Title: Phase I, Randomized, Open Label, Three-arm, Single Dose, Parallel Group Study to Compare AZD7442 (AZD8895 + AZD1061) Pharmacokinetic Exposure Following Intramuscular Administration as a Coformulation versus Administration From Two Separate Vials of the Individual Monoclonal Antibodies in Adult Healthy Participants

Sponsor Study Code: D8850C00009

NCT Number: NCT05166421

Date: 10-Jun-2022

Clinical Study Protocol

Phase 1, Randomized, Open label, Three-arm, Single Dose, Parallel Group Study to Compare AZD7442 (AZD8895 + AZD1061) Pharmacokinetic Exposure Following Intramuscular Administration as a Co-formulation versus Administration from Two Separate Vials of the Individual Monoclonal Antibodies in Adult Healthy Participants

Parexel Study No.:	PXL265185
Sponsor Study Code:	D8850C00009
IND No.:	150712
Study Type:	PK comparability study
Study Intervention (Test Product):	AZD7442 as a co-formulation of individual monoclonal antibodies (AZD8895 + AZD1061)
Study Intervention (Reference Product):	AZD7442 administered from two separate vials of the individual monoclonal antibodies (AZD8895 + AZD1061)
Therapeutic Indication:	Prophylaxis and treatment of COVID-19
Pharmacological Class:	Antiviral monoclonal antibodies
Development Phase:	Phase I
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden
Study Center:	Parexel International, LLC 275 Grove Street, Newton, MA 02466, United States of America
Date of Protocol:	21 September 2021
Protocol Amendment No. 1	28 January 2022
Protocol Amendment No. 2	10 June 2022

This clinical study will be conducted according to the protocol and in compliance with Good Clinical Practice, with the Declaration of Helsinki, and with other applicable regulatory requirements.

PROTOCOL AMENDMENTS

Protocol Amendment No. 2, dated 10 June 2022

The Protocol Amendment No. 1, dated 28 January 2022 was amended to remove the Interim Analysis from the protocol, the positive cotinine test at screening, the Exclusion criterion 14, and to update Exclusion criterion 13, and other editorial changes listed below.

The following sections of the protocol have been changed:

- Synopsis: the estimated date of last participant completed was updated from April 2023 to Q3 2023, according to current enrolment status.
- Synopsis, Section 4.1.2, Section 6.2, Section 6.3.2.7: cotinine test removed from eligibility assessments throughout the protocol as it is not applicable to this study.
- Synopsis, List of abbreviations and definition of terms, Table 2-1, Table 2-2, Figure 3-1, Section 10.2, Section 10.2.1, Section 11.2.6.5, Section 11.2.6.6, Section 11.5 (removed section): Interim Analysis removed from the protocol as it is no longer required. References to final analysis removed from the protocol.
- Synopsis, Section 11.1.1: Updated pharmacokinetic analysis conclusions for clarity.
- Synopsis, Section 1.2, Section 3.2.1: Language referring to 'formulations' updated to 'materials' for clarity.
- Investigators and Study Administrative Structure: Adverse event reporting Fax number updated.
- Section 4.1.2: Exclusion criterion 13 'Aspartate aminotransferase, ALT, or serum creatinine above the ULN; bilirubin and ALP > 1.5 × ULN.' updated to increase the serum creatinine limit for exclusion to 'above 2 × the ULN', as it has no impact on the safety of the participants enrolled in the study or the study results.
- Section 4.1.2: Exclusion criterion 14 'Hemoglobin or platelet count below LLN at screening. White blood cell or neutrophil count outside the normal reference ranges.' removed as it is covered by Exclusion criterion 15 (14 in the current amendment) 'Any laboratory value in the screening panel that, in the opinion of the investigator, is clinically significant or might confound analysis of study results.'
- Section 4.2.1.2: 'injectable' method of combined contraception added for clarity.
- Section 6.3.1.7: Language updated to align with current protocol template.
- Section 6.4.2: Language updated to clarify that additional analyses on biological samples may be conducted for other compound-related purposes.
- Section 7.2.2: Section name updated from 'Pharmacodynamic Samples' to 'Immunogenicity Samples' for clarity.
- Section 10.4 'CCI [redacted]' moved up to Section 10.3 for clarity.
- Section 10.3 'Pharmacodynamic Variables' updated to 'Immunogenicity Variables' and moved down to Section 10.4 for clarity.

- Section 11.2.7.2 '[redacted]' moved up to Section 11.2.7.1 for clarity.
- Section 11.2.7.1 'Pharmacodynamic Assessment' updated to 'Immunogenicity Assessment' and moved to Section 11.2.8 for clarity.
- Additional editorial and grammatical updates throughout the protocol for clarity.

Protocol Amendment No. 1, dated 28 January 2022

The original Clinical Study Protocol (CSP) dated 21 September 2021 was amended to provide clarifications to some inclusion and exclusion criteria and to include new Adverse Events of Special Interest (AESI).

The following sections of the protocol have been changed:

- Synopsis, Investigators and Study Administrative Structure: Text regarding Principal Investigator removed as there is no lead Principal Investigator in this study.
- Synopsis, Section 3.1, Table 3-1, Section 4.1.1: The requirement for participants to be non-vaccinated or fully vaccinated against SARS-CoV-2 was updated to state non-vaccinated or vaccinated. Stratification by anti-SARS-CoV-2 vaccination status at randomization was also updated to state non-vaccinated or vaccinated with added clarification for vaccinated status to mean having received one or more locally approved/authorized COVID-19 vaccine doses.
- Synopsis (Targeted Study Population), Table 3-1, Table 3-2, Section 4.1.1: Number of days between last vaccine dose against SARS-CoV-2 infection received and IMP administration updated to at least 14 calendar days.
- Synopsis (Targeted Study Population), Table 3-2, Section 4.1.2: Text updated to specify that vaccination status will be documented throughout the study in the eCRF.
- Synopsis (Targeted Study Population), Table 3-1, Section 4.1.1: Text regarding the requirement for non-vaccinated participants against SARS-CoV-2 infection to have negative results for a serology test within 2 weeks prior to randomization has been removed.
- List of Abbreviations: CDC added to list of abbreviations.
- Section 1.1: Omicron variant added to list of SARS-CoV variants.
- Figure 3-1: Figure updated to correct a typographical error in the visits numbering.

- Table 3-1: Removed SARS-CoV-2 RT-PCR assessment from screening and added SARS-CoV-2 RT-PCR assessment under Day 1 with the clarification that SARS-CoV-2 RT-PCR test should be taken ≤ 3 days before Day 1 and if a documented SARS-CoV-2 RT-PCR test is not available at screening, a rapid SARS-CoV-2 antigen test will be performed on the day of randomization, pre-dose (for screening criteria). Footnote h updated with this clarification and to state that either test must be negative before dosing.

- Table 3-1, Section 6.3.2.8: Removed screening SARS-CoV-2 serology as an assessment.

- Table 3-1: Footnote b updated to include text regarding repeat of serum chemistry, hematology and coagulation being allowed once during Screening period, if values at Screening visit were outside of reference range and documented as not clinically significant.

- Section 4.1.1: Inclusion criterion 4 updated to documented negative results of a SARS-CoV-2 RT-PCR test collected ≤ 3 days prior to IMP dose administration (Day 1) or a negative rapid SARS-CoV-2 antigen test on Day 1 (pre-dose). NOTE was also updated to allow participants who do not meet this criterion to be re-screened more than once and up to a maximum of two times as per investigator discretion but with prior approval of the Medical Monitor.

- Section 4.1.2: Exclusion criterion 5 updated to remove history of laboratory confirmed SARS-CoV-2 infection and to clarify SARS-CoV-2 result can be based on available data at screening or at Day 1.

- Section 4.1.2: Exclusion criterion 11 updated to list cotinine, to be consistent with section 6.2.

- Section 4.1.2: Exclusion criterion 19 updated to include text regarding use of routine vaccines.

- Section 4.1.2: Exclusion criterion 28 added.

- Section 5.1: Text regarding re-screening removed.

- Section 5.1.1: Renamed to Re-screening and added guidance on requirements and procedures for re-screening.

- Section 5.1.2: Moved text from section 5.1.1: Procedures for Randomization under this section.

- Table 5-3: Text added to clarify that routine vaccines are permitted if administered at least 14 days prior to Day 1 dosing or > 30 days after IMP dose.
- Section 5.4.5: Text updated to clarify that if a participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection, but before the second IM injection, further IMP should not be given.
- Section 5.4.5: Text updated to clarify that water and food will be allowed ad libitum from 1 hour after the start of dosing.
- Section 5.4.6: Text added to provide guidance on the size and length of the needle commonly used for IM injections.
- Section 5.4.6.1: Text updated to clarify that co-formulated AZD7442 should be administered as a single 2 mL IM injection.
- Section 6.3.1.3: Cardiac ischemia, cardiac failure and thrombotic events added as AESIs.
- Section 6.3.2.8: Added rapid SARS-CoV-2 antigen test to list of SARS-CoV-2 tests.
- Section 6.3.7: Text regarding SARS-CoV-2 testing updated.
- Section 6.5.1: Renamed to CCI [redacted] and moved text from section 6.6: CCI [redacted] Samples under this section.
- Section 6.6: Renamed to Immunogenicity Assessments and moved text from section 6.5.1: Collection of Pharmacodynamic Samples (regarding analysis of blood samples for determination of serum anti-AZD8895 and anti-AZD1061) under this section.
- Section 11.2.4.1: Added requirement for last dose of anti-COVID-19 vaccine received prior to randomization, to be recorded in the EDC system.
- Section 12.1: Replaced Principal Investigator with Medical Monitor and provided contact details for the Medical Monitor.
- Reference list updated.
- Additional minor formatting and grammatical corrections were made.
- Minor inconsistencies in the original protocol were clarified throughout the protocol.

PROTOCOL SYNOPSIS

Title of the Study
Phase I, Randomized, Open label, Three-arm, Single Dose, Parallel Group Study to Compare AZD7442 (AZD8895 + AZD1061) Pharmacokinetic Exposure Following Intramuscular Administration as a Co-formulation versus Administration from Two Separate Vials of the Individual Monoclonal Antibodies in Adult Healthy Participants

Study Center
This study will be conducted at a minimum of three different Clinical Units.

