cohort, such that one participant will be randomised to receive placebo and one participant will be randomised to receive AZD7442. The safety data from the sentinel participants up to 24 hours post-dose will be reviewed by the PI before the remaining participants in the cohort are dosed. The remaining 10 participants for each cohort will be dosed at least 24 hours after the sentinel cohort at a ratio of 9:1 active to placebo.

3.3.2. Co-administration of Monoclonal Antibodies

Mixing the mAbs prior to dosing, and co-administering the mAbs as a single IV infusion, offers a simplified process for administering AZD7442, and allows for a faster infusion rate, shortening the time needed for dosing. Intravenous co-administration of the mAbs will be performed in this study only after their sequential administration has been tested and observed to have had an acceptable safety profile. Instructions for dosing are provided in the pharmacy manual.

3.4. Risk-Benefit and Ethical Assessment

3.4.1. Description of AZD7442

AZD7442 is a combination of two recombinant human IgG1κ mAbs, AZD8895 and AZD1061, directed against the RBD of the spike protein of SARS-CoV-2. AZD7442 is comprised of the 2 mAbs to minimise the potential of virus mutational escape. AZD8895 and AZD1061 mAbs have been engineered with triple amino acid substitutions M252Y/S254T/T256E (YTE) in the Fc region to prolong the t1/2, which is expected to provide protection from COVID-19 for a duration of at least 5 months. In addition, the triple amino acid substitutions L234F/L235E/P331S (TM) in the Fc region were engineered for both AZD8895 and AZD1061 to abrogate Fc-mediated effector function, which is expected to reduce potential risk of antibody-dependent enhancement of disease.

3.4.2. Mode of Action

3.4.2.1. Primary Pharmacodynamics

AZD7442 consists of two separate mAbs which bind to distinct, non-overlapping sites on the SARS-CoV-2's spike protein's receptor binding domain. Binding to either of these sites blocks the virus's ability to bind to its human cellular receptor, ACE2. By blocking virus entry into human cells, AZD7442 has the potential to prevent or treat illness due to SARS-CoV-2 infection, COVID-19. AZD7442 has no human targets, and no human pharmacodynamic effects are expected.

3.4.3. Toxicology Pre-clinical Data

3.4.3.1. Toxicology

A pre-clinical safety program including assessment of tissue cross-reactivity in human and cynomolgus monkey tissues and a single dose toxicology study in cynomolgus monkeys. As of 24 July 2020: To date, no pre/clinical findings indicating risks to participating

participants were observed. Assessment of tissue cross-reactivity of AZD7442 and the individual antibodies AZD8895 and AZD1061 to human and cynomolgus monkey tissues is ongoing. Results to date demonstrated no binding of AZD7442 or its individual components to any human tissue. Assessment of binding to cynomolgus monkey tissues is pending. The single dose toxicity study in cynomolgus monkeys is ongoing.

Further information on pre-clinical findings is available in the IB [6].

3.4.4. Clinical Studies

AZD7442 has not been evaluated in clinical studies previously. This is a FTIH clinical study.

3.4.5. Risk Assessment for AZD7442

For AZD7442, no adverse reactions have been identified yet due to non-availability of clinical data. Any adverse event that is deemed to be related to the IMP by the investigator or the company, which is also serious will be treated as a SUSAR and appropriately expedited.

As no clinical data on AZD7442 is available, the safety precautions and the study design are based on previous AstraZeneca experiences of similar mAbs (mAbs containing the YTE substitution: nirsevimab , suvratoxumab, and motavizumab; mAbs that contain TM substitution: imfinzi, anifrolumab, and oleclumab). The development program for AZD7442 resembles a platform approach as the safety of IgG1 mAbs with either YTE or TM substitutions has been previously demonstrated in clinical trials.

AstraZeneca considers that the data gathered in the Phase 1 studies for both MEDI4893 (mAb that binds the *Staphylococcus aureus* alpha toxin; survatoxumab) and MEDI8897 (mAb that binds the RSV fusion protein; nirsevimab) support using safety data to initiate future studies with AZD7442. Like AZD7442, both antibodies do not have human host cell targets, and both mAbs also have the YTE substitutions introduced for half-life extension. Safety follow-up in both studies was for one year, which is also the planned safety Follow-up Period for AZD7442. In general, in both programs the safety profile of the mAbs, whether administered IV or IM, was similar to that seen for placebo.

In the MEDI4893 Phase 1 study, the incidence of TEAEs was not elevated in participants who received the mAb compared to placebo participants. In addition, no grade 3 or higher TEAEs or TESAEs were recorded and no participants discontinued from the study due to a TEAE.

In the MEDI8897 Phase 1 study, the overall incidence of TEAEs was similar in mAb recipients compared to placebo recipients, and while there were three events that were classified as either Grade 3 TEAEs or as TESAEs in participants who received 300 mg of MEDI8897 IM (eye injury, gunshot wound and appendicitis), these events were not considered related to receipt of IMP. No participants discontinued from the study due to a TEAE.

Based on this, the safety information available to date supporting dosing in the FTIH trial is considered appropriate and the risk for any undesired adverse effects is considered low.

Further, the FTIH study design with the safety precautions outlined below is considered appropriate and in line with FTIH guidelines.

The planned dosing scheme for this study has been designed to test a range of doses being considered for prophylaxis and/or treatment, while escalating doses in a controlled manner.

Overall, it is considered that the AZD7442 nonclinical data available to date and clinical data from similar compounds along with the sentinel dosing strategy and appropriate clinical monitoring applied in the FTIH study provide confidence that the risk to healthy volunteers will be minimised.

3.4.6. Risk Assessment for COVID-19 Pandemic

The regulatory authorities have issued new guidelines that aim to provide recommendations for actions for conduct of clinical studies of medical products during COVID-19 pandemic [9]. Since the pandemic situation is evolving, guidelines, recommendations, national laws, and local restrictions may change at high pace. Given the circumstances of potentially relapsing pandemic or epidemic situation with regard to the spread of COVID-19 in future, special attention will be paid to protect participants in the study and site staff involved in the investigations against infection with SARS-CoV-2 as requested by the newly issued MHRA guidelines.

Measures to mitigate possible risks caused by SARS-CoV-2 are:

- Current national laws and local recommendations for prevention of pandemic will be strictly adhered to.
  - COVID-19 serology testing will be performed at Screening.
  - Negative SARS-CoV-2 qRT-PCR test is required for admission.
  - Further COVID-19 testing during the study, including Follow-up Period can be performed as per PI's discretion.
- Participants will be closely monitored for any signs and symptoms of SARS-CoV-2, including fever, dry cough, dyspnoea, sore throat and fatigue throughout the study. Once clinical signs of infection are reported by participants, the PI needs to determine whether samples can be collected, and safety data can be recorded on site. In such circumstances, if samples cannot be collected on site, every effort should be made to collect scheduled samples off-site in a manner safe for staff and participants. If not, AEs and concomitant medications will be obtained via phone calls. Daily oral temperature measurements during in-house stay and outpatient visits will be implemented.
- Confirmation of SARS-CoV-2 infection by optional laboratory assessment will be conducted based on availability (test capacity and turnaround time) of approved tests and at PI's discretion.
- The probability of virus transmission will be controlled as much as possible by:

  - Advice for participant to adhere to local requirements for reduction of the public exposure while ambulatory.
  - The EPCU will include additional precautionary and safety measures in this study, such as social distancing, the use of PPE for both staff and volunteers to reduce the risk of SARS-CoV-2 infection guided by local requirements and current government advice.
  - Information on COVID-19 considerations, testing and precautionary unit measures are described in Unit specific Consent form which is approved by the generic EC. The study participants will be consented with the Unit specific Consent form in addition to the study specific Consent form.
- Confirmed and suspected SARS-CoV-2 infection and COVID-19 will be recorded in the adverse event fields.
- Participants may be withdrawn by the PI based on discussion with the Sponsor and Lead Physician under the following circumstances:
  - Any confirmed COVID-19 case that warrants discontinuation in the judgement of the PI or Sponsor to protect the safety of the participant, other study participants or study site staff. Participants that are withdrawn due to confirmed COVID-19 case will be followed up until the final outcome of the AE.

4. STUDY POPULATION

4.1. Selection of Study Population

The PI should keep a participant screening log of all potential participants who consented and were subjected to screening procedures.

Participants who fail to meet the inclusion criteria or meet any exclusion criterion should not, under any circumstances, be randomised into the study. There can be no exceptions to this rule.

This study will be conducted on male and female participants. The study may not necessarily be balanced regarding gender. The study was not formally powered to detect differences between genders for the primary endpoint. It is not planned to perform sub-analyses on gender.

4.1.1. Inclusion Criteria

For inclusion in the study participants should fulfil all of the following criteria:

1 Aged 18 through 55 years (both inclusive) at the time of screening.

2 Written informed consent and any locally required authorisation obtained from the participant prior to performing any CSP-related procedures, including screening evaluations.

3 Negative SARS-CoV-2 qRT-PCR and/or serology tests prior to randomisation.

4 Weight ≥ 50 kg and ≤ 110 kg at screening, including a BMI of ≥ 18.0 to ≤ 30.0 kg/m^2.

5 Healthy by medical history, physical examination, and baseline safety laboratory studies, according to the judgement of the PI.

6 Electrocardiogram without clinically significant abnormalities at screening.

7 Able to complete the Follow-up Period through Day 361 as required by the CSP.

8 Females of childbearing potential who are sexually active with a non-sterilised male partner must have used a stable and highly effective method of contraception for at least 3 months prior to dosing with IMP and must agree to continue using such precautions until 360 days after the dose of IMP. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

- Females of non-childbearing potential are defined as those who are surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or postmenopausal defined as 12 months with no menses without an alternative medical cause and confirmed by FSH in postmenopausal range.
- A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly (see Section 4.2.1.2).

4.1.2. Exclusion Criteria

Participants must not be randomised in the study if any of the following exclusion criteria are fulfilled:

1 Known hypersensitivity to any component of the IMP.

2 History of allergic disease or reactions likely to be exacerbated by any component of the IMP.

3 Previous hypersensitivity, infusion-related reaction or severe adverse reaction following administration of a mAbs.

4 Acute (time-limited) illness, including fever above 37.5°C (99.5 F), on day prior to or day of planned dosing; participants excluded for transient acute illness may be dosed if illness resolves within the 27-day Screening Period or may be rescreened once.

5 Any drug therapy within 7 days prior to Day 1 (except 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). Vitamins and other nutritional supplements that are not newly introduced, ie, have been taken for at least 30 days prior to enrolment, are not exclusionary.

6 Blood drawn in excess of a total of 450 mL (1 unit) for any reason within 2 months prior to screening.

7 Receipt of immunoglobulin or blood products within 6 months prior to screening.

8 SARS-CoV-2 or COVID-19:

   a. Participants with any confirmed current or previous COVID-19 infection before randomisation.

   b. Participant has 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 on admission.

   c. Any prior receipt of investigational or licensed vaccine indicated for the prevention of SARS-CoV-2 or COVID-19 or expected receipt during the period of study follow-up.

9 Receipt of any IMP in the preceding 90 days or expected receipt of IMP during the period of study follow-up, or concurrent participation in another interventional study.

10 Previous receipt of a mAb within 6 months, or five antibody half-lives (whichever is longer), prior to study start.

11 Immunodeficiency due to illness, including HIV infection, or due to drugs, including any course of glucocorticoid therapy exceeding 2 weeks of prednisone or equivalent at a dose of 20 mg daily or every other day within 6 months prior to screening. HIV testing must be negative at screening.

12 Either history of active infection with hepatitis B or C or positive test for hepatitis C or for hepatitis B surface antigen at screening.

13 History of infection with SARS or MERS.

14 Aspartate aminotransferase, ALT, or serum creatinine above the ULN; bilirubin and ALP >1.5 × ULN.

15 Haemoglobin or platelet count below the LLN at screening. White blood cell or neutrophil count outside normal references ranges.

16 History of malignancy.

17 Any laboratory value in the screening panel that, in the opinion of the PI, is clinically significant or might confound analysis of study results.

18 Pregnant or nursing female.

19 History of alcohol or drug abuse within the past 2 years that, according to the PI, might affect assessments of safety or ability of participant to comply with all study requirements OR positive urine drug or alcohol screening.

20 Any condition that, in the opinion of the PI, might compromise participant safety or interfere with evaluation of the IMP or interpretation of participant safety or study results.

21 Employees of the sponsor, clinical study site, or any other individuals involved with the conduct of the study, or immediate family members of such individuals.

22 Absence of suitable veins for blood sampling (IM and IV cohorts) and administration of IMP (IV cohorts).

4.2. Restrictions During the Study

The following restrictions apply for the specified times during the study period:

1 Participants should rest comfortably during the IV infusion or lie supine for an hour after IM administration. Participants should not engage in any strenuous activity from 72 hours prior to check-in until discharge and 72 hours before every outpatient visit and their final Follow-up Visit.

2 Prior to the Treatment Period and outpatient visits, participants should abstain from alcohol for 72 hours prior to check-in until after their last PK sampling visit. Participants should also abstain from alcohol for 72 hours before their final Follow-up Visit.

3 Prior to the Treatment Period and outpatient visits, participants should abstain from caffeine containing foods and beverages for 24 hours prior to check-in until discharge from the Clinical Unit.

4 During admission period, participants will receive a standard diet, which excludes all alcohol and caffeinated products.

5 Prior to admission, participant should avoid food containing poppy seeds for at least 72 hours.

6 Participants will be required to abstain from blood or plasma donation until 3 months after the final medical examination at the study Follow-up.

7 Participants are not required to abstain from food and drink intake prior to sample collection for safety assessments.

For medication restrictions, please refer to Section 5.5.

4.2.1. Reproductive Restrictions

4.2.1.1. Women of Non-Childbearing Potential

Women of non-childbearing potential are defined as female participants who are permanently surgically sterilised or postmenopausal.

Permanent sterilisation includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy at least six weeks before screening but excludes bilateral tubal ligation. Bilateral oophorectomy alone is acceptable only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.

Females are considered postmenopausal if they have had amenorrhea for at least 12 months or more following cessation of all exogenous hormonal treatments and without an alternative medical cause and the FSH level is in the postmenopausal range.

4.2.1.2. Women of Childbearing Potential

A woman is considered of childbearing potential, ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Women of childbearing potential who are sexually active must agree to use, with their non-sterilised male partner, an approved method of highly effective contraception from the time of IMP administration until 360 days after the dose of IMP. Women should be stable on their chosen method of birth control for at least 3 months before dosing.

Highly effective contraception form of birth control, ie, a form of birth control with a failure rate of less than 1% per year when used consistently and correctly, which are allowed in this clinical study, are:

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device

- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomised partner (only acceptable provided that partner is the sole sexual partner of the participant and that the vasectomised partner has received medical assessment of the surgical success)
- Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. It is only acceptable if preferred and usual lifestyle of the participant.

In addition, a barrier method must also be used ie, condom (without spermicidal foam/gel/film/cream/suppository or fat- or oil-containing lubricants); or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

Pregnancy Testing

Women of childbearing potential can be included only after a negative, highly sensitive serum pregnancy test. Additionally, urine pregnancy testing will be done as per the SoA (Table 3-1, Table 3-2, and Table 3-3).

Pregnancy

If the participant becomes pregnant during the study this should be reported to the PI. The PI should also be notified of pregnancy occurring during the study but confirmed after completion of the study. The pregnancy will be followed, and the status of mother and/or child will be reported to the Sponsor after delivery.

A pregnancy notification form and follow-up will be completed. Pregnancy occurring and reported during the study will be followed up for safety from the post-dose administration to end of the study or until term to identify pregnancy outcome, whichever is later. Female participants who become pregnant after dosing will continue to have all safety, PK (serum and nasal fluid), ADA serum sample, and neutralising antibody samples collected. These do not represent a safety risk, and serum samples are already being collected as part of safety follow-up. Any complications during the planned follow-up of any pregnant participant (if any) will be discussed between the PI and AstraZeneca, and a decision to halt or continue any further sampling will be made on a case-by-case basis.

Ova Donation

Female participants should not donate ova for 360 days after the IMP dose.

4.2.1.3. Male Participants

Restrictions for Male Participants

There is no information about effects that AZD7442 could have on the development of the foetus in humans. Therefore, it is important that women of childbearing potential, who are the partners of male participants, do not become pregnant during the study and for a total period of 360 days after the male participant has a received the IMP.

Male participants who have been sterilised are required to use one barrier method of contraception (condom) from the time of IMP administration until after the Follow-up Visit. The participant must have received medical assessment of the surgical success.

As a precaution, all non-sterilised male participants should avoid fathering a child by either true abstinence[1] or use a condom and their female partner/spouse has to be either of non-childbearing potential or has to use a highly effective contraception form of birth control, starting from the time of IMP administration until 3 months after the study Follow-up Visit. The female partner/spouse of the male participant should be stable on their chosen method of birth control for least 3 months prior to dosing with IMP and must agree to continue using such precautions until 360 days after the dose of IMP.

Highly effective contraception form of birth control, ie, a form of birth control with a failure rate of less than 1% per year when used consistently and correctly, are:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- IUD
- IUS
- Bilateral tubal occlusion of female partner

Sperm Donation

Male participants should not donate sperm for the duration of the study and for at least 3 months after the study Follow-up Visit.

Pregnancy

Participants will be instructed that if their partner becomes pregnant during the study this should be reported to the PI. The PI should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a participant's partner is subsequently found to be pregnant after the volunteer is included in the study, then consent will be sought from the partner and if granted any pregnancy will be

[1] Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. It is only acceptable if preferred and usual lifestyle of the participant.

followed, and the status of mother and/or child will be reported to the Sponsor after delivery.

A pregnancy notification form and follow-up will be completed.

4.3. Replacement of Participants

Participants who are withdrawn from the study, for any reason, will not be replaced. Rescreened participants will be provided with new run-in numbers, however, will have the same participant ID.

4.4. Interim Analysis

There will be four unblinded interim analyses. The first will assess data from Cohort 1a and Cohort 1b once all participants in those two cohorts have completed their Day 8 visit. The second will assess cumulative data from all cohorts once all participants in Cohort 4 have completed their Day 8 visit. The third interim analysis will assess all available data from all cohorts once all participants in Cohort 4 have completed their Day 151 visit. The fourth interim analysis will assess data from all cohorts once all participants have completed their Day 211 visit and participants and Cohort 1a and Cohort 1b have completed their Day 271 visit. The results of these analyses will be used to assist AstraZeneca's internal operational planning. The primary analysis will be conducted when all treated participants for each planned analysis have completed follow-up through Day 31. All available data at the time of data cut-off will be included in the interim analyses. The unblinded safety, PK, ADA data (ADA data if available), neutralising antibody and nasal fluid data will be used to determine whether to initiate a Phase 2/3 prophylaxis study in broader populations. AstraZeneca personnel, associated personnel at the CRO conducting the study and the testing laboratories will be unblinded as needed to perform the analysis and planning. Unblinded data may be shared with regulatory agencies and other parties for the development programs, as needed, in regulatory applications and other development-required correspondence. It is anticipated that study site personnel and participants will remain blinded.