Study Rationale
The study will assess pharmacokinetic (PK) comparability between different formulations of AZD7442, which is a combination of two individual monoclonal antibodies (mAbs), AZD8895 and AZD1061. The materials to be assessed will be:

- A co-formulation of clonal cell line material of AZD8895 + AZD1061 mAbs as a single intramuscular (IM) injection from a single mixture,
- Individual formulations of clonal cell line material of AZD8895 and AZD1061 mAbs as separate sequential IM injections, and
- Individual formulations of cell pool material of AZD8895 and AZD1061 mAbs as separate sequential IM injections.

An open label, parallel group design has been chosen for this single dose PK comparability study.

Number of Participants Planned
Approximately 207 evaluable participants will be enrolled in this study.

Study Period
Estimated date of first participant enrolled: November 2021 (signing of informed consent)
Estimated date of last participant completed: Q3 2023

Study Objectives

The objectives of the study are:

Primary Objectives:

- To evaluate the PK comparability between AZD7442 administered as a single IM dose (co-formulation) (AZD8895 + AZD1061) and two separate IM doses (AZD8895 and then AZD1061) (clonal cell line material of AZD8895 and AZD1061) of the individual mAbs in healthy adult participants.
- To evaluate the PK comparability between AZD7442 administered as a single IM dose (co-formulation) (AZD8895 + AZD1061) and two separate IM doses (AZD8895 and then AZD1061) (cell pool material of AZD8895 and AZD1061) of the individual mAbs in healthy adult participants.
- To evaluate the PK comparability between the clonal cell line material and the cell pool material of AZD7442 administered as two separate sequential IM doses (AZD8895 and then AZD1061) of the individual mAbs in healthy adult participants.

Secondary Objectives:

- To examine the serum PK profiles of AZD7442 when administered as a single IM dose (co-formulation) (AZD8895 + AZD1061) and as two separate IM doses (AZD8895 and then AZD1061) (clonal cell line or cell pool material) of the individual mAbs in healthy adult participants.
- To further assess the safety of AZD7442 when administered as a single IM dose (co-formulation) (AZD8895 + AZD1061) and as two separate IM doses (AZD8895 and then AZD1061) (clonal cell line or cell pool material) of the individual mAbs in healthy adult participants.
- To evaluate the anti-drug-antibody (ADA) responses to AZD7442 in serum following administration as a single IM dose (co-formulation) (AZD8895 + AZD1061) and as two separate IM doses (AZD8895 and then AZD1061) (clonal cell line or cell pool material) of the individual mAbs in healthy adult participants.

Exploratory Objective:

- CCI [redacted]

Study Design

This is a randomized, open label, three-arm, single dose, parallel group, multi-center, PK comparability study. A total of 207 evaluable healthy male and female participants will be randomized in a 1:1:1 ratio between the 3 treatment groups (69 participants per group). Each participant will receive AZD7442 as either a single IM dose (co-formulation; AZD8895 + AZD1061), or as two separate IM doses of the individual mAbs (AZD8895 and then AZD1061) from either clonal cell line material or cell pool material.

Treatment Groups:

- **Treatment A**: 300 mg (total protein) AZD7442 as a single IM dose (co-formulation of 150 mg AZD8895 + 150 mg AZD1061) (clonal cell line material).
- **Treatment B**: 300 mg (total protein) AZD7442 as two separate IM doses of the individual mAbs (150 mg AZD8895 and then 150 mg AZD1061) (clonal cell line material).
- **Treatment C**: 300 mg (total protein) AZD7442 as two separate IM doses of the individual mAbs (150 mg AZD8895 and then 150 mg AZD1061) (cell pool material).

The product in Treatment Groups A and B is derived from material that originated from a clonal cell line, with a separate cell line, GMP cell bank, and manufacturing process for AZD8895 and AZD1061. The product in Treatment Group C is derived from material that originated from a non-clonal cell pool, with a separate pool of cells, GMP cell bank, and manufacturing process for AZD8895 and AZD1061. The clonal cell line is derived from a subpopulation of the respective cell pool, and there are no differences in antibody sequence between these cell banks. These materials have been demonstrated to be analytically comparable to each other.

Additionally, within each of the treatment groups, participants will be randomized 1:1:1 to injection sites of lateral thigh, gluteal dorsal, or gluteal ventral. The study will then also further be stratified by body weight category (< 70 kg; 70 to < 80 kg; and ≥ 80 kg) and anti-SARS-CoV-2 vaccination status (non-vaccinated or vaccinated).

After a Screening Period of up to 28 days, eligible participants will present themselves at the study clinic on Day 1. Participants will be randomized to one of the three treatment groups to receive their dose of investigational medicinal product (IMP) (AZD7442 as either a single IM dose or two separate IM doses). Following an observation and PK and pharmacodynamic (PD) sampling period of approximately 8 hours post-dose, participants will be discharged from the Clinical Unit at the discretion of the investigator. During the Follow-up Period of approximately 1 year, participants will return for a total of 11 outpatient follow-up visits starting on Day 2 through to Day 361. At the follow-up visits, data on adverse events (AEs) and serious adverse events (SAEs) will be collected in addition to collection of blood samples for PK, PD, and ADA assessments.

On the day of IMP administration (Day 1), participants should follow a diet, which excludes all alcohol (from at least 72 hours prior to dosing) and caffeinated products (from at least 24 hours prior to dosing). Participants are not required to abstain from food and drink intake until 45 minutes to 1 hour before IMP administration.

Expected Duration of the Study

The total duration of the study for a participant will be approximately 389 days comprising of a Screening Period that can last up to 28 days, Treatment Period of 1 day, and a Follow-up Period of 360 days.

Targeted Study Population

This study will be conducted in healthy volunteers, who may be male or female, ≥ 18 years of age, weighing ≥ 50 to ≤ 110 kg, and with a body mass index of ≥ 18 to ≤ 30 kg/m^2. Participants should be either non-vaccinated against SARS-CoV-2 infection or vaccinated with the last vaccine dose received at least 14 calendar days before IMP dose. Participants will be allowed to receive anti-COVID-19 vaccination during the study, however, should wait 14 days after their dose of IMP. Participant vaccination status will be documented throughout the study in the eCRF.

All participants must have negative results for SARS-CoV-2 RT-PCR test ≤ 3 days prior to randomization or negative results for rapid SARS-CoV-2 antigen test on day of randomization. Participants with a medical history of infection with SARS or Middle East Respiratory Syndrome or with any clinical signs or symptoms consistent with COVID-19 will be excluded from the study.

Outcome Endpoints

Safety Endpoints:

Safety variables will include

- AEs and SAEs.
- Vital signs (systolic and diastolic blood pressure and pulse rate).
- 12-lead ECGs.
- Physical examination.
- Laboratory assessments (hematology, clinical chemistry, and urinalysis).

Viral serology, drugs of abuse and alcohol will be assessed for eligibility. Coagulation, FSH (to confirm postmenopausal status for female participants) and pregnancy testing (for all female participants of childbearing potential), and use of concomitant medication will also be assessed and reported.

Pharmacokinetic Endpoints:

Where possible, PK parameters will be assessed from serum concentrations for the individual mAbs AZD8895 and AZD1061, as well as for the sum of the individual mAbs (AZD8895 + AZD1061), referred to as AZD7442.

- Primary PK parameters: AUCinf, AUClast, and Cmax.
- Secondary PK parameters: Tmax, AUC0-31d, AUC0-61d, AUC0-91d, AUC0-181d, tlast, t½λz, CL/F, and Vz/F.

Additional PK parameters may be determined where appropriate.

Exploratory Endpoints:

- CCI [redacted]

Statistical Methods

Analysis Sets

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

Presentation and Analysis of Pharmacokinetic Data:

The serum concentrations and PK parameters will be listed and presented in tabular and graphical form, as appropriate for the individual mAbs AZD8895 and AZD1061, as well as for the sum of the individual mAbs of AZD7442 (AZD8895 + AZD1061). The serum concentrations for each scheduled time point will be summarized by treatment group, treatment group and injection site, treatment group and bodyweight category, and treatment group, injection site, and bodyweight category using appropriate descriptive statistics, based on the PK analysis set for the individual mAbs AZD8895 and AZD1061, as well as for the sum of the individual mAbs of AZD7442 (AZD8895 + AZD1061). The PK parameters will be derived using non-compartmental methods for the individual mAbs AZD8895 and AZD1061, as well as for the sum of the individual mAbs of AZD7442 (AZD8895 + AZD1061). All PK parameters will be summarized by treatment group, treatment group and injection site, treatment group and bodyweight category, and treatment group, injection site, and bodyweight category using appropriate descriptive statistics, based on the PK analysis set.

The natural log transformed primary PK parameters (eg, AUCinf, AUClast, and Cmax) will be analyzed using a mixed effects model with treatment, injection site, anti-COVID-19 vaccination status, and continuous baseline body weight on the log scale as fixed effects and participant as a random effect. Transformed back from the logarithmic scale, geometric means together with confidence intervals (CIs) (2-sided 95%) for AUCinf, AUClast, and Cmax, will be calculated and presented. Also, ratios of geometric means together with CIs (2 sided 90%) will be estimated and presented.

If the 90% CIs for the geometric mean ratios for both AUCinf (AUClast for some agencies) and Cmax are entirely contained within 0.8000 and 1.2500 for all comparisons according to the study objectives, it may be concluded that the 2 formulations (the co-formulation and the formulation from the individual vials) are comparable, and the 2 materials (clonal cell line material and cell pool material) are comparable.

Presentation and Analysis of Safety Data:

Standard safety data analysis will be performed. The frequency and proportion of AEs and SAEs will be summarized by treatment group.

Presentation and Analysis of Exploratory Data:

CCI [redacted]

Determination of Sample Size:

Preliminary analysis of PK data from the first-in-human study, D8850C00001, indicated that after an IM dose of IMP (separate AZD8895 and then AZD1061 doses) at a dose of 300 mg total protein, the coefficients of variation (CV%) for Cmax of the individual mAbs, AZD8895 and AZD1061, were 35.6% and 38.5%, respectively, while the CV% for AUCs of both individual mAbs, AZD8895 and AZD1061 were < 36.4%. Therefore, assuming a mean ratio of 1 between comparators, 69 participants per group will provide at least 95% power to demonstrate comparability (90% CI contained within 0.8 and 1.25).

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Definitions of abbreviations for pharmacokinetic variables are presented in Section 10.2.

Abbreviation or special term	Explanation
ACE	Angiotensin-converting enzyme 2
ADA	Anti-drug antibody
ADE	Adverse device effect
AE	Adverse event (see definition in Section 6.3.1.1)
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the serum concentration-time curve
AUC0-31d	Area under the serum concentration-time curve from time zero to 30 days post-dose
AUC0-61d	Area under the serum concentration-time curve from time zero to 60 days post-dose
AUC0-91d	Area under the serum concentration-time curve from time zero to 90 days post-dose
AUC0-181d	Area under the serum concentration-time curve from time zero to 180 days post-dose
AUCinf	area under the serum concentration-time curve extrapolated to infinity
AUClast	area under the serum concentration-time curve from Day 0 to the last measurable concentration
BE	bioequivalence
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CDC	Centers for Disease and Control Prevention
CIOMS	Council for International Organizations of Medical Sciences
CL/F	apparent clearance after extravascular administration
Cmax	maximum observed serum (peak) concentration
COVID-19	Corona virus disease 2019
CRO	Contract research organization
CRP	C-reactive protein
CSP	Clinical study protocol
CSR	Clinical study report
DAE	Adverse event leading to the discontinuation of IMP
DMP	Data management plan
DNA	Deoxyribonucleic acid

Abbreviation or special term	Explanation
DVS	Data validation specification
ECG	Electrocardiogram
EDC	Electronic data capture
eCRF	Electronic case report form
Fc	Fragment crystallizable
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyl transpeptidase (transferase)
GMP	Good Manufacturing Practice
gSD	Geometric standard deviation
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
HCl	Hydrochloric acid
HIV	Human immunodeficiency virus
HL	Hy's Law
IB	Investigator's Brochure
IATA	International Airline Transportation Association
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	Investigational medicinal product
IRB	Institutional Review Board
IRT/RTSM	Interactive Response Technology/Randomization and Trial Supply Management
IV	intravenous
LLN	Lower limit of normal
mAb	Monoclonal antibody
MDR	Medical Device Regulation
MDT	Mean dissolution time
MedDRA	Medical Dictionary for Regulatory Activities
n	Number of participants
NIMP	Non-investigational medicinal products
NA	Not applicable
NR	No result
NQ	Not quantifiable
OTC	Over the counter

Abbreviation or special term	Explanation
PC	polycarbonate
PD	Pharmacodynamics
PHL	Potential Hy's Law
PI	Principal Investigator
PK	Pharmacokinetics
PP	polypropylene
PT	Preferred Term
QRS	ECG interval measured from the onset of the QRS complex to the J point
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	Red blood cell
RBD	Receptor binding domain
RNA	Ribonucleic acid
RR	The time between corresponding points on two consecutive R waves on ECG
RSV	Respiratory syncytial virus
SAE	Serious adverse event (see definition in Section 6.3.1.2).
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Corona Virus 2
SD	Standard deviation
SoA	Schedule of assessments
SOC	System Organ Class
SOP	Standard operating procedure
TBL	Total bilirubin
t½λz	terminal elimination half-life
tlast	time of last quantifiable concentration
Tmax	time to maximum observed serum concentration
TSH	Thyroid-stimulating hormone
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
Vz/F	volume of distribution based on terminal phase after extravascular administration
WAD	Windows Allowance Document
WBC	White blood cell

INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden
Sponsor's Lead Physician:	PPD PPD PPD PPD Tel: PPD E-mail: PPD
Sponsor's Biostatistician:	PPD PPD PPD Tel: PPD E-mail: PPD
Contract Research Organization:	Parexel International 275 Grove Street, Newton MA 02466 USA
Clinical Laboratory:	Local laboratories at individual study Clinical Units. LabCorp Central Laboratory Services LP 8211 SciCor Dr. Indianapolis, IN 46214, USA

Analytical Laboratory: (Pharmacokinetic and Pharmacodynamic sample analysis)	PPD Bioanalytical Services 2246 Dabney Road Richmond, VA 23230, USA Serum Neutralizing Antibody test Viroclinics Biosciences, B.V. Rotterdam Science Tower Marconistraat 16 3029 AK Rotterdam The Netherlands Tel: +31 88-668 4787 E-mail:PPD Monogram Biosciences – LabCorp Specialty Testing Group (Serum Neutralizing Antibody test) 345 Oyster Point Blvd South San Francisco CA 94080, USA
Adverse Event Reporting:	AstraZeneca Patient Safety Data Entry Site Tata Consultancy Services Fax: PPD or PPD E-mail: PPD

A list and contact details of investigators and other key study team members are provided in the Project Plan in the electronic Trial Master File. A list of all participating investigators will be provided in the Clinical Study Report.

1. INTRODUCTION

1.1. Background

Coronaviruses are spherical, enveloped viruses with positive-sense single-stranded RNA genomes. One fourth of their genome is responsible for coding structural proteins, such as the spike glycoprotein, envelope, membrane, and nucleocapsid proteins. Envelope, membrane, and nucleocapsid proteins are mainly responsible for virion assembly, while the spike protein is involved in receptor binding, mediating virus entry into host cells during coronavirus infection via different receptors (Li 2016).

Severe Acute Respiratory Syndrome Corona Virus 2 is a coronavirus responsible for the current COVID-19 global pandemic. SARS-CoV-2 belongs to the phylogenetic lineage B of the genus Beta-coronavirus and it recognizes the ACE2 as the entry receptor (Zhou et al 2020). Several new SARS-CoV-2 variants have been identified: the Alpha variant (B.1.1.7), the Beta variant (B.1.351), the Gamma variant (P.1), the Delta variant (B.1617.2) and the Omicron variant (B.1.1.529) (US CDC 2021; US CDC 2022; WHO 2021). These variants contain multiple spike protein mutations and mutations in other genomic regions.

AZD7442 is a combination product of two mAbs (AZD8895 and AZD1061) directed against RBD of the SARS-CoV-2 spike protein for neutralization of the virus. The two component mAbs bind unique, non-overlapping epitopes on the RBD of the viral spike protein. The use of two such mAbs provides redundancy in protection in case of virus mutation and escape. In response to the emergence of the B.1.1.7 and B.1.351 SARS-CoV-2 strains, preliminary in vitro neutralization assays demonstrated that the two component mAbs neutralized both emergent strains.

AZD8895 and AZD1061 mAbs have been engineered with triple amino acid substitutions (YTE) in the Fc region to prolong the half-life, which is expected to confer protection from COVID-19 for a duration of at least 5 months. An additional triple amino acid substitution (TM) in the Fc region was engineered for both AZD8895 and AZD1061 to reduce Fc mediated effector function, which is expected to reduce theoretical risk of antibody-dependent enhancement of disease. Importantly, incorporation of these YTE and TM substitutions did not alter the neutralization potency of AZD7442 in vitro.

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

1.2. Rationale for Conducting this Study

The study will assess PK comparability between different formulations of AZD7442, which is a combination of two individual mAbs, AZD8895 and AZD1061, and the individual formulations for each mAb. The materials to be assessed will be:

- A co-formulation of clonal cell line material of AZD8895 + AZD1061 mAbs as a single IM injection from a single mixture,
- Individual formulations of clonal cell line material of AZD8895 and AZD1061 mAbs as separate sequential IM injections, and
- Individual formulations of cell pool material of AZD8895 and AZD1061 mAbs as separate sequential IM injections.

2. STUDY OBJECTIVES

2.1. Primary Objectives

Table 2-1 Primary Objective and Outcome Measures

Primary Objectives	Outcome Measures
• To evaluate the PK comparability between AZD7442 administered as a single IM dose (co-formulation) (AZD8895 + AZD1061) and two separate IM doses (AZD8895 and then AZD1061) (clonal cell line material of AZD8895 and AZD1061) of the individual mAbs in healthy adult participants	• AUCinf, AUClast, and Cmax
• To evaluate the PK comparability between AZD7442 administered as single IM dose (co-formulation) (AZD8895 + AZD1061) and two separate IM doses (AZD8895 and then AZD1061) (cell pool material of AZD8895 and AZD1061) of the individual mAbs in healthy adult participants	• AUCinf, AUClast, and Cmax
• To evaluate the PK comparability between the clonal cell line material and the cell pool material of AZD7442 administered as two separate sequential IM doses (AZD8895 and then AZD1061) of the individual mAbs in healthy adult participants	• AUCinf, AUClast, and Cmax

Abbreviations: AUC: area under the serum concentration-time curve; Cmax: maximum observed serum (peak) concentration; IM: intramuscular; mAbs: monoclonal antibodies; PK: pharmacokinetic.

2.2. Secondary Objectives

Table 2-2 Secondary Objectives and Outcome Measures

Secondary Objectives	Outcome Measures
• To examine the serum PK profiles of AZD7442 when administered as a single IM dose (co-formulation) (AZD8895 + AZD1061) and as two separate IM doses (AZD8895 and then AZD1061) (clonal cell line or cell pool material) of the individual mAbs in healthy adult participants	• Tmax, AUC0-31d, AUC0-61d, AUC0-91d, AUC0-181d, tlast, t½λz, CL/F, and Vz/F

Secondary Objectives	Outcome Measures
• To further assess the safety of AZD7442 when administered as a single IM dose (co-formulation) (AZD8895 + AZD1061) and two separate IM doses (AZD8895 and then AZD1061) (clonal cell line or cell pool material) of the individual mAbs in healthy adult participants	• AEs including serious AEs and AEs of special interest • Laboratory assessments (hematology, clinical chemistry, and urinalysis) • Physical examination • Electrocardiogram • Vital signs (systolic and diastolic blood pressure, pulse rate)
• To evaluate the ADA responses to AZD7442 in serum following administration a single IM dose as a co-formulation (AZD8895 + AZD1061) and as two separate IM doses (AZD8895 and then AZD1061) (clonal cell line or cell pool material) of the individual mAbs in healthy adult participants	• Incidence and titers of anti-AZD8895 and anti-AZD1061 antibodies

Abbreviations: AE: adverse events; AUC: area under the serum concentration-time curve; CL/F: apparent clearance after extravascular administration; IM: intramuscular; PK: pharmacokinetic; t½λz: terminal elimination half-life; tlast: time of last quantifiable concentration; Tmax: time to maximum observed serum concentration; Vz/F: volume of distribution based on terminal phase after extravascular administration.

2.3. Exploratory Objectives

Table 2-3 Exploratory Objectives and Outcome Measures

Exploratory Objectives	Outcome Measures
• CCI [redacted]	• CCI [redacted]

Abbreviation: IM: intramuscular.

Refer to Section 10.2 for PK variables, Section 6.3 for safety variables.

3. STUDY DESIGN

3.1. Overall Study Design and Flow Chart

This study will be an open label, randomized, three-arm, parallel group, single dose, study in healthy participants (males and females), performed at multiple study centers.