The results will be based on clean data and nominal times will be used for the derivation of the serum PK parameters.

A subset of the outputs that will be required for the interim analyses will be identified in the table, listings, and figures shells of this study and the results will be provided only on whichever data is available.

Parexel will not be responsible for the interim clinical study reports.

5. STUDY CONDUCT

5.1. Participant Enrolment and Randomisation

The PI will ensure:

- Signed informed consent is obtained from each potential participant before any study specific procedures are performed.
- Each potential participant is assigned a unique enrolment number at Screening upon signing the ICF.
- The eligibility of each participant is in accordance with the inclusion and exclusion criteria.
- Each eligible participant is assigned a unique randomisation code (participant number).

Randomisation will be done on Day 1.

Randomisation codes will be assigned strictly sequentially as participants become eligible for randomisation, starting from eg, 101 (codes to be used without leading zero[s]).

When using unique enrolment number, the specific format must be followed (ie, reduced enrolment number, eg, "1001" in ClinBase™ and on labels, full enrolment number, eg, "E0001001" for outputs).

There will be no participant replacements.

5.1.1. Procedures for Randomisation

Upon completion of the randomisation requirements specifications form, the randomisation list and code break envelopes for each participant will be produced by Parexel according to the AZRand.

For all cohorts, sentinel dosing will be applied. Participants will be randomised to AZD7442 or placebo in a ratio of 1:1 for the sentinel group and 9:1 in the remaining 10 participants of the cohort such that 10 out of 12 participants in each overall cohort will receive AZD7442 and 2 out of 12 will receive placebo.

The randomisation will be completed for each cohort using consecutive randomisation codes.

Since additional cohorts may be added, randomisation will include additional cohorts 5, 6 and 7.

Participants will be assigned as given in Table 5-1.

Table 5-1 Participant Randomisation

Cohort Number	Participants
1a	101 to 112
1b	201 to 212
2	301 to 312
3	401 to 412
4	501 to 512
5	601 to 612
6	701 to 712
7	801 to 812

Once a randomisation number has been allocated to one participant, it may not be assigned to another participant.

5.2. Procedures for Handling Incorrectly Randomised Participants

Participants who fail to meet the inclusion criteria or meet any exclusion criterion should not, under any circumstances, be randomised into the study. There can be no exceptions to this rule.

Where a participant, who does not meet the selection criteria, is randomised in error and this is identified before dosing, the participant should be withdrawn from the study. If a participant is withdrawn prior to dosing they will be replaced.

If a participant, who does not meet the selection criteria, has been dosed before the error is identified, the participant should be advised to continue safety assessments to ensure their safety. The PI will inform the AstraZeneca Lead Physician of the error.

5.3. Blinding and Procedures for Unblinding the Study

5.3.1. Methods for Ensuring Blinding

This is a blinded study in which the participants and Investigator are blinded to IMP, and AstraZeneca staff who are involved in the study are unblinded. Unblinded data may be shared with regulatory agencies and other parties for the development programs, as needed, in regulatory applications and other development-required correspondence. As this is a dose escalation study, the Investigator, study site staff and participants will be blinded to the treatment allocation (AZD7442 or placebo), but not to the dose. The DEC responsible for the dose escalation decisions after review of up to and including Day 8 safety data from Cohort 1a, Cohort 1b, and Cohort 2 will also remain blinded. This committee includes the AstraZeneca Lead Physician, the AstraZeneca Patient Safety Physician, and the PI for the study.

AZD7442 and placebo will, as far as possible, be matched for formulation, appearance, and amount. Participants randomised to placebo will receive the same volume of solution as participants on active treatment. In cases of the IM injection, syringe masking may be

required in order to keep the blind (possibility of slight yellowish discolouration of the suspension for IM injection).

The Covance pharmacokineticist will remain blinded during the study conduct, unless otherwise required based on study findings.

The following personnel will have access to the randomisation list from study start:

- The AstraZeneca personnel carrying out the labelling and packaging of participant specific treatments.
- Pharmacy staff preparing the IMP.
- Bioanalytical staff analysing performing the bioanalysis of the PK serum samples, PK nasal fluid samples, and ADA serum samples.
- Dedicated unblinded Covance PK Scientist performing the PK analyses for the interim analysis and possible input in the DEC.
- Dedicated unblinded team (Biostatistical programmers and study Biostatistician) from Parexel involved in the unblinded interim analyses.
- Dedicated unblinded AstraZeneca personnel involved in analyses, and preparation of outputs for the formal interim and project decisions.

The randomisation list should be kept in a secure location until the data base is locked.

5.3.2. Methods for Unblinding the Study

The treatment code should not be broken, except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomisation or regulatory requirements exist (eg, for SAEs), or to enable proper guidance to a subject who wishes to receive an approved vaccine to protect against infection with SARS-CoV-2. If an emergency unblinding becomes necessary, the PI could break the blind using code break envelopes for a specific participant or complete cohort and should notify the Sponsor prior to unblinding, if possible, unless identification of the IMP is required for emergency therapeutic measures. If a PI or participant is prematurely unblinded, the participant may continue to be followed in the clinical study for safety, PK, neutralizing antibody titers, anti-drug antibodies, and, in female participants, monitoring for development of pregnancy. In the event that a participant wishes to withdraw completely from the study after unblinding, ie, the participant withdraws consent for continued participation, then, dependent upon the participant's agreement, and procedures accompanying withdrawal are to be performed. The decision to break the blind will be made on a case-by-case basis and, if possible, such emergencies are to be discussed with AstraZeneca prior to disclosure of the treatment allocation. If the blind is broken, the date, time and reason together with the identity of the person responsible must be recorded in ClinBase™ and any associated AE report.

The PI will document and report the action to AstraZeneca staff.

Details of the code breaking procedure will be provided in the Safety Review and Management Plan.

5.4. Study Treatments

5.4.1. Identity of the Investigational Medicinal Product

Details on the identity of the IMP are presented in Table 5-2.

Table 5-2 Identity of the Investigational Medicinal Product

Supplier:	AZD7442 (AZD8895 + AZD1061): AstraZeneca. Placebo/Diluent: 0.9% Sodium Chloride (Ph.Eur., British Pharmacopoeia): Parexel.
Formulation:	Each vial of AZD8895 and AZD1061 is formulated as a sterile, white to off-white, lyophilised powder, in a glass vial, 150 mg. After reconstitution in sterile water for injection/infusion; each vial yields 100 mg/mL of active ingredient (AZD8895 or AZD1061), 20 mM L-histidine/L-histidine hydrochloride, 240 mM sucrose, and 0.04% (w/v) polysorbate 80, at pH 6.0.
Strength/concentration:	Supplied as a powder for solution for injection/infusion. After reconstitution, each vial contains 100 mg/mL AZD8895 or 100 mg/mL AZD1061, with a unit dose strength of 150 mg AZD8895 vial or 150 mg AZD1061.
Dose:	AZD7442 doses (combined doses of AZD8895 and AZD1061 each represents half of the total dose) to be administered sequentially are 300 mg IM (direct gluteal IM injections) (Cohort 1a), 300 mg IV (Cohort 1b), 1000 mg IV (Cohort 2), and 3000 mg IV (Cohort 3) at 20 mg/minute for the IV infusions, and the AZD7442 dose to be co-administered is 3000 mg IV at 50 mg/minute (Cohort 4) for the IV infusion.
Route of administration:	IV infusion or IM injection.
Specific device for drug administration, if applicable:	IV bags, lines, and catheters for IV infusion as well as the syringes and needles for injection will be provided by Parexel.
Regimen:	Single, separate, sequential doses as IV infusions will be administered at maximal infusion rate of 20 mg/minute or direct IM injections of each mAbs. A co-administered dose of both mAbs mixed in a single IV infusion will be administered at a maximal infusion rate of 50 mg/minute.
Special handling requirements:	Will be provided in a separate document.
Availability of the IMP:	Will be shipped when approvals are in place.

IM: intramuscular; IMP: investigational medicinal product; IV: intravenous; mAbs: monoclonal antibodies.

Details of the batch numbers will be included in the trial master file, pharmacy manual, and the final CSR.

5.4.2. Supply of Investigational Medicinal Product

The IMP will be supplied by AstraZeneca as lyophilised vials in one vial kits.

A technical agreement between the PI and AstraZeneca will be in place to cover all pharmacy related activities, detailing roles and responsibilities prior to receipt of the IMPs at the Clinical Unit.

A release document signed by a legally authorised Qualified Personnel at the Clinical Unit will be placed in the appropriate section of the Trial Master File to document labelling and dispensing of the IMP to the participant.

5.4.3. Dose and Treatment Regimens

Each participant will receive a single IV infusion or IM dose of AZD7442 or placebo. Participants will not be fasted and will be allowed to drink water to prevent dehydration until 1 hour before dosing. Water will be allowed ad libitum from 1 hour after the start of dosing (depending on the duration of the IV infusions) and a standard meal will be given 4 hours after the start of dosing.

Participants in the first cohort (Cohort 1a) will receive a dose of 300 mg AZD7442 or placebo to be administered sequentially as direct gluteal IM administrations starting with AZD8895/placebo and followed by AZD1061/placebo.

Participants in the first 3 cohorts to be dosed via IV infusion (Cohorts 1b, 2, and 3) will receive a dose of 300 mg/1000 mg/3000 mg AZD7442 or placebo to be administered sequentially via IV infusion at a maximal infusion rate of 20 mg/minute starting with AZD8895/placebo and followed by AZD1061/placebo.

Participants in Cohort 4 will receive a dose of 3000 mg AZD or placebo via co-administered (both mAbs mixed in a single infusion) IV infusion at a maximal infusion rate of 50 mg/minute.

The maximum dose will not exceed 3000 mg (total dose, 1500 mg per mAb).

Other restrictions are described in Section 4.2. Data of participants may be excluded from the PK analysis set.

5.4.4. Labelling

Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements and medical device directive for labelling.

5.4.5. Storage and Handling Procedures

The IMP will be stored in a secure facility under appropriate storage condition of 2 to 8°C and protect from light within its original packaging. Details of storage conditions will be provided on the label of the IMP.

No special procedures for the safe handling of AZD7442 are required.

AstraZeneca will be permitted upon request to audit the supplies, storage, dispensing procedures, and records provided that the blind of the study is not compromised.

5.5. Concomitant and Post-study Treatment(s)

Please see exclusion criteria #5 for restrictions and allowed concomitant medications.

The participants should be instructed that no other medication is allowed, without the consent of the PI.

Medication, which is considered necessary for the participant's safety and well-being, may be given at the discretion of the PI during the residential period.

When any medication is required, it should be prescribed by the PI. Following consultation with AstraZeneca Lead Physician, the PI should determine whether or not the participant should continue in the study. Administration of concomitant medications that may influence the measurement of the PK endpoints will be documented as a protocol deviation after consultation of the PI with AstraZeneca Lead Physician.

When an individual participant becomes eligible for the nationally deployed COVID-19 vaccine and it is locally available, the participant can 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 300 mg dose may provide 6 to 9 months of protection, that the 1000 mg dose may provide 11 to 14 months of protection, and that the 3000 mg dose may provide up to 15 to 18 months of protection, but that such protection 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 neutralizing antibody titers, expected for the durations noted, 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 different doses, before receiving an anti-SARS-CoV-2 vaccine. For AZD7442, the number of months identified above for each dose represent the approximate number of elimination half-lives of the mAbs, that may need to pass before the potential of the mAbs to protect against COVID-19 should be reduced, and after which their potential interference with a vaccine may be reduced. If the participant decides to receive the vaccination despite these considerations the subject can proceed and continue in the study.
- For participants who have received IMP (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.

5.6. Treatment Compliance

Dosing will take place at the Parexel EPCU.

The administration of all medications will be recorded in ClinBase™.

Compliance will be assured by direct supervision and witnessing of the IMP administration.

In addition, bioanalysis of AZD7442 in serum sample at Cmax from all presumed placebo-treated participants may be used to confirm lack of AZD7442 in the serum.

5.6.1. Drug Accountability, Dispensing and Destruction

The IMP provided for this clinical study will be used only as directed in the CSP.

In accordance with GCP, the Clinical Unit will account for all supplies of AZD7442 and placebo. Details of receipt, storage, assembly/dispensing, and return will be recorded.

All used and unused supplies of AZD7442 (AZD8895, AZD1061) and placebo will be destroyed by Parexel at the end of the study. The certificate of delivery and destruction must be signed, in accordance with instruction by AstraZeneca. Destruction must not take place unless the responsible person at AstraZeneca has approved it.

5.7. Discontinuation of Investigational Medicinal Product and Withdrawal from Study

Healthy participants may be discontinued from IMP in the following situations:

- Healthy participant decision. The healthy participant is at any time free to discontinue treatment, without prejudice to further treatment.
- Severe non-compliance to study protocol.
- Any significant and clinically relevant changes in the safety parameters (eg, ECG, BP, pulse, laboratory assessments and AE) making the continuation of IMP administration unjustified.
- Any case of PHL according to Appendix C.

The appropriate AE form in the CRF is to be completed.

5.7.1. Procedures for Withdrawal of a Participant from the Study

If a participant withdraws or is withdrawn from the study, the participant will be encouraged to return to the Clinical Unit for an Early Termination Visit (to follow the procedures of the Final Follow-up Visit) to ensure the participants' safety.

6. COLLECTION OF STUDY VARIABLES

6.1. Recording of Data

Standard measures to assess PK, safety, and tolerability apply during the study. For the single doses of AZD7442 planned to be given during this study, no safety issues are expected.

For timing of assessments refer to the SoA (Table 3-1, Table 3-2, and Table 3-3).

6.2. Enrolment and Screening Procedures

Viral serology, urine drugs of abuse, and alcohol will be assessed for eligibility. Follicle stimulating hormone (females only), pregnancy testing (females only) and use of concomitant medication will also be assessed and reported.

6.3. Safety

Safety and tolerability variables will include:

- AEs/SAEs.
- Vital signs (systolic and diastolic BP, pulse rate, and oral temperature).
- 12-Lead safety ECGs.
- Physical examination.
- Laboratory assessments (haematology, clinical chemistry, coagulation, and urinalysis).

6.3.1. Adverse Events

6.3.1.1. Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a participant 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 treatment has been administered.

The term AE will be used for any event as described above that is reported pre-dose and AE for all events post-dose.

6.3.1.2. Definitions of Serious Adverse Event

A 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 or substantial disruption of the ability to conduct normal life functions.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardise the participant or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix A of this CSP.

Adverse events for malignant tumours reported during a study should generally be assessed as SAEs. If no other seriousness criteria apply, the "Important Medical Event" criterion should be used. In certain situations, however, medical judgement 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 include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

6.3.1.3. Other Significant Adverse Events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as serious or where relevant discontinuation events and withdrawal from the study. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Safety Physician, be considered OSAEs and reported as such in the CSR. A similar review of other data from laboratory tests, vital signs, ECGs and other safety assessments will be performed for identification of other SAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

6.3.1.4. Recording of Adverse Events

Time Period for Collection of Adverse Events

Adverse events will be collected from the time of IMP administration throughout the Treatment Period up to and including the Follow-up Visit.

Serious adverse events will be recorded from the time of informed consent.

Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the participant's last visit in the study are followed up by the PI for as long as medically indicated, but without further recording in ClinBase™.

AstraZeneca retains the right to request additional information for any participant with ongoing AEs and SAEs at the end of the study, if judged necessary.

Variables

The following variables will be collected for each AE, including whether treatment of the AE was required:

- AE event diagnosis/description.
- The date and time when the AE started and stopped.
- Intensity.
- Whether the AE is serious or not.
- PI causality rating against the IMP (yes or no).
- Action taken with regard to IMP administration.
- If the 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 PI became aware of SAE.
- The cause leading to an AE being considered serious.
- Date of hospitalisation (if hospitalised).
- Date of discharge.
- Probable cause of death (if death occurred).
- Date of death.
- Autopsy performed.
- Causality assessment in relation to Study procedures.
- Causality assessment to other medication.

The following intensity ratings will be used:

1 Mild (awareness of sign or symptom, but easily tolerated).
2 Moderate (discomfort sufficient to cause interference with normal activities).
3 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 Section 6.3.1.2.
- An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

Causality Collection

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

For SAEs, causal relationship will also be assessed for other medication, any additional drug 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 A of this CSP.

Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study personnel: *"Have you had any health problems since you were last asked?"* or revealed by observation will be collected and recorded in ClinBase™.

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.

Adverse Events Based on Examinations and Tests

The results from CSP-mandated laboratory tests, vital signs, ECGs and other safety assessments will be summarised in the CSR.

Deterioration as compared to baseline in CSP-mandated laboratory values, vital signs, ECGs and other safety assessments should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IMP.

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result, or vital sign will be considered as additional information.

Wherever possible the reporting PI should use 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-CSP-mandated parameters should be reported as AEs.

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.

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 total bilirubin ≥ 2 × ULN may need to be reported as SAEs. Please refer to Appendix C for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.3.1.5. Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the IMP, or to the study procedure(s). All SAEs will be recorded in ClinBase™.

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

The designated AstraZeneca representative will work with the PI 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.

PIs or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** of when he or she becomes aware of it.

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

6.3.1.6. Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the PI to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of an IMP 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, EC, and PIs.

For all studies, except those utilising medical devices, PI safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to the PIs as necessary.

A PI who receives a PI safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the EC, if appropriate according to local requirements.

6.3.2. Laboratory Assessments

6.3.2.1. Haematology

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

6.3.2.2. Serum Clinical Chemistry

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

6.3.2.3. Urinalysis

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

6.3.2.4. Coagulation

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

6.3.2.5. Pregnancy Testing

Pregnancy test (females only)	
Serum human-beta chorionic gonadotrophin (screening)	Urine human-beta chorionic gonadotrophin (pre- and post-dose)

6.3.2.6. Viral Serology and SARS-CoV-2 Testing

Viral Serology	
Human immunodeficiency virus (HIV) I and II	Hepatitis C Virus antibody
Hepatitis B surface antigen (HBsAg)	SARS-CoV-2 serology
SARS-CoV-2 quantitative real-time polymerase chain reaction (qRT-PCR)	

6.3.2.7. Drugs of Abuse and Alcohol

Drugs of Abuse and Alcohol	
Amphetamine	Benzodiazepines
Ethanol	Methadone Metabolites
Cannabinoids	Barbiturates
Cocaine	Phencyclidine
Opiates	Urine Creatinine
Tricyclic anti-depressants (TCA)	Methamphetamines

6.3.3. Vital Signs

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

- Systolic BP (mmHg),
- Diastolic BP (mmHg),
- Pulse rate(beats per minute [bpm]),
- Oral temperature, and

- Respiratory rate (breaths per minute).

The measurement of vital signs will be carried out according to the relevant Parexel SOPs.

6.3.4. Electrocardiography

6.3.4.1. Resting 12-lead Electrocardiogram

At the time points specified in the SoA (Table 3-1, Table 3-2, and Table 3-3), a 12-lead safety ECG will be obtained after at least 5 minutes supine rest, using the sites own ECG machines.