A total of 207 evaluable healthy male and female participants will be randomized in a 1:1:1 ratio between the three treatment groups (69 participants per group). Each participant will receive AZD7442 as either a single IM dose (co-formulation; AZD8895 + AZD1061) from a single vial or as two separate IM doses of the individual mAbs (AZD8895 and then AZD1061) from two separate vials from either clonal cell line material or cell pool material as follows:

- **Treatment A**: 300 mg (total protein) AZD7442 as a single IM dose (co-formulation of 150 mg AZD8895 + 150 mg AZD1061) (clonal cell line material).
- **Treatment B**: 300 mg (total protein) AZD7442 as two separate IM doses of the individual mAbs (150 mg AZD8895 and then 150 mg AZD1061) (clonal cell line material).
- **Treatment C**: 300 mg (total protein) AZD7442 as two separate IM doses of the individual mAbs (150 mg AZD8895 and then 150 mg AZD1061) (cell pool material).

The product in Treatment Groups A and B is derived from material that originated from a clonal cell line, with a separate cell line, GMP cell bank, and manufacturing process for AZD8895 and AZD1061. The product in Treatment Group C is derived from material that originated from a non-clonal cell pool, with a separate pool of cells, GMP cell bank, and manufacturing process for AZD8895 and AZD1061. The clonal cell line is derived from a subpopulation of the respective cell pool, and there are no differences in antibody sequence between these cell banks. These materials have been demonstrated to be analytically comparable to each other. Refer to Table 5-1 for details on the IMP.

Additionally, within each of the treatment groups, participants will be randomized 1:1:1 to one of the three injection sites:

- Lateral thigh,
- Gluteal dorsal,
- Gluteal ventral.

Further, participants will be stratified based on the body weight and vaccination status at randomization as follows:

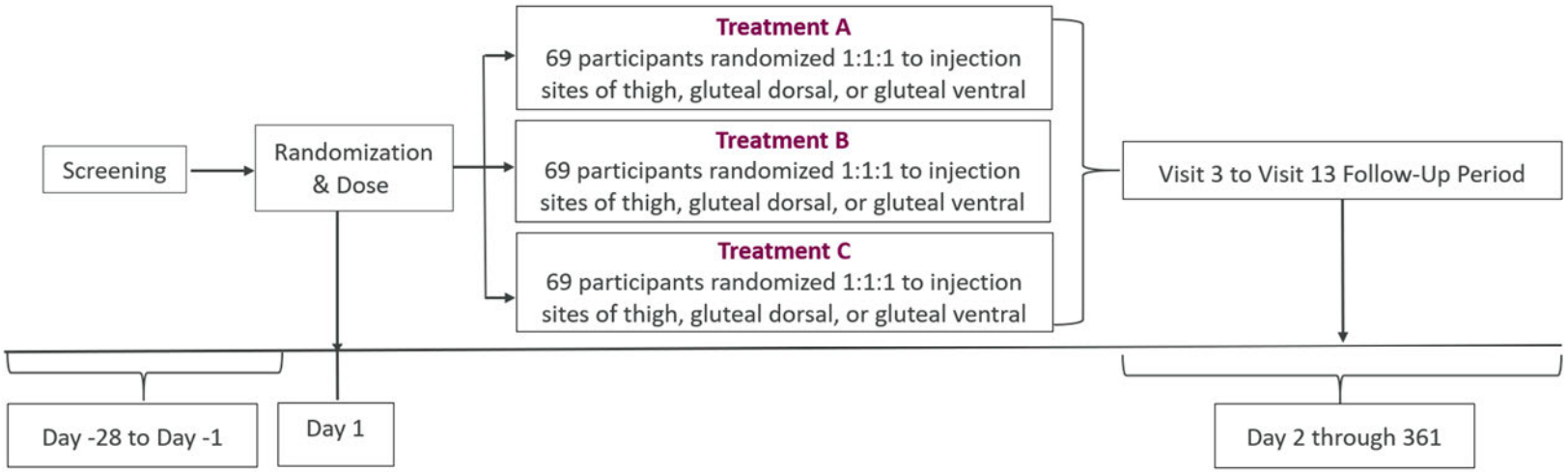
- Body weight at randomization: < 70 kg; 70 to < 80 kg; and ≥ 80 kg
- Anti-SARS-CoV-2 vaccination status at randomization: non-vaccinated or vaccinated (with one or more locally approved/authorized COVID-19 vaccine doses)

The study will comprise of:

- A Screening Period of up to 28 days that requires participants to visit the Clinical Unit (Visit 1).
- A Treatment Period of 1 day (Day 1; Visit 2) during which participants will be admitted to the study Clinical Unit and be randomized to receive their dose of IMP (AZD7442 as either a single IM dose or two separate IM doses). Participants will stay at the study clinic for at least 8 hours after dosing and will be discharged from the Clinical Unit at the discretion of the investigator, on the same day.
- A Follow-up Period of approximately 1 year consisting of regular visits to the study Clinical Unit starting from the day after dosing, Day 2 through to Day 361. The subsequent study visits total in 11 outpatient follow-up visits (Visits 3 to 13).

Details of IMP administration are provided in Section 5.4.6.

Figure 3-1 Study Flow Chart



Abbreviation: IM: Intramuscular

Treatment A: 300 mg IM coformulation in one injection of 2 mL (clonal cell line material)
Treatment B: 300 mg IM from individual vials, 2 injections of 1.5 mL (clonal cell line material)
Treatment C: 300 mg IM from individual vials, 2 injections of 1.5 mL (cell pool material)

Table 3-1 Schedule of Assessments: Screening, Randomization, and IMP Administration

Procedures	**Screening Period**	**Treatment Period**
Study Day	**Day −28-to −1**	**Day 1**
Study Visit	**Visit 1**	**Visit 2**
Written informed consent and assignment of enrollment code	X	
Medical history	X	X [a]
Demographics	X	
Full physical examination, height, weight, and BMI	X	X [a]
12-Lead ECG	X	X
Vital signs	X	X
Serum chemistry [b]	X	X
Hematology [b]	X	X
Coagulation [b]	X	X
Urinalysis [b]	X	X
FSH (postmenopausal women only) [b,c]	X	
Pregnancy test (serum β-hCG) [c]	X	
Pregnancy test (urine dipstick) [c,d]		X
HIV, hepatitis B, hepatitis C testing	X	
Urine drug and alcohol screen [b,e]	X	X
Assessment of AEs/SAEs [f]	X	X
Concomitant medications	X	X
Verify eligibility criteria	X	X
Anti-COVID-19 vaccination status [g]	X	X
Monitoring for COVID-19 symptoms and exposure history	X	X
Documented SARS-CoV-2 RT-PCR test taken ≤ 3 days before Day 1 OR Rapid SARS-CoV-2 antigen test (for screening criteria) [h]		X
SARS-CoV-2 serology [i]		X
Randomization		X
Participant identification card		X
AZD7442 administration [j]		X
Injection site monitoring		X

Procedures	Screening Period	Treatment Period
Study Day	**Day −28-to −1**	**Day 1**
Study Visit	**Visit 1**	**Visit 2**
Serum sample for AZD7442 PK [k]		X
Serum sample for anti-AZD7442 antibodies [l]		X
Serum sample for CCI [redacted]		X
AstraZeneca Thank you Card		X

[a] Update of the screening medical history and physical examination (any new findings since screening).
[b] Serum chemistry, hematology, coagulation, FSH, urinalysis, urine drug, and alcohol screen do not need to be repeated on Day 1 as per investigator's discretion, if they were performed within 2 days prior to Day 1. Serum chemistry, hematology and coagulation may be repeated only once during Screening period, if values at Screening visit were outside of reference range and documented as not clinically significant.
[c] Female participants only. Pregnancy test must be negative at screening as well as before randomization and study drug administration.
[d] Urine dipstick pregnancy test will be done on female participants of childbearing potential only (not postmenopausal female participants that will be identified based on FSH test).
[e] On Day 1, alcohol breathalyzer test needs to be performed before randomization if urine alcohol screen was done more than 2 days before Day 1. If alcohol breathalyzer test is positive, participant cannot be included in the study.
[f] SAE data will be collected from screening until Day 361. AE data will be collected from Day 1 until Day 361.
[g] Participants will be asked about anti-COVID-19 vaccination status. Participants should be either non-vaccinated or vaccinated (with one or more locally approved/authorized COVID-19 vaccine dose) with the last dose of the vaccine received at least 14 calendar days before Day 1. Vaccination status will be entered into IRT/RTSM during randomization on Day 1 visit to allow for balanced recruitment.
[h] SARS-CoV-2 RT-PCR test or a rapid SARS-CoV-2 antigen test will be done at a local laboratory/site. If a documented SARS-CoV-2 RT-PCR test is not available at screening, a rapid SARS-CoV-2 antigen test will be performed on the day of randomization, pre-dose (for screening criteria). Either test must be negative before dosing.
[i] SARS-CoV-2 serology analysis will be done at the central laboratory for all participants.
[j] Participants will be randomized in a 1:1:1 ratio by site of injection to receive the IM dose of the IMP in the lateral thigh, gluteal dorsal or gluteal ventral. This information will be provided to the investigator via IRT/RTSM. Participant should be monitored for injection site reaction on Day 1.
[k] On Day 1 PK samples will be collected at pre-dose, and then 2 h, 4 h, and 8 h post dosing; on Day 2 PK sample will be collected 24 h post dosing.
[l] On Day 1 sample will be collected as pre-dose only.
[m] On Day 1 samples will be collected as pre-dose and then 2 h and 4 h post dosing; on Day 2 sample will be collected 24 h post dosing.

Abbreviations: AE: adverse event; β-hCG: beta human chorionic gonadotropin; BMI: body mass index; ECG: electrocardiogram; FSH: follicle-stimulating hormone; HIV: human immunodeficiency virus; IRT/RTSM Interactive Response Technology/Randomization and Trial Supply Management; PK: pharmacokinetics; SAE: serious adverse events; RT-PCR: reverse transcriptase polymerase chain reaction; SAE: serious adverse event; SARS-CoV-2: Severe Acute Respiratory Syndrome Corona Virus 2.