The PI will judge the overall interpretation as normal or abnormal and this evaluation will be reported in ClinBase™. If abnormal, it will be further documented as to whether or not the abnormality is clinically significant by the PI. For all abnormalities (regardless of clinical significance) the specific type and nature of the abnormality will be documented in ClinBase™. Clinically significant findings should also be documented on the AE page of the CRF if applicable.

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

All ECG readings will be digitally stored as source documents.

6.3.5. Physical Examination

Full

The complete physical examinations will include an assessment of the general appearance, skin, cardiovascular, respiratory, abdomen, head, and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal and neurological systems.

Brief (Abbreviated)

The brief physical examinations will include an assessment of the general appearance, skin, cardiovascular system, lungs and abdomen. Site-directed physical exam should be performed to assess symptoms reported by participant.

6.3.6. Injection Site Reactions

Injection site reactions will be monitored time points indicated in the SoA (Table 3-1, Table 3-2, and Table 3-3), including assessment of erythema, swelling, induration itching, pain or tenderness, and discolouration. Injection site reactions might be documented by photography, at the discretion of the PI/Designee, with visible measuring tape and be documented in each participants CRF in appropriate modules (not to be delivered to AstraZeneca unless requested).

6.4. Pharmacokinetics

6.4.1. Collection of Pharmacokinetic Samples

6.4.1.1. Serum Samples

Blood samples for the determination of serum concentrations of AZD7442 mAbs (AZD8895 and AZD1061) will be collected as specified in the SoA (Table 3-1, Table 3-2, and Table 3-3).

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

6.4.1.2. Nasal Fluid Samples

Nasal fluid samples for the determination of nasal fluid concentrations of AZD7442 mAbs (AZD8895 and AZD1061) will be collected as specified in the SoA (Table 3-1, Table 3-2, and Table 3-3).

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

6.4.2. Pharmacokinetic Drug Assays

Blood samples for determination of AZD7442 mAbs (AZD8895 and AZD1061) concentrations in serum will be analysed using a validated assay conducted at PPD. Nasal fluid analysis may be performed at AstraZeneca using a qualified assay. Additional analyses may be conducted on the biological samples to further investigate the presence and/or identity of drug metabolites.

Full details of the analytical method and analyses performed will be described in a separate Bioanalytical Report.

Additional analyses may be conducted on the biological samples to further investigate the presence and/or identity of drug metabolites.

Placebo samples will not be analysed, unless there is a need to confirm that correct treatment has been given to study participants.

Full details of the analytical method and analyses performed will be described in a separate Bioanalytical Report.

6.5. Immunogenicity

6.5.1. Collection of Immunogenicity Samples

Blood samples for determination of ADA antibodies in serum will be conducted at PPD and analysed by Covance on behalf of AstraZeneca, using a validated assay. Blood samples for determination of ADA antibodies in serum will be collected as specified in the SoA (Table 3-1, Table 3-2, and Table 3-3). Unscheduled samples for ADA analysis should be collected in response to suspected immune-related AEs.

If a participant's sample at the last study visit is confirmed ADA positive, the subject may be asked to return to the clinic for additional sampling if judged necessary by the AstraZeneca Lead Physician and the PI.

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

6.5.2. Immunogenicity Assays

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

Full details of the analytical method and analyses performed used will be described in a separate Bioanalytical Report.

6.5.3. Exploratory Study-Related Biomarkers

Collected biospecimens may be utilised for exploratory study-related biomarker research (ie, to investigate additional humoral and/or mucosal immune responses, as well as potential correlates of protection) as determined by the Sponsor based upon emerging safety, efficacy, and immunogenicity data. Analysis may include, but is not limited to,

CCI [redacted]

For storage, re-use, and destruction of biomarker samples see Section 7.2.

6.6. Neutralising Antibody Assessments

Serum samples to measure functional activity of AZD7442 (ie, SARS-CoV-2 neutralising antibody levels) will be collected from participants according to the time points specified in the SoA (Table 3-1, Table 3-2, and Table 3-3). Authorised laboratories will measure neutralising antibodies to SARS-CoV-2 using validated wild-type neutralisation assay or pseudoneutralisation assays.

7. BIOLOGICAL SAMPLING PROCEDURES

All biological samples collections will be performed by trained staff and in accordance with the Clinical Unit's SOPs.

7.1. Total Blood Volume

The approximate total amount of blood to be collected from each participant in this study, excluding repeat samples, is estimated at 240.2 mL for participants in the IV group and 230.2 mL for participants in the IM group.

Table 7-1 Total Blood Volume

	Volume per Sample	Number of Samples	Total
Haematology	2 mL	6	12 mL
Clinical chemistry	5 mL	6	30 mL
Serology [a, b]	0 mL	1	0 mL
Coagulation	2.7 mL	6	16.2 mL
PK (IV)	2.5 mL	18	45 mL
PK (IM)	2.5 mL	14	35 mL
ADAs	3.5 mL	7	24.5 mL
Neutralising antibodies	12.5 mL	9	112.5 mL
FSH [b]	0 mL	1	0 mL
Pregnancy test (serum hCG) [b]	0 mL	1	0 mL
Total			**240.2 mL (IV)** **230.2 mL (IM)**

a. SARS-CoV-2 serology to be performed at the discretion of the PI.
b. Serology, FSH, and Serum pregnancy test to be performed on the same sample as for clinical chemistry.

ADAs: anti-drug antibodies; FSH: follicle stimulating hormone; hCG: human chorionic gonadotropin; IM: intramuscular; IV: intravenous; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Repeat blood samples may be collected for safety reasons. The maximum volume to be drawn from each participant must not exceed 500 mL over a period of 56 consecutive days.

7.2. Handling, Storage and Destruction of Biological Samples

Samples will be disposed of, on instruction from AstraZeneca, after the CSR has been finalised, unless samples are retained for additional or future analyses.

7.2.1. Pharmacokinetic Samples

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

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

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR, but separately in a Bioanalytical Report.

7.2.2. Immunogenicity and Pharmacodynamic Samples

Remaining serum sample aliquots for neutralising antibody assessments and ADA will be retained at AstraZeneca or its designee for a maximum of 15 years following the last participant's last visit in the study. Additional use includes but is not limited to further characterisation of any ADAs, future exploration of correlates of protection, confirmation and/or requalification of the assay, as well as additional assay development work based upon emerging safety, efficacy, and immunogenicity data as determined by the Sponsor. The results from future analysis will not be reported in the CSR.

7.3. Labelling and Shipment of Biohazard Samples

Samples will be labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix B of this CSP 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials will not be shipped and no further samples will be taken from the participant unless agreed with AstraZeneca and appropriate labelling, shipment, and containment provisions are approved.

7.4. Chain of Custody of Biological Samples

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

The PI will ensure full traceability of collected biological samples from the participants while in storage at the centre until shipment and will keep documentation of receipt of arrival.

The sample receiver will keep full traceability of samples while in storage and during use, until used, disposed of, or until further shipment or disposal (where appropriate) and will keep documentation of receipt of arrival.

Samples retained for further use will be registered in the AstraZeneca biobank system during the entire life cycle.

7.5. Withdrawal of Informed Consent for Donated Biological Samples

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed if not already analysed and the action documented.

As collection of donated biological samples is an integral part of the study, then the participant is withdrawn from further study participation.

AstraZeneca ensures the central laboratory holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented, and the signed document returned to the Clinical Unit.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2. Participant Data Protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

All clinical study findings and documents will be regarded as confidential. The PI and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating participants must be maintained. Participants will be specified in outputs and other documents containing participant data by their participant number, not by name. Documents that identify the participant (eg, signed ICF) will be maintained in confidence by the PI.

Study data will be stored in accordance with local and global data protection laws.

8.3. Ethics and Regulatory Review

The study will be submitted to the National Regulatory Agency, MHRA, for review and approval, by Parexel in accordance with local regulatory procedures.

The study will be submitted to the IEC for ethical review and approval by the PI in accordance with local procedures.

Parexel will provide the IEC and PI with safety updates/reports according to local requirements, including SUSARs, where relevant.

AstraZeneca will provide the Regulatory Authority with safety updates/reports according to local requirements, including SUSARs, where relevant.

Compensation will be reasonable and related to the nature and degree of inconvenience and discomfort as a result of participation in the study. Information on how participants will be compensated is contained in the ICF.

8.4. Informed Consent

The participants shall be informed of the nature, significance, implications and risks of the trial, and informed consent will be freely given and evidenced in writing, dated and signed, or otherwise marked, by the participant as evidence to indicate his/her free informed consent, prior to the start of the study.

The nature of the informed consent will comply with the Declaration of Helsinki, the current requirements of GCP (CPMP/ICH/135/95) and local regulation which ever offers the greater participant protection.

8.5. Insurance

The Sponsor has covered this clinical study by means of an insurance of the clinical study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the PI's Site File.

8.6. Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the PI and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol.

The amendment should be approved by the EC/IRB and the National Regulatory Authority, before implementation, as appropriate. Local requirements should be followed for revised protocols.

If a protocol amendment requires a change to the ICF the IEC/IRB should approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by the IEC/IRB.

8.7. Audits and Inspections

Not applicable.

9. DATA QUALITY ASSURANCE AND DATA MANAGEMENT

9.1. Quality Control and Source Data Verification

Source data verification will be conducted with due regard to participant confidentiality.

The Clinical Unit will allow the study monitor and Sponsor representative direct access to all study documents, medical files and source documents to enable verification of the study data, while maintaining the anonymity of the participant and confidentiality of the data.

Internal quality control will be performed at all stages of the study by the Clinical Unit.

9.2. Audit/Inspections

The Clinical Unit facilities and all study data/documentation may be audited/inspected by independent auditor/inspector/any representatives of regulatory authorities. The PI must allow the applicable persons access to all relevant facilities and data/documents. The PI must be available to discuss any findings/issues.

If an audit was performed, the audit certificate will be included in the CSR.

9.3. Study Monitoring

The conduct of the study will be monitored by an independent Parexel monitor or a subcontracted monitor to ensure compliance with applicable regulatory requirements and GCP. The summary of the documentation of the monitoring visits will form part of the study documentation and will be archived as such.

9.4. Data Collection

The ClinBase™ system is an electronic source data capturing and information management system. The system combines all aspects of source data capturing with process control and clinical study management. All clinical and laboratory data, except those which are paper-based or provided by external vendor, will be collected in ClinBase™. Only paper-based data will be participant to data entry. For electronic source data, no data entry will be performed.

The responsible study monitor will check data at the monitoring visits to the Clinical Unit. The PI will ensure that the data collected are accurate, complete and legible. Data will be monitored within ClinBase™ by the study monitor before being exported. Any changes made during monitoring will be documented with a full audit trail within ClinBase™.

9.4.1. Case Report Forms and Source Documents

All data obtained using paper collection methods during the clinical study will be recorded in ClinBase™. All source documents from which ClinBase™ entries are derived should be placed in the participant's personal records.

The original ClinBase™ entries for each participant will be checked against source documents by the study monitor. Instances of missing or uninterpretable data will be discussed with the PI for resolution.

9.4.2. Access to Source Documents

During the course of the clinical study, a study monitor will make Clinical Unit visits to review protocol compliance, compare ClinBase™ entries and individual participant's personal records, assess IMP accountability and ensure that the clinical study is being conducted according to pertinent regulatory requirements. ClinBase™ entries will be verified against source documents. The review of medical records will be handled confidentially to ensure participant anonymity.

Checking of the ClinBase™ entries for completeness and clarity and verifying with source documents, will be required to monitor the clinical study for compliance with GCP and other regulations. Moreover, regulatory authorities of certain countries, IECs/IRBs may wish to carry out source data inspections on-site, and the Sponsor's clinical quality assurance group may wish to carry out audits. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and participant confidentiality. The PI assures the Sponsor of the necessary support at all times.

9.5. Data Management

Parexel will utilise standardised and validated procedures and systems to collect, process and file the clinical data of this study. Any system used will be compliant with FDA 21 CFR Part 11 requirements.

A DMP will be prepared to describe the processes and data-flow within the clinical study. Timelines, versions for the computer systems and the coding will be defined in the DMP, and if applicable, sponsor specific requests will also be documented within. The DMP will be finalised before first dose where possible but before database lock.

A DVS will be created to outline the validation checks to be performed during the study. The DVS must be finalised before data validation.

After the data has been monitored by the responsible study monitor all data received will be reviewed, logged and filed.

The raw data intended for further processing will be checked by standard routines or according to the DVS and queries will be generated and sent to the PI for review and resolution. Corrections resulting from these queries will be confirmed on the DCFs. This process will be repeated until no further discrepancies are found. The data will then be declared as clean. Applicable documentation will be stored in the study files.

Only trained study staff will have access to the clinical database and every change in data will have a full audit trail.

10. EVALUATION AND CALCULATION OF VARIABLES

10.1. Safety Variables

10.1.1. Adverse Events

All AEs will be coded using MedDRA vocabulary and will be listed for each participant.

For assigning AEs to a specific treatment/dose, the following guidelines should be followed:

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

For purpose of the AE summaries, the following will apply:

- AEs with unknown intensity will be treated as “severe” for the tabulations.
- AEs with unknown relationship will be treated as “related” for the tabulations.
- AEs with unknown seriousness will be treated as “serious” for the tabulations.

There will be no imputation of AE data for the data listings. All data will be listed as recorded in ClinBase™.

Adverse events with onset (start date/time) after dosing will be summarised by treatment group (dose level or administration process of AZD7442, total AZD7442 and pooled placebo). Tabulations will include causality and severity (mild, moderate and severe). All tabulations will be presented by SOC and PT with the exception of the causality and severity tables, which will be presented by PT only. Furthermore, listings of SAE and AEs that led to withdrawal will be made and the number of participants who had any AE, SAEs, and discontinuation events will be summarised. The AEs that occur before dosing will be excluded from the summary tables.

Adverse events will be listed by each dose of AZD7442 and pooled placebo. The following information will be included in the listings: verbatim term, MedDRA SOC, PT and lowest level term, start date/time, end date/time, time from last dose, causality, action taken, whether the AE was classified as serious and the outcome.

All tabulations will include the number and percentage of participants.

10.1.2. Laboratory Assessments

Haematology and clinical chemistry values will be listed by participant and time point including changes from baseline and repeat/unscheduled measurements. Summary tabulations will be presented by treatment group (dose level or administration process of AZD7442, total AZD7442 and pooled placebo) and time point for the safety analysis set. The baseline for the measurements will be the last pre-dose assessment performed on admission. Changes from baseline will be calculated and presented for all follow-up visits. Shift tables will also be presented.

Any laboratory parameters with results from the laboratory given as '<xx' or '>xx' in the database will be imputed with the absolute value of the number without the sign (eg, <2.2 will be imputed as 2.2) for the descriptive statistics and changes from baseline.

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

Additional listings will be presented for the following:

- Urinalysis (macroscopic and microscopic, if applicable)
- Pregnancy testing (including FSH)

10.1.3. Vital Signs

The results of the vital signs measurements will be listed by participant and time point including the date/time of the assessment, changes from baseline and repeat/unscheduled measurements. The baseline for vital signs measurements will be the pre-dose assessment on Day 1. Descriptive statistics will be presented by treatment group (dose level or administration process of AZD7442, total AZD7442, and pooled placebo) and time point for both observed values and changes from baseline.

10.1.4. Resting 12-lead Electrocardiogram

The results of the 12-lead ECG results will be listed for each participant with interpretation by the PI as "Normal", "Abnormal CS" and "Abnormal NCS".

10.1.5. Physical Examination

The baseline/screening results of the physical examination will be documented in medical history for each participant.

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

10.1.5.1. Injection Site Reaction

Results of the injection site reaction (including assessment of size, redness/erythema, swelling, itching/pruritus, pain or tenderness, induration, discolouration) will be listed by participant for Cohort 1b (IM administration cohort).

10.2. Pharmacokinetic Variables

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

10.2.1. Serum PK Parameters

Cmax	Observed maximum concentration
tmax	Time to reach maximum concentration
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
$t_{½\lambda z}$	Terminal elimination half-life, estimated as (ln2)/λz
CL	Systemic clearance (IV administration only)
CL/F	Apparent total clearance (IM administration only)
Vss	Volume of distribution at steady state (IV administration only)
Vz	Volume of distribution at terminal phase (IV administration only)
Vz/F	Apparent volume of distribution at terminal phase (IM administration only)
tlast	Time of last quantifiable concentration
Bioavailability (F)	Bioavailability for extravascular administration, calculated as AUC ratio of IM administration to IV administration.

Dose normalised Cmax, AUCinf, and AUClast will be calculated for each mAb: AZD8895 and AZD1061.

The following parameters will be calculated for 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
λz, N	Number of data points included in the log-linear regression analysis
λz span ratio	Time period over which λz was determined as ratio of $t_{½\lambda z}$
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.

10.2.2. Calculation or Derivation of Pharmacokinetic Parameters

The PK analyses of the serum concentration data for AZD7442 mAbs (AZD8895 and AZD1061) will be performed at Covance on behalf of Clinical Pharmacokinetic Alliance, AstraZeneca R&D and will be calculated according to the AstraZeneca standards (Guideline for PK Evaluations in Clinical Studies, v3, Feb 2020).

The PK analysis will, where data allow, be carried out using actual elapsed times determined from the PK sampling and dosing times recorded in the database. If actual elapsed times are missing, nominal times may be used

Nominal sampling times will be used for interim PK parameter calculations.

PK parameters will be derived using noncompartmental methods with Phoenix® WinNonlin® Version 8.1, or higher.

10.3. Immunogenicity and Pharmacodynamics

The presence or absence of ADAs to AZD7442 from Day 1 pre-dose to Day 361 will be collected, including the titer for samples confirmed positive for ADA.

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

11.1. Description of the Analysis Sets

11.1.1. Safety Analysis Set

The safety analysis set will include all participants who were randomised and received any amount of AZD7442.

Unless otherwise stated, the safety analysis set will be used for the presentation of all safety analyses and immunogenicity. Exposure to IMP will also be presented using the safety analysis set.

11.1.2. Pharmacokinetic Analysis Set

The PK analysis set will consist of all participants in the safety analysis set who received AZD7442 and who have evaluable serum PK data, with no important protocol deviations thought to impact on the analysis of the PK data.

The exclusion of any participants from PK analysis set or any time points from the calculation of the PK parameters will be documented by the PK Scientist including the reason(s) for exclusion.

The available concentration data and PK parameter data for any participants excluded from the PK analysis set will be listed only. Concentration data for participants excluded from the PK analysis set will be presented in the individual figures of concentration versus time plots.

11.1.3. Randomised Set

The Randomised Set will consist of all participants randomised into the study.

11.2. Methods of Statistical Analyses

11.2.1. General Principles

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

If circumstances should arise during the study rendering the analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be performed. A separate SAP will not be written for the study. Any deviations from the statistical methodology defined in this protocol, reasons for such deviations and all alternative/additional statistical analyses that may be performed will be described in the CSR. Such changes to analyses may be written into an abbreviated SAP, if appropriate. The verification and review of all statistical modelling assumptions will be documented appropriately.