Table 3-2 Schedule of Assessments: Follow-up Period

Procedures	Follow-up Period										
Study Day	**Day 2**	**Day 5 ±1 day**	**Day 8 ±1 day**	**Day 15 ±1 day**	**Day 22 ±2 days**	**Day 31 ±2 days**	**Day 61 ±5 days**	**Day 91 ±5 days**	**Day 181 ±5 days**	**Day 271 ±7 days**	**Day 361/ET ±7 days**
Study Visit	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**
Full physical examination, height, weight, and BMI			X			X					X
12-Lead ECG		X	X			X					X
Vital signs		X	X			X					X
Serum chemistry		X	X			X					X
Hematology		X	X			X					X
Coagulation		X	X			X					X
Urinalysis		X	X			X					X
Pregnancy test (urine dipstick) [a]	X	X	X	X	X	X	X	X	X	X	X
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Anti-COVID-19 vaccination status [b]	X	X	X	X	X	X	X	X	X	X	X
Monitoring for COVID-19 symptoms and exposure history	X	X	X	X	X	X	X	X	X	X	X
Serum sample for AZD7442 PK	X	X	X	X	X	X	X	X	X	X	X
Serum sample for anti-AZD7442 antibodies						X		X	X		X
Serum sample for [redacted]	X		X			X	X	X	X	X	X
SARS-CoV-2 serology	X		X			X	X	X	X	X	X

[a] For female participants only. Pregnancy test should be negative for continued participation in the study.

[b] Participants will be allowed to receive anti-COVID-19 vaccination during the study, however, should wait 14 days after their dose of AZD7442, and will be asked about the vaccination status at each visit. Participant vaccination status will be documented throughout the study in the eCRF.

Abbreviations: AE: adverse event; BMI: Body mass index; COVID-19: coronavirus disease 2019; ECG: electrocardiogram; ET: Early Termination; SAE: serious adverse event; PK: pharmacokinetics; SARS-CoV-2: Severe Acute Respiratory Syndrome Corona Virus 2.

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 to the time point. Another aspect for the proposed timing is that physiological assessments such as heart rate or blood pressure as well as inquiring for AEs should not be accidentally influenced by physical interventions such as a venous puncture. The sequence at a particular time point is:

1 Electrocardiograms
2 Vital signs (blood pressure and pulse)
3 Pharmacokinetic blood sampling

Details of acceptable tolerance windows for safety, PK and PD assessments will be included in a WAD which will be agreed upon and signed off before the start of the study. Participants should be counseled to be available for repeat sampling within the windows of allowance, if required.

3.1.2. End of Study

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

3.1.3. Expected Duration of the Study

Each participant will be involved in the study for approximately 1 year.

3.2. Rationales for Study Design and Dose Selection

3.2.1. Rationale for Study Design

An open label, parallel group design has been chosen for this single dose PK comparability study.

The study will assess PK comparability between different formulations of AZD7442, which is a combination of two individual mAbs, AZD8895 and AZD1061. The materials to be assessed will be:

- A co-formulation of clonal cell line material of AZD8895 + AZD1061 mAbs as a single IM injection from a single mixture,
- Individual formulations of clonal cell line material of AZD8895 and AZD1061 mAbs as separate sequential IM injections, and
- Individual formulations of cell pool material of AZD8895 and AZD1061 mAbs as separate sequential IM injections.

3.2.2. Dose Rationale

The 300 mg (total protein) IM dose selected for investigation in this study is the anticipated therapeutic dose for prophylaxis of COVID-19. The data generated on the 300 mg IM dose is also expected to support a single IM dose of 600 mg for treatment of mild to moderate COVID-19 as the 600 mg dose (co-formulation) will be administered as two IM injections of 300 mg each.

3.3. Risk-benefit Assessment

Detailed information about the known and expected benefits and potential risks of AZD7442 may be found in the IB.

3.3.1. Description of AZD7442

AZD7442 is a combination product of two mAbs: tixagevimab (AZD8895) and cilgavimab (AZD1061) that are neutralizing mAbs that bind specifically to the RBD of the SARS-CoV-2 spike protein. Neither mAb has any human target. There are no potential risks based on mechanism of action.

3.3.2. Clinical Pharmacokinetics

Measured serum AZD8895 and AZD1061 concentrations support that the PK of these mAbs are similar to each other and are consistent with what has been observed for another IgG1κ mAb that has been engineered to include YTE amino acid substitutions to extend the half-life (Griffin et al 2017). Therefore, the half-life of AZD7442 is estimated to be approximately 90 days which will allow for long-term protection.

3.3.3. Adverse Events, Contraindications and Warnings

Potential risks of AZD7442 are those that are associated with the administration of any immunoglobulin, including polyclonal immunoglobulin preparations and mAbs. The important potential risks associated with the administration of immunoglobulin, include, but are not limited to, anaphylaxis and other serious hypersensitivity reactions including immune complex disease. Other potential risks include, but are not limited to, injection site reactions, infusion-related reactions, and ADE disease.

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

1 Antibody-dependent enhanced disease that involves increased binding efficiency of virus-antibody complexes to Fc receptor bearing cells and which triggers virus entry. The mAbs in AZD7442 have been designed with a modification to prevent binding to cellular Fc receptors, so the risk of antibody-dependent enhanced disease occurring via this mechanism should range from very low to none.

2 Vaccine-associated enhanced respiratory disease, which is a distinct clinical syndrome that occurred in young children in the 1960s when whole inactivated virus vaccines for measles and RSV were tested.

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

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

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

Refer to the IB for the most up to date study safety findings with regards to completed AZD7442 administration.

4. STUDY POPULATION

4.1. Selection of Study Population

The investigator 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 any exclusion criterion should not, under any circumstances, be randomized or dosed in the study. There can be no exceptions to this rule.

This study will be conducted in 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 fulfill the following criteria:

1 Provision of signed and dated, written informed consent prior to any study specific procedures.

2 Male and female participants, aged 18 years and older, vaccinated or non-vaccinated against SARS-CoV-2, with suitable veins for cannulation or repeated venipuncture. Vaccinated participants should have received their last dose of the vaccine at least 14 calendar days before IMP administration (Day 1).

3 Healthy participants according to medical history, physical examination, and baseline safety laboratory tests, according to the judgment of the investigator.

4 Documented negative results of a SARS-CoV-2 RT-PCR test collected ≤ 3 days prior to IMP dose administration (Day 1) or a negative rapid SARS-CoV-2 antigen test on Day 1 (pre-dose) NOTE: A negative SARS-CoV-2 RT-PCR retest result or a negative rapid SARS-CoV-2 antigen test is required if participant has symptoms of infection or has any known/suspected exposure after the initial SARS-CoV-2 RT-PCR test. Participants who do not meet this criterion may be re-screened more than once and up to a maximum of two times as per investigator discretion but with prior approval of the Medical Monitor.

5 Able to complete the Follow-up Period up to Day 361 as required by the protocol.

6 Electrocardiogram without clinically significant abnormalities at screening.

7 Body weight ≥ 50 kg to ≤ 110 kg at screening and a BMI ≥ 18.0 to ≤ 30 kg/m^2 at the time of the Screening Visit.

8 All participants must adhere to the contraception methods details in Section 4.2.1.

(1) Male participants: to avoid the transfer of any fluids to a sexual partner, all male participants must use a condom from Day 1 and agree to continue through 90 days following administration of the study intervention.

(2) Female participants: Female participants of childbearing potential should be willing to use a highly effective form of birth control from Day 1 up to Day 361. These must include the use of at least one highly effective form of birth control. Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal.

4.1.2. Exclusion Criteria

Participants will not enter the study if any of the following exclusion criteria are fulfilled:

1 Known history of allergy or reaction to any component of AZD7442 (AZD8895 + AZD1061).

2 Previous hypersensitivity, or severe adverse reaction following IM administration of a mAb.

3 Significant infection or other acute illness, including fever > 100°F (> 37.8°C) on the day prior to or day of randomization. Participants excluded for transient acute illness may be dosed if illness resolves within the 28-day Screening Period. Otherwise, the participant will be reported as a screen failure.

4 History of infection with SARS or Middle East Respiratory Syndrome.

5 Positive SARS-CoV-2 result based on available data at screening or at Day 1.

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

7 History of malignancy.

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

9 Active infection with hepatitis B or C or positive test for hepatitis C or for hepatitis B surface antigen at screening.

10 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.

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

requirements OR positive urine drug or alcohol at screening, and positive breathalyzer test at randomization. Excessive intake of alcohol defined as the regular consumption of more than 24 g of alcohol per day for men or 12 g of alcohol per day for women.

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

13 Aspartate aminotransferase, ALT, or serum creatinine above 2 × the ULN; bilirubin and ALP > 1.5 × ULN.

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

15 Pregnant or nursing female.

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

17 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.

18 Any drug therapy within 7 days or 5 drug half-lives (whichever is longer) 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). Routine vaccines within 14 days prior to Day 1. Vitamins and other nutritional supplements that are not newly introduced, ie, have been taken for at least 30 days prior to screening, are not exclusionary.

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

20 Any prior receipt of another mAb indicated for the prevention or treatment of SARS-CoV-2 or COVID-19. NOTE: Participants are permitted to receive anti-COVID-19 vaccination during study. Participant vaccination status will be documented throughout the study in the eCRF.

21 Receipt of a mAb within 6 months or 5 antibody half-lives (whichever is longer) prior to screening.

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

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

24 Plasma donation within 1 month of screening or any blood donation/loss more than 500 mL during the 3 months prior to screening.

25 Participants who cannot communicate reliably with the investigator.

26 Vulnerable participants, eg, kept in detention, protected adults under guardianship, trusteeship, or committed to an institution by governmental or juridical order.

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

4.2. Restrictions During the Study

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

1 Prior to Day 1 participants should abstain from alcohol for 72 hours prior to Day 1 visit and for 72 hours prior to every outpatient visit.

2 Participants should abstain from caffeine-containing foods and beverages for 24 hours prior to Day 1 and for 24 hours prior to every outpatient visit.

3 At the study Clinical Unit on Day 1, participants will receive a standard diet, which excludes all alcohol and caffeinated products. No additional food or beverages must be consumed while in the study Clinical Unit. Participants will not be asked to fast before the IMP administration and will be allowed to drink water to prevent dehydration from 45 minutes to 1 hour before dosing under medical supervision. Water and food will be allowed ad libitum from 1 hour after the start of dosing.

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

5 Participants should abstain from strenuous activity for 72 hours prior to Day 1 visit and 72 hours prior to each outpatient visit.

6 Participants should rest comfortably for 1 hour after IM administration.

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

For concomitant medication restrictions, please refer to Section 5.5.

4.2.1. Reproductive Restrictions

No genotoxicity studies have been conducted with AZD7442 and are not planned because this requirement is not applicable to biotechnology-derived large protein products. AZD7442 is a large protein molecule that is not expected to cross the nuclear or mitochondrial membranes to interact directly with DNA or other chromosomal materials.

4.2.1.1. Women of Non-childbearing Potential

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

Permanent sterilization includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy 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 partner, an approved method of highly effective contraception from Day 1 to Day 361.

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 (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Injectable
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner (only acceptable provided that partner is the sole sexual partner of the participant and that the vasectomized 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 intervention. 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).

Pregnancy

If the participant becomes pregnant during the study this should be reported to the investigator. The investigator 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.

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 fetus in humans.

All male participants should avoid the transfer of any fluids to a sexual partner by using a condom from the day of IMP administration (Day 1) up to 90 days following IMP administration. Female partners of male participants should be either of non-childbearing potential or should use a highly effective contraception form of birth control as mentioned in Section 4.2.1.2 above, from the day of IMP administration (Day 1) up to 90 days following IMP administration.

Sperm Donation

Male participants should not donate sperm for the duration of the study until after the last study Follow-up Visit.

Pregnancy

Participants will be instructed that if their partner becomes pregnant during the study this should be reported to the investigator. The investigator 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 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 after receiving any dose of IMP will not be replaced. Participants randomized in error or withdrawn prior to dosing may be replaced after consultation between the PI and AstraZeneca.

5. STUDY CONDUCT

5.1. Participant Enrollment and Randomization

The investigator (or designee) 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 enrollment number at screening upon signing the Informed Consent.
- The eligibility of each participant is in accordance with the inclusion and exclusion criteria.
- Each eligible participant is assigned a unique randomization code.

Randomization will be done on Day 1 before IMP dosing. Randomization codes will be assigned strictly sequentially as participants become eligible for randomization (codes to be used without leading zeros). Randomization numbers will be generated within the AstraZeneca randomization system (AZRand).

The enrollment number will be used to identify the participant during the screening process and throughout study participation, if applicable, and will be recorded in the eCRF. This number will be composed of two parts: the first part will have 4 digits (fixed) representing the study Clinical Unit site identifier. The second part will have 3 digits (ascending) which will be assigned sequentially within each study Clinical Unit starting with 001.

If a participant withdraws his/her participation in the study, then his/her enrollment/randomization code cannot be reused. For each treatment sequence, an additional set of random numbers will be generated with AZRand.

5.1.1. Re-screening

Rescreening is permitted only with the prior approval of the Medical Monitor if the participant has not met the eligibility criteria within the screening period and/or the reason for screen failure was transient (including but not limited to study equipment failure, unforeseen personal events that mandate missed screening visit). Each participant can be re-screened only once. A second re-screening is allowed for participants who do not meet inclusion criterion 4, per investigator discretion and prior approval of the Medical Monitor. Re-screened participants should be assigned the same participant number as for the initial screening. Participants who are re-screened are required to sign a new Informed Consent. All procedures from screening should be repeated.

5.1.2. Procedures for Randomization

Upon completion of the randomization request form, the randomization list will be produced by the IRT vendor according to AZRand and participants will be randomized using IRT.

An IRT will be used for randomization to a treatment group and assignment of IMP kit numbers. A participant is considered randomized into the study when the investigator notifies the IRT that the participant meets eligibility criteria and the IRT provides the assignment of the IMP kit numbers to the participant.

Specific information concerning the use of the IRT will be provided in a separate manual.

The number of participant identifiers generated for the study will account for the required number of randomized participants per the sample size calculation (N = 207, see Section 11.4).

5.2. Procedures for Handling Incorrectly Randomized Participants

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

Where a participant, who does not meet the selection criteria, is randomized 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 follow-up visits and safety assessments to ensure their safety. The investigator will inform the AstraZeneca Lead Physician of the error immediately.

5.3. Blinding and Procedures for Unblinding the Study

This is an open label study and blinding is not applicable.

The randomization lists should be kept in a secure location until database lock.

5.4. Study Intervention

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

5.4.1. Investigational Products

Details on the identity of the investigational product are presented in Table 5-1.

Table 5-1 Investigational Products

Treatment Group	Treatment A	Treatment B	Treatment C
Formulation	AZD7442 co-formulation of AZD8895 + AZD1061 clonal cell line material in the same vial 20 mM histidine/histidine-HCl, 220 mM arginine-HCl, 0.04% (w/v) polysorbate80, pH 6.0	AZD8895 and AZD1061 clonal cell line material in separate vials 20 mM histidine/histidine-HCl, 240 mM sucrose, 0.04% (w/v) polysorbate80, pH 6.0	AZD8895 and AZD1061 cell pool material in separate vials 20 mM histidine/histidine-HCl, 240 mM sucrose, 0.04% (w/v) polysorbate80, pH 6.0
Strength/ Concentration	75 mg/mL AZD8895 + 75 mg/mL AZD1061; ie, 150 mg/mL total protein in a single vial	100 mg/mL AZD8895 and 100 mg/mL AZD1061 in separate vials	100 mg/mL AZD8895 and 100 mg/mL AZD1061 in separate vials
Dose	300 mg AZD7442 co-formulation as a single IM injection (1 × 2 mL IM injection)	150 mg AZD8895 and 150 mg AZD1061 as two IM injections (1 × 1.5 mL IM injection of each, two injections total)	150 mg AZD8895 and 150 mg AZD1061 as two IM injections (1 × 1.5 mL IM injection of each, two injections total)
Dosage level	Single dose (300 mg total protein)		
Route of administration	IM injection		
Use	Experimental		
IMP and NIMP	IMP		
Sourcing	Provided centrally by the sponsor		
Packaging and labeling	The IMP components will be provided in vials. Each vial will be labeled per country requirement.		

IM: intramuscular; IMP: investigational medicinal product; HCl: hydrochloric acid; NIMP: non-investigational medicinal product.

Details of the batch numbers will be included in the Trial Master File and the final CSR.

Treatment A
AZD7442 will be supplied by AstraZeneca as a solution for injection. AZD7442 300 mg will be supplied in a single vial containing 75 mg/mL AZD8895 and 75 mg/mL AZD1061, 20 mM histidine/histidine-HCl, 220 mM arginine-HCl, 0.04% (w/v) polysorbate-80, pH 6.0. The label-claim volume for AZD7442 is 2 mL.

Treatment B
AZD7442 will be supplied by AstraZeneca as solutions for injection. AZD7442 300 mg will be supplied in two vials, one containing 100 mg/mL AZD8895 and one containing 100 mg/mL AZD1061, both in 20 mM histidine/histidine-HCl, 240 mM sucrose, 0.04% (w/v) polysorbate-80, pH 6.0. The label-claim volume for each vial is 1.5 mL.

Treatment C
AZD7442 will be supplied by AstraZeneca as solutions for injection. AZD7442 300 mg will be supplied in two vials, one containing 100 mg/mL AZD8895 and one containing 100 mg/mL AZD1061, both in 20 mM histidine/histidine-HCl, 240 mM sucrose, 0.04% (w/v) polysorbate-80, pH 6.0. The label-claim volume for each vial is 1.5 mL.

All formulations will be provided as sterile, clear to opalescent, colorless to yellow solutions.

5.4.2. Supply of Investigational Product

The IMP will be supplied by AstraZeneca as cartons containing one vial of either AZD7442, AZD8895 or AZD1061.

A release document signed by a legally authorized Qualified Person in EU/UK or Pharmacist in US at the study Clinical Unit will be placed in the appropriate section of the Trial Master File to document labeling and dispensing of the investigational product(s) to the participant.

Dispensing and retention of reserve BE samples of investigational product will be performed in accordance with the FDA Code of Federal Regulations 21, Part 320 Bioavailability and Bioequivalence requirements.

5.4.3. Labeling

Labels will be prepared in accordance with GMP and local regulatory guidelines.

5.4.4. Storage and Handling Procedures

AZD7442 vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. The investigator, or an approved representative (eg, pharmacist), will ensure that all study intervention is stored in a secured area, in refrigerated temperatures (2°C to 8°C; 36°F to 46°F) and in accordance with applicable regulatory requirements. A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the

permissible range listed in the clinical supply packaging are to be reported to the monitor upon detection. A calibrated temperature monitoring device will be used to record the temperature conditions in the drug storage facility. Storage conditions stated in the IB may be superseded by the label storage.

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

The dose of AZD7442 must be prepared by the investigators or site's designated study intervention manager using aseptic technique. Total time from needle puncture of the study intervention vial to the start of administration must not exceed:

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

If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hours otherwise a new dose must be prepared from new vials. AZD7442 vials do not contain preservatives; any unused portion of the vial must be discarded immediately after use.

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.

5.4.5. Dose and Treatment Regimens

Each participant will receive a single IM dose of AZD7442 on Day 1 after randomization to one of the three treatment groups (Table 5-2). Additionally, within each of the treatment groups, participants will be randomized 1:1:1 to injection sites of lateral thigh (vastus lateralis), gluteal dorsal, or gluteal ventral.

Participants receiving Treatment A will be administered a dose via a single IM injection from a single drug product vial.

Participants receiving Treatment B or Treatment C will be administered a dose via two separate IM injections, each from a separate drug product vial containing AZD8895 or AZD1061. AZD8895 is administered first, followed by AZD1061. If a participant experiences an immediate hypersensitivity reaction after receipt of the first IM injection, but before the second IM injection, further IMP should not be given.

Participants will be allowed to drink water until 45 min to 1 hour before dosing to prevent dehydration. Water and food will be allowed ad libitum from 1 hour after the start of dosing.

After dosing, participants will remain semi-supine on their bed or sitting (except when necessary for study procedures) until completion of the Day 1 assessments.

Other restrictions, including posture control are described in Section 4.2. Data of participants may be excluded from the PK analysis set as described in Section 11.1.3.

5.4.6. Dose Preparation and Administration

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

No incompatibilities between AZD7442 and PC or PP syringes have been observed.

Commonly used needles for IM injections are of 22 – 25 gauge and 1 – 1.5 in (25 – 38 mm) length and can be selected based on characteristics of each patient according to standard procedures for IM injections (US CDC 2022).

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

AZD7442 preparation and the doses to be administered are given in Table 5-2.

Table 5-2 AZD7442 Preparation and Administration

Treatment	*Product*	*Formulation*	*Number of Vials*	*Injection Volume*	*Dose Level*
A	Test	Co-formulation of AZD8895 and AZD1061 clonal cell line material in a single vial	1	2.0 mL (single IM injection)	300 mg total protein of AZD7442 (150 mg each of AZD8895 and AZD1061)
B	Reference (when compared with Treatment A) or test (when compared with Treatment C)	AZD8895 and AZD1061 clonal cell line material in two separate vials	2 (1 vial AZD8895 + 1 vial AZD1061)	1.5 mL each (two IM injections)	
C	Reference	AZD8895 and AZD1061 cell pool material in two separate vials	2 (1 vial AZD8895 + 1 vial AZD1061)	1.5 mL each (two IM injections)	

Note: All treatments will be administered as IM injections either in the lateral thigh, gluteal dorsal, or gluteal ventral.

5.4.6.1. Treatment A: Co-formulation of AZD8895 and AZD1061 Clonal Cell Line Material in a Single Vial

Obtain one vial of co-formulated AZD7442 for administration and equilibrate to room temperature prior to use.

Accurately withdraw 2 mL of co-formulated AZD7442 into a single appropriately sized syringe.

Administer the co-formulated AZD7442 as a single 2 mL IM injection in the appropriate region (lateral thigh, gluteal dorsal, or gluteal ventral) according to standard procedures for IM injections.

5.4.6.2. Treatment B: AZD8895 and AZD1061 Clonal Cell Line Material in Separate Vials

AZD7442 must be administered as separate injections to the participant in sequential order, with no participant receiving a dose of AZD8895 without also receiving the matching dose of AZD1061.

Obtain one vial each of AZD8895 and AZD1061 clonal cell line material for administration and equilibrate to room temperature prior to use.

Accurately withdraw 1.5 mL of AZD8895 into an appropriately sized syringe. Accurately withdraw 1.5 mL of AZD1061 into a separate appropriately sized syringe.

Administer the injections of AZD7442 (AZD8895 and AZD1061) with an appropriate needle according to standard procedures for IM injections in the appropriate region (lateral thigh, gluteal dorsal, or gluteal ventral). AZD8895 must be administered first in the appropriate region followed by AZD1061 in the second region on the opposite side.

5.4.6.3. Treatment C: AZD8895 and AZD1061 Pool Cell Material in Separate Vials

AZD7442 must be administered as separate injections to the participant in sequential order, with no participant receiving a dose of AZD8895 without also receiving the matching dose of AZD1061.

Obtain one vial each of AZD8895 and AZD1061 pool cell material for administration and equilibrate to room temperature prior to use.

Accurately withdraw 1.5 mL of AZD8895 into an appropriately sized syringe. Accurately withdraw 1.5 mL of AZD1061 into a separate appropriately sized syringe.

Administer the injections of AZD7442 (AZD8895 and AZD1061) with an appropriate needle according to standard procedures for IM injections in the appropriate region (lateral thigh, gluteal dorsal, or gluteal ventral). AZD8895 must be administered first in the appropriate region followed by AZD1061 in the second region on the opposite side.

5.5. Concomitant and Post-study Treatments

Any medication or vaccine that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

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

Permitted and prohibited medications are summarized in Table 5-3.

Table 5-3 Concomitant Medications

Concomitant Medication	Type of Medication/Treatment	Timeline/Instructions
Permitted	Contraceptives or a single use of acetaminophen, aspirin, antihistamine, or combination OTC product that contains acetaminophen with an antihistamine, or OTC nonsteroidal anti-inflammatory agent	At a dose equal to or lower than that recommended on the package (at the discretion of the investigator)
	Vitamins and other nutritional supplements	Not newly introduced, ie, have been taken for at least 30 days prior to screening
	Routine vaccines	Routine vaccines are permitted if administered at least 14 days prior to Day 1 dosing or > 14 days after IMP dose.
Prohibited	Anti-SARS-CoV-2 mAbs other than AZD7442	From Day 1 to Day 361
	Any other drug therapy	Newly initiated drugs within 7 days or 5 half-lives (whichever is longer) prior to Day 1 are not allowed until the completion of the study, unless, in the opinion of the investigator, the medication will not interfere with the study.
	Any other investigational product	Investigational products within 90 days or 5 half-lives (whichever is longer) prior to Day 1 are not allowed until completion of the study. Investigational products other than the study drug are not allowed during the study, after Day 1.

Abbreviations: OTC: over the counter; mAb: monoclonal antibody; SARS-Cov-2: Severe Acute Respiratory Syndrome Corona Virus 2.

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

When any medication is required, it should be prescribed by the investigator. Following consultation with AstraZeneca Lead Physician, the investigator should determine whether or not the participant should continue in the study. Administration of concomitant medications

that may influence the measurement of the PK and PD endpoints may be documented as a protocol deviation after consultation of the investigator with AstraZeneca Lead Physician.

5.6. Study Intervention Compliance

Dosing will take place at the study Clinical Unit.

The administration of all study intervention will be recorded in the EDC system.

Compliance will be assured by direct supervision and witnessing of study intervention administration.

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 study Clinical Unit will account for all supplies of IMP. Details of receipt, storage, assembly/dispensing, and return will be recorded.

All used and unused supplies of IMP will either be destroyed by the study Clinical Unit or returned at the end of the study in accordance with instruction by the sponsor. 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 Study Intervention 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 must be completed.

5.7.1. Procedures for Withdrawal of a Participant from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an Early Termination visit should be conducted, identical to the final Follow-up Visit (Day 361) as shown in the SoA (Table 3-2). See the SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

5.8. Premature Termination of the Study

The study will be terminated prematurely if:

- The investigator and the sponsor assess that the number and/or severity of AEs justify discontinuation of the study.
- The sponsor considers the applied doses of the study drug to be no longer relevant.
- The sponsor decides to discontinue the study.
- New data become available and raise concern about the safety of IMP so that continuation would pose potential risks to the participants.

Premature termination of the study must be mutually agreed upon by the investigator and the sponsor and must be documented. However, study results will be reported according to the requirements outlined in this CSP as far as applicable.

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 and Table 3-2.

6.2. Enrollment and Screening Procedures

Viral serology, COVID-19 infection, and urine drugs of abuse and alcohol will be assessed for eligibility. Coagulation, FSH (for postmenopausal female participants) and pregnancy testing (for female participants of childbearing potential), and use of concomitant medication will also be assessed and reported.

6.3. Safety Measurements

Safety and tolerability variables will include:

- Adverse events
- Laboratory assessments (hematology, clinical chemistry, and urinalysis)
- Physical examination
- Electrocardiogram
- Vital signs (systolic and diastolic BP, pulse rate)

Note that all safety laboratory assessments except for Hy's Law tests will be done at a local laboratory/site. SARS-CoV-2 serology and Hy's Law test will be done at the central laboratory.

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 unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

6.3.1.2. Definitions of Serious Adverse Event

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

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

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

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

6.3.1.3. Adverse Events of Special Interest

Adverse events of special interest are events of scientific and medical interest, specific to the further understanding of the study intervention safety profile and require close monitoring and rapid communication by the investigators to the sponsor. An AESI can be serious or non-serious. All AESIs will be recorded in the eCRF. Serious AESIs will be recorded and reported as per Section 6.3.1.6. See also the AZD7442 IB for additional information on AESIs.

The AESIs for AZD7442 are:

- Anaphylaxis and other serious hypersensitivity reactions, including immune complex disease
- Injection site reactions
- Cardiac ischemia, cardiac failure, and thrombotic events

6.3.1.4. Other Significant Adverse Events

Medical monitoring of all the safety data will be conducted on ongoing basis by the qualified medical expert to ensure the safety of the participants and other relevant reporting requirements.

6.3.1.5. Recording of Adverse Events

Time Period for Collection of Adverse Events

Adverse events will be collected from the start of Day 1 until Day 361.

Serious adverse events will be recorded from the time of informed consent until Day 361.

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

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 investigator for as long as medically indicated, but without further recording in the eCRF.

AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collected for each AE:

- AE term (diagnosis/verbatim)
- The date and time when the AE started and stopped
- Intensity
- Whether the AE is serious or not
- Investigator causality rating against the investigational product (yes or no)
- Outcome

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

- Date AE met criteria for serious AE
- Date investigator became aware of serious AE
- Adverse event is serious due to
- Date of hospitalization

- Date of discharge from hospital
- Probable cause of death
- Date of death
- Autopsy performed (yes/no)
- Causality assessment in relation to study procedure(s)
- 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 an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

Causality Collection

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

For SAEs, causal relationship 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 the EDC system.

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 protocol-mandated laboratory tests, vital signs, ECGs and other safety assessments will be summarized in the CSR.

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

If deterioration in a laboratory value 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 investigator should use the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value).

In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-protocol-mandated parameters should be reported as AE(s).

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

Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq$ 3 x ULN together with TBL $\geq$ 2 x 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.

6.3.1.6. Reporting of Serious Adverse Events

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

If any SAE occurs in the course of the study, then the investigator 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 investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events and **within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately.

Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE 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.

6.3.1.7. Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local Regulatory Authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the Regulatory Authority, IRB, and investigators.

For all studies, investigator safety reports must be prepared for Suspected Unexpected Serious Adverse Reactions according to local regulations and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB, if appropriate according to local regulations.

6.3.2. Laboratory Assessments

6.3.2.1. Hematology

Hematology	
White blood cell (WBC) count	Neutrophils absolute count
Red blood cell (RBC) count	Lymphocytes absolute count
Hemoglobin (Hb)	Monocytes absolute count
Hematocrit (HCT)	Eosinophils absolute count
Mean corpuscular volume (MCV)	Basophils absolute count

Hematology	
Mean corpuscular hemoglobin (MCH)	Platelets
Mean corpuscular hemoglobin 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	FSH [a,b] (Follicle-stimulating hormone)
Glucose	
C-reactive protein (CRP)	
T_4 [a]	
TSH [a] (Thyroid-stimulating hormone)	

[a] Screening only
[b] Postmenopausal women

6.3.2.3. Coagulation

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

6.3.2.4. Urinalysis

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

6.3.2.5. Pregnancy Testing

Pregnancy Tests	
Serum Human-beta chorionic gonadotrophin (Screening only)	Urine (dipstick) (for female participants of childbearing potential only) (all post-dose visits)

6.3.2.6. Viral Serology

Viral Serology	
Human immunodeficiency virus (HIV) I and II	Hepatitis C Virus antibody
Hepatitis B surface antigen (HBsAg)	

6.3.2.7. Drugs of Abuse and Alcohol

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

Drugs of abuse screen will be done via a urine sample. Alcohol screen will be done via a urine sample at screening. On Day 1, alcohol breathalyzer test needs to be performed if urine alcohol screen was done more than 2 days before Day 1.

6.3.2.8. SARS-CoV-2 Testing

SARS-CoV-2 RT-PCR test OR Rapid SARS-CoV-2 antigen test [a]	SARS-CoV-2 serology [b]

[a] SARS-CoV-2 RT-PCR test or rapid SARS-CoV-2 antigen test will be done at a local laboratory/site.
[b] SARS-CoV-2 serology will be analyzed at the central laboratory.