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

Demographic and baseline data will be summarised by treatment group (dose level or administration process of AZD7442, total AZD7442 and pooled placebo). Pharmacokinetic data will be summarised by treatment group. Safety and tolerability data will be summarised by treatment group (dose level or administration process of AZD7442, total AZD7442 and pooled placebo).

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

The following rules will apply to any repeated safety assessments occurring within each cohort:

- If the repeated measurement of a specific parameter occurs prior to IMP administration (Day 1), then the last obtained value prior to dosing will be used in the descriptive statistics and in the calculation of changes from baseline;
- If the repeated measurement of a specific parameter occurs after IMP administration (Day 1), then the first (non-missing) value after dosing will be used in descriptive statistics and in the calculation of changes from baseline.

The planned sequence for measurement of multiple assessments at the same time point is described in Section 3.1.1.

For safety assessments performed at screening and the follow-up, the following rules will apply for any repeated assessments:

- If the repeated assessment occurs at Screening, the last available value will be used in the summary statistics;
- If the repeated assessment occurs at the Follow-up Visit, the first non-missing assessment will be used in the summary statistics.

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

11.2.1.1. Missing Data

Missing dates and times in the AE data will be handled as described in Section 10.1.1. Concentrations that are NQ in the PK data will be handled as described in Section 11.2.5.

There will be no imputations of other missing data. All participants will be included into the safety analyses as far as the data permit.

11.2.2. Participant Characteristics

A randomisation listing will be presented and include the following: each participant's randomisation number, the participant's full enrolment number, the treatment to which the participant has been randomised and the country where the study centre is located.

Participants and/or data excluded from the PK analysis set will be listed including the reason for exclusion. Participant disposition will be summarised and will include the following information: number of participants randomised and dosed, number and percentage of participants completing the study and the number and percentage of participants who were withdrawn (including reasons for withdrawal). Disposition data will be presented based on all participants randomised.

Participant discontinuations will be listed including the date of study exit, duration of treatment and reason for discontinuation. A listing of informed consent response will also be presented.

11.2.2.1. Demographic and Baseline Data

Demographic variables (age, gender, race, ethnicity, height, weight and BMI) will be listed by participant. Demographic characteristics (age, gender, race and ethnicity) and participant characteristics (height, weight and BMI) will be summarised by treatment group (dose level or administration process of AZD7442, total AZD7442 and pooled placebo) for all randomised participants. The denominator for percentages will be the number of randomised participants.

Medical history data will be listed by participant including visit, description of the disease/procedure, MedDRA SOC, MedDRA PT, start date and stop date (or ongoing if applicable).

11.2.3. Prior and Concomitant Medication and Drug Administration

11.2.3.1. Prior and Concomitant Medication

Prior medications are those that started and stopped prior to signing of the ICF; all medications taken after the ICF signing are considered as concomitant (including medications that started prior to dosing and continued after). Prior medication started within 3 months prior to the first dose of IMP will be recorded also in the concomitant medication module of ClinBase™.

Prior and concomitant medication will be listed by participant and will include the following information: reported name, PT, the route of administration, dose, frequency, start date/time, duration and indication. Prior and concomitant medication will be coded according to the Sponsor's drug dictionary.

The duration will be calculated as:

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

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

Medications with missing or partial start date/time and/or end date/time such that it is not possible to classify as prior or concomitant will be considered as concomitant in the listings.

11.2.3.2. Drug Administration

Drug administration dates and times will be listed for each participant.

11.2.4. Safety and Tolerability

All safety data (scheduled and unscheduled) will be presented in the data listings, sorted by treatment group and participant. Continuous variables will be summarised using descriptive statistics (n, mean, SD, minimum, median, maximum) by treatment group (dose level or administration process of AZD7442, total AZD7442 and pooled placebo). Categorical variables will be summarised in frequency tables (frequency and proportion) by treatment group (dose level or administration process of AZD7442, total AZD7442 and pooled placebo). The analysis of the safety variables will be based on the safety analysis set.

Adverse events will be summarised by PT and SOC using MedDRA vocabulary. Furthermore, listings of SAEs and AEs that led to withdrawal will be made and the number of participants who had any AE, SAEs, AEs that led to withdrawal, and AEs with severe intensity will be summarised. Adverse events that occur before dosing will be reported separately.

Tabulations and listings of data for vital signs, clinical laboratory tests and ECGs (listings only), will be presented. Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment will be reported as an AE. Data will be summarised for the observed values at each scheduled assessment, together with the corresponding changes from the baseline when baseline is defined. Clinical laboratory data will be reported in the units provided by the clinical laboratory for the DEC meeting, and in Système International units in the CSR.

Out-of-range values for safety laboratory will be flagged in individual listings, as well as summarised descriptively using agreed standard reference ranges and/or extended reference ranges (eg, AstraZeneca, program, or laboratory ranges).

11.2.5. Pharmacokinetics

The serum AZD7442 mAbs (AZD8895 and AZD1061) concentrations and PK parameters will be listed and presented in tabular and graphical form as appropriate according to the most recent version of the AstraZeneca CPE tables, listings, and figures standards, that includes applicable descriptive statistics, handling of individual concentrations below the LLOQ for listings, descriptive statistics and figures, and precision and rounding rules for concentrations and PK parameter data.

11.2.5.1. Serum Concentration Data

For AZD7442 mAbs (AZD8895 and AZD1061), the serum concentrations for each scheduled time point will be summarised by treatment group using appropriate descriptive statistics, based on the PK analysis set. A listing of all concentration-time data, ie, PK scheduled times, actual sample collection times, sample actual relative times, as well as derived sampling time deviations will be presented by treatment group for all participants in the safety analysis set. A listing of concentration versus scheduled time data will be presented by treatment group for the safety analysis set.

11.2.5.2. Serum Pharmacokinetic Parameter Listings

All reportable AZD7442 PK parameters, including individual diagnostic and λz-related parameters, will be listed for each participant by treatment group, based on the safety analysis set.

11.2.5.3. Serum Pharmacokinetic Parameter Descriptive Statistics

All PK parameters will be summarised by treatment group using appropriate descriptive statistics, based on the PK analysis set.

11.2.5.4. Graphical Presentation for Serum Concentration Data

Individual concentration-time data will be graphically presented on linear and semi-logarithmic scales, for all participants in the safety analysis set. Combined individual serum concentration versus actual times will be plotted on both the linear and semi-logarithmic scale for all participants in the PK analysis set. Plots will be grouped by treatment group. Figures for the geometric mean (-/+gSD) serum concentration-time data will be presented for all treatment groups on both a linear and semi-logarithmic scale (no gSD presented), for all participants in the PK analysis set.

All plots will be based on the PK analysis set, with the exception of individual plots by participant which will be based on the safety analysis set.

11.2.6. Immunogenicity and Pharmacodynamics

11.2.6.1. Anti-drug Antibody Titers

The presence or absence of ADA to AZD7442 (either AZD8895 and/or AZD1061) collected, including the titer for samples confirmed positive for ADA for each treatment group (dose level or administration process of AZD7442) will be listed by participant and time point. Tabulations will be provided for each treatment group (dose level or

administration process of AZD7442). The results will be presented based on the safety analysis set.

The results of the ADA assessments will be listed for each participant and time point. This will include the classification of the response (positive/negative) and the measured titers where appropriate. Summary tables will be presented, by treatment group (dose level or administration process of AZD7442), for the number and percentage of participants with positive/negative results at each time point, based on the Safety analysis set.

In addition, the ADA titers (n, median, minimum and maximum) will be summarised by treatment group (dose level or administration process of AZD7442) for all participants with a positive confirmatory assay at each time point; this tabulation will include a summary of the highest titer across all time points for each participant.

The impact of ADA on PK, and association with AEs and SAEs may be assessed.

11.2.6.2. Nasal Fluid Pharmacokinetic Analysis

Sample collection will take place for nasal fluid PK analysis and the results will be listed for each participant and time point. Summary tables will be presented, by treatment group (dose level or administration process of AZD7442), for the number and percentage of participants at each time point, based on the safety analysis set.

11.2.6.3. Neutralising Antibody Concentrations

Sample collection will take place for neutralising antibodies against SARS-CoV-2; however, the evaluation of the functional inhibition of SARS-CoV-2 by AZD7442 concentrations in serum will be reported separately from the study's report.

11.3. Protocol Deviations

Protocol deviations are considered any deviation from the CSP relating to a participant, and include the following:

- Inclusion/exclusion criteria deviations.
- Dosing deviations (eg, incorrect treatment received).
- Time window deviations for safety and/or PK assessments.
- Participants receiving prohibited concomitant medications.
- Other procedural and study conduct deviations recorded by the Clinical Unit on a protocol deviation log.

Planned protocol deviations are not considered acceptable. A protocol deviation that is suspected or known to have the potential to significantly impact on a participant's safety, physical or mental integrity, or scientific value will be classified as a serious breach. The criteria for the assessment and reporting of protocol deviations will be stipulated in a separate study specific PDS document. This will include a WAD which stipulates tolerance windows for safety and PK assessments. Measurements performed within these tolerance windows will not be considered as protocol deviations and will not be reported.

All protocol deviations will be discussed at the data review meeting prior to database hard lock in order to define the analysis sets for the study.

Important protocol deviations will be listed by participant. Protocol deviations (missing assessments/visits) related to COVID-19 will be listed separately.

Protocol deviations will be handled in accordance with Parexel SOPs.

For handling of protocol amendments, see Section 8.6.