6.3.3. Physical Examination

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

6.3.4. Electrocardiograms

Electrocardiograms will be performed at the time points specified in the SoA (Table 3-1 and Table 3-2) and whenever it is required by the investigator. Safety 12-lead ECGs will allow the site investigator to review the ECG tracings at bedside and determine any potential abnormalities and risks.

A 10-second 12-lead safety ECG will be obtained after the participant has been resting in the supine position for at least 10 minutes. All ECGs will be evaluated with respect to rhythm; heart rate; and PR, RR, QRS, QT, and QTcF intervals from the 12-lead safety ECG, and the

investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided whether the abnormality is clinically significant or not, and the abnormality will be recorded. The investigator or delegate will evaluate the safety ECG in real time.

The date/time and the physician interpretation (normal, abnormal clinically significant, abnormal not clinically significant) for the safety ECGs will be recorded in the EDC system and stored as source documents.

6.3.5. 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 (bpm)

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

6.3.6. Monitoring of Injection Site Inspection

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

An inspection of the injection sites should be performed after IMP administration on Day 1 (Table 6-1).

Table 6-1 Injection Site Inspection on Day 1

Procedure		Up to 90 min Pre-dose	Time After AZD7442 Injection(s) Administration	
			Within 10 min	30 (± 10) min, 60 (± 10) min, and 8 h (± 20 min)
Visual inspection of site		X	X	X
Palpation of site		X	X	X
Participant will be asked	Are you experiencing any discomfort?	X	X	X
	If yes, has the feeling of discomfort changed since you received the injection?	X	X	X

All AEs should be reported as described in Section 6.3.1.5.

6.3.7. Monitoring of COVID-19 Symptoms and Exposure History

Monitoring of COVID-19 symptoms and exposure history will be performed as specified in the SoA (Table 3-1 and Table 3-2). Additionally, a participant should be instructed to contact the study site if he/she has symptoms of COVID-19 infection (Table 6-2) or any known/suspected exposure to COVID-19. Testing for SARS-CoV-2 should be performed at the discretion of the investigator at a local laboratory. Data on COVID-19 symptom(s), SARS-CoV-2 test results, and/or COVID-19 diagnosis will be collected.

Table 6-2 COVID-19 Symptoms

Duration	Symptom
No minimum duration	Fever
	Shortness of breath
	Difficulty breathing
Must be present for ≥ 2 days	Chills
	Cough
	Fatigue
	Muscle aches
	Body aches
	Headache
	New loss of taste
	New loss of smell
	Sore throat
	Congestion

Duration	Symptom
	Runny nose
	Nausea
	Vomiting
	Diarrhea

Adapted from (US CDC 2021)
CDC, Centers for Disease Control and Prevention

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 component mAbs (AZD8895 and AZD1061) will be collected from all participants as specified in the SoA (Table 3-1 and Table 3-2).

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

6.4.2. Pharmacokinetic Drug Assays

Blood samples for determination of AZD7442 component mAbs (AZD8895 and AZD1061) concentrations in serum will be analyzed by PPD on behalf of AstraZeneca, using a validated assay. The serum concentrations for each individual mAb will then be added at each collection timepoint to obtain serum concentrations of combined AZD7442. Additional analyses may be conducted on the biological samples for other compound-related purposes.

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

6.5. Pharmacodynamics

6.5.1. CCI

CCI [redacted]

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

6.6. Immunogenicity Assessments

Blood samples for determination of serum anti-AZD8895 and anti-AZD1061 antibodies will be analyzed by PPD on behalf of AstraZeneca, using a validated assay. Blood samples for

determination of these ADAs will be collected as specified in the SoA (Table 3-1 and Table 3-2). 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 participant 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, labeled, stored, and shipped as detailed in the Laboratory Manual.

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 will be described in a separate bioanalytical report.

7. BIOLOGICAL SAMPLES PROCEDURES

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

7.1. Total Blood Volume

The maximum volume to be drawn from each participant, including repeat samples, must not exceed 450 mL in total in any 56 day period of a study.

7.2. Handling, Storage and Destruction of Biological Samples

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

7.2.1. Pharmacokinetic Samples

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

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

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 Samples

Remaining ADA sample aliquots 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 characterization of any ADAs, confirmation and/or requalification of the assay as well as additional assay development work. The results from future analysis will not be reported in the CSR.

7.3. Labeling and Shipment of Biohazard Samples

Samples will be labeled 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.

Any samples identified as Infectious Category A materials will not be shipped and no further samples will be collected from the participant unless agreed with AstraZeneca and appropriate labeling, 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 investigator will ensure full traceability of collected biological samples from the participants while in storage at the center 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 analyzed 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 informed about the withdrawn consent immediately and that samples are disposed of or destroyed, the action documented, and the signed document returned to the study Clinical Unit.

8. REGULATORY AND ETHICAL CONSIDERATIONS

8.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines:
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO, but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, and all other applicable local regulations.

8.2. Data Protection

- Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

All clinical study findings and documents will be regarded as confidential. The investigator 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 investigator.

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

8.3. Informed Consent Process

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

A participant is required to sign a new ICF if rescreened.

8.4. 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 Investigator's Site File.

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 study 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 study Clinical Unit.

9.2. Audit/Inspections

The study Clinical Unit facilities and all study data/documentation may be audited/inspected by independent auditor/inspector/any representatives of regulatory authorities. The investigator must allow the applicable persons access to all relevant facilities and data/documents. The investigator 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 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 Medidata Rave 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 Medidata Rave. 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 study Clinical Unit. The investigator will ensure that the data collected are accurate, complete and legible. Data will be monitored within Medidata Rave by the study monitor before being exported. Any changes made during monitoring will be documented with a full audit trail within Medidata Rave.

9.4.1. Case Report Forms and Source Documents

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

The original Medidata Rave 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 investigator for resolution.

9.4.2. Access to Source Documents

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

Checking of the Medidata Rave 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 or 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 investigator assures the sponsor of the necessary support at all times.

9.5. Data Management

Parexel will utilize standardized 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 finalized 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 finalized 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 investigator for review and resolution. Corrections resulting from these queries will be confirmed on the Data Clarification Forms. 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 Medidata Rave.

Adverse events with onset (start date/time) after dosing will be summarized by treatment group (dose level or administration process of AZD7442, Total AZD7442). Tabulations will include causality and severity (mild, moderate and severe). All tabulations will be presented by MedDRA 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 summarized. The AEs that occur before dosing will be excluded from the summary tables.

Adverse events will be listed by each dose of AZD7442. 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

Hematology 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 (Treatment Groups A, B, and C and Total) and for the safety analysis set. The baseline for the measurements will be the pre-dose assessment on Day 1. Shift tables will also be presented.

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 System International units in the CSR.

Additional listings will be presented for the following:

- Urinalysis (macroscopic and microscopic, if applicable)
- Pregnancy testing (including FSH)
- The results of viral serology and the drugs of abuse and alcohol screen will not be listed in the CSR.

10.1.3. 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.

10.1.4. Resting 12-lead Electrocardiogram

12-lead ECG results will be listed for each participant with interpretation by the investigator as “Normal”, “Abnormal CS” (clinically significant) or “Abnormal NCS” (not clinically significant).

10.1.5. 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 (Treatment Groups A, B, and C and Total) and time point for both observed values and changes from baseline.

10.1.6. Injection Site Reaction

Results of the injection site reaction assessment (including assessment of size, redness/erythema, swelling, itching/pruritus, pain or tenderness, induration, discoloration) will be listed by treatment group and participant.

10.2. Pharmacokinetic Variables

Where possible, the PK parameters will be estimated from the serum concentration-time data of the individual mAbs AZD8895 and AZD1061 as well as for the sum of the individual mAbs (AZD8895 + AZD1061), referred to as AZD7442.

Primary PK parameters

AUCinf	Area under serum concentration-time curve from time zero extrapolated to infinity
AUClast	Area under the serum concentration-time curve from time zero to the last quantifiable concentration
Cmax	Maximum observed serum (peak) concentration

Secondary PK parameters

Tmax	Time to reach maximum observed serum concentration
AUC0-31d	Area under the serum concentration-time curve from time zero to 30 days post-dose
AUC0-61d	Area under the serum concentration-time curve from time zero to 60 days post-dose
AUC0-91d	Area under the serum concentration-time curve from time zero to 90 days post-dose
AUC0-181d	Area under the serum concentration-time curve from time zero to 180 days post-dose
t½λz	Terminal elimination half-life, estimated as (ln2)/λz
tlast	Time of last quantifiable serum concentration
CL/F	Apparent total body clearance after extravascular administration
Vz/F	Volume of distribution (apparent) based on terminal phase after extravascular administration

The following parameters will be calculated for diagnostic purposes and will be summarized:

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

Additional PK parameters may be determined where appropriate.

10.2.1. Calculation or Derivation of Pharmacokinetic Parameters

The derivation of PK parameters from the serum concentration-time data of the individual mAbs AZD8895 and AZD1061, as well as for the sum of the individual mAbs of AZD7442 (AZD8895 + AZD1061) will be performed by LabCorp, on behalf of Clinical Pharmacokinetic Alliance, AstraZeneca R&D.

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

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

10.3. CCI

CCI

10.4. Immunogenicity Variables

The date and time of the blood samples collected for assessment of ADAs (samples to confirm the presence or absence of anti-AZD8895 and anti-AZD1061 antibodies from pre-dose Day 1 to Day 361, including the titer for samples confirmed positive for ADA) and neutralizing Abs will be listed. The incidence of ADA to AZD7442 will be summarized as number and percentage of participants who are ADA positive by treatment group.

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

11.1. Description of Analysis Sets

11.1.1. General Principles

A separate SAP will be compiled for this study. The details of the formal hypothesis testing will be detailed in the SAP.

Regarding PK comparability, if the 90% CIs for the geometric mean ratios for both AUCinf (AUClast for some agencies) and Cmax are entirely contained within 0.8000 and 1.2500 for all comparisons according to the study objectives, it may be concluded that the 2 formulations (the co-formulation and the formulation from the individual vials) are comparable and the 2 materials (clonal cell line material and cell pool material) are comparable.

11.1.2. Safety Analysis Set

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

Unless otherwise stated, the safety analysis set will be used for the presentation of all demographic and disposition data, safety analyses, as well as any immunogenicity assessments. Exposure to IMP will also be presented using the safety analysis set.

11.1.3. Pharmacokinetic Analysis Set

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

Data from participants for whom the pre-dose concentration is > 5% of their respective Cmax for AZD8895 or AZD1061 may be excluded from the summary tables