11.4. Determination of Sample Size

Approximately 60 healthy adult participants will be randomised to AZD7442 or placebo across 5 fixed-dose cohorts as below. Because all analyses will be descriptive in nature and no hypothesis is being tested statistically, no formal sample size calculations were performed, however, the sample size is considered sufficient for an early assessment of safety, tolerability, immunogenicity, and PK. Additional cohorts may be added with lower or intermediate doses of AZD7442 if the DEC determines they are warranted:

- Cohort 1a (12 participants): 300 mg AZD7442 (150 mg AZD8895 and 150 mg AZD1061) (n=9) or placebo (n=1), administered IM,
  - Sentinel dosing: 300 mg AZD7442 (150 mg AZD8895 and 150 mg AZD1061) (n=1) or placebo (n=1).
- Cohort 1b (12 participants): 300 mg AZD7442 (150 mg AZD8895 and 150 mg AZD1061) (n=9) or placebo (n=1), administered IV,
  - Sentinel dosing: 300 mg AZD7442 (150 mg AZD8895 and 150 mg AZD1061) (n=1) or placebo (n=1).
- Cohort 2 (12 participants): 1000 mg AZD7442 (500 mg AZD8895 and 500 mg AZD1061) (n=9) or placebo (n=1), administered IV,
  - Sentinel dosing: 1000 mg AZD7442 (500 mg AZD8895 and 500 mg AZD1061) (n=1) or placebo (n=1).
- Cohort 3 (12 participants): 3000 mg AZD7442 (1500 mg AZD8895 and 1500 mg AZD1061) (n=9) or placebo (n=1), administered IV,
  - Sentinel dosing: 3000 mg AZD7442 (1500 mg AZD8895 and 1500 mg AZD1061) (n=1) or placebo (n=1).
- Cohort 4 (12 participants): 3000 mg AZD7442 (1500 mg AZD8895 and 1500 mg AZD1061 mixed in single infusion) (n=9) or placebo (n=1), administered IV,
  - Sentinel dosing: 3000 mg AZD7442 (1500 mg AZD8895 and 1500 mg AZD1061 mixed in single infusion) (n=1) or placebo (n=1), administered IV.

12. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

12.1. Medical Emergencies and AstraZeneca Contacts

In case of medical emergency, the primary contact is the PI. The PI may contact the Sponsor's Lead Physician. If the PI cannot be reached, the site's staff will contact the PI's deputy or may contact Sponsor's Lead Physician.

Name	Role in the Study	Contact Details
Dr Pablo Forte Soto (MD, MSc, PhD)	Principal Investigator	Tel: PPD
PPD	PPD	Tel: PPD

12.2. Overdose

For this study, any dose of AZD7442 greater than 1500 mg of either individual mAb during the course of the study will be considered an overdose.

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

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

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the PI or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the PI to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, and within 30 days for other overdoses.

12.3. Pregnancy

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

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

If a pregnancy is reported, the PI should inform the Sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Please refer to Section 4.2.1.2 and Section 4.2.1.3 for further details.

12.3.1. Maternal Exposure

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/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 abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the PI 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 PI 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 CSP process for SAE reporting) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

Please refer to Section 4.2.1.2 for further details.

12.3.2. Paternal Exposure

Male participants should refrain from fathering a child during the study and for 360 days following the last dose.

In case of pregnancy of the partner of a male patient, 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 patient's partner is not considered to be an AE. These pregnancies will also be followed up, and the outcome of the pregnancy (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should, if possible, be obtained and documented.

Please refer to Section 4.2.1.3 for further details.

13. LEGAL AND ADMINISTRATIVE ASPECTS

13.1. Archiving of Study Documents

All source documents generated in connection with the study will be retained in the limited access file storage area, respecting the privacy and confidentiality of all records that could identify the participants. Direct access is allowed only for authorised people for monitoring and auditing purposes. Source documents will be handled, stored and archived according to in house procedures.

The Investigator's Site File will be archived by the CRO for 15 years after completion of the study.

13.2. Publication of Study Results

All of the study information and data collected during the study are confidential and the property of AstraZeneca. After completion of the study, AstraZeneca may prepare a joint publication with the PI. The PI must undertake not to submit any data from this CSP for publication without prior consent of AstraZeneca at a mutually agreed time.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

13.3. Clinical Study Report

An integrated CSR will be prepared in accordance with the standards of the ICH guideline for structure and content of CSRs (ICH E3). Copies of the CSR will be provided to the IEC and the National Regulatory Authority in accordance with regulatory requirements and Parexel SOPs. In the event of premature termination of the study or other conditions specified in ICH E3, an abbreviated CSR may be prepared.

14. LIST OF REFERENCES

1 Perlman S, McIntosh K. Coronaviruses, Including Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). In: Bennett J, Dolin R, Blaser MJ. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th Ed. Philadelphia: Elsevier; 2020. P. 2072-2080.

2 Fehr R, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol. 2015 1282:1-23.

3 MERS-situation update. WHO [cited January 2020]. Available from: URL: http://www.emro.who.int/pandemic-epidemic-diseases/mers-cov/mers-situation-update-january-2020.html.

4 COVID-19 Coronavirus Pandemic cases updates [accessed on 20 July 2020]. URL: https://www.worldometers.info/coronavirus/#countries accessed 20 July 2020.

5 COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University [accessed on 20 July 2020] URL:https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6 accessed 20 July 2020.

6 Investigator's Brochure for AZD7442, version 1.0 - 23 July 2020.

7 MHRA (2020) Medicines and Healthcare products Regulatory Agency guidance on Managing clinical trials during Coronavirus (COVID-19), Updated on 21 May 2020;

URL: https://www.gov.uk/guidance/managing-clinical-trials-during-coronavirus-covid-19, accessed on 08 Jun 2020.

8 Manivannan V, Decker WW, Latha G et al. Visual representation of National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network criteria for anaphylaxis. Int J Emerg Med. 2009 Apr; 2(1): 3–5.

9 Guidance on the Management of Clinical Trials during the COVID 19 (Coronavirus) pandemic, EMA, Version 3 (28/04/2020)
URL: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf.

15. APPENDICES

Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event

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 a 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 Intervention

Medical and scientific judgement 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 intervention to prevent 1 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 judgement must be used.

Examples of such events are:

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

A Guide to Interpreting the Causality Question

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the IMP.

- 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?
- Dechallenge 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 other etiology such as the underlying disease, other drugs, other host or environmental factors.
- Rechallenge experience:
  Did the AE reoccur if the suspected drug was reintroduced after having been stopped?
  Note: AstraZeneca would not normally recommend or support a rechallenge.
- 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 judgement. With limited or insufficient information in the case, it is likely that 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.

Appendix B International Airline Transportation Association 6.2 Guidance Document

Labelling and Shipment of Biohazard Samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories (http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm). For transport purposes, the classification of infectious substances according to risk groups was removed from the DGR in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are for example, Ebola and Lassa Fever viruses:

- Are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are for example, hepatitis A, B, C, D and E viruses, and HIV types 1 and 2. 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 refers to all other materials with minimal risk of containing pathogens.

- Clinical trial samples will fall into Category B or Exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging. (http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content.**
- An IATA compliant courier and packaging materials should be used for packing and transportation. Packing should be done by an IATA certified person, as applicable.
- Samples routinely transported by road or rail are participant to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix C Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

C 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report 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 PI will remain vigilant for increases in liver biochemistry. The PI is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

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

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

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

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

C 2 Definitions

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\geq 3 \times$ ULN **together with** TBL $\geq 2 \times$ ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law (HL)

AST or ALT $\geq 3 \times$ ULN **together with** TBL $\geq 2 \times$ 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.

C 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:

- AST $\geq 3 \times$ ULN
- ALT $\geq 3 \times$ ULN
- TBL $\geq 2 \times$ ULN

If Central Laboratories Being Used:

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

The PI will also remain vigilant for any local laboratory reports where the PHL identification criteria are met, where this is the case the PI 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 CRF module(s) with the original local laboratory test result.

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

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

If Local Laboratories Being Used:

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

- Notify the AstraZeneca representative.
- Determine whether the participant meets PHL criteria (see Section 2 within this appendix for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory CRF module(s).

C 4 Follow-Up

C 4.1 Potential Hy's Law Criteria not met

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

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

C 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the PI will:

- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the PI 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 PI is not required to submit a PHL SAE unless there is a significant change[2] in the participant's condition.
- The Study Physician contacts the PI, 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 PI will:
    - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
    - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the HL laboratory kit should be used (if applicable).
    - Complete the three liver CRF modules as information becomes available.

C 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 PI 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 the date the PHL criteria were met. The AstraZeneca Global Clinical Lead or equivalent and

[2] 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 total bilirubin) 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.

Global Safety Physician will also be involved in this review together with other participant matter experts as appropriate.

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

Where There Is an Agreed Alternative Explanation for the AST or ALT and TBL Elevations, a Determination of Whether the Alternative Explanation Is an AE Will Be Made and Subsequently Whether the AE Meets Any Criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF module(s).
- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE CRF entries 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 AST or ALT and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' seriousness criterion should be used if no other seriousness 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 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:

- Provide any further update to the previously submitted SAE of PHL (report term now 'Hy's Law case'), ensuring causality assessment is 'related to IMP' and seriousness criterion 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.

C 6 Laboratory Tests

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

Hy's Law laboratory kit for central laboratories (18 December 2018)

Additional standard biochemistry and coagulation tests	GGT LDH Prothrombin time INR	
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA	anti-HCV HCV RNA* IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV	
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)**	
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)	
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin** Transferrin saturation	

* HCV RNA is only tested when anti-HCV is positive or inconclusive
** Carbohydrate deficient transferrin (CD-transferrin) is not available in China. Study teams should amend this list accordingly.

REFERENCES

Aithal GP, Watkins PB, Andrade RJ, et al. Case definition and phenotype standardisation in drug-induced liver injury. Clinical Pharmacology & Therapeutics 2011;89(6):806–15.

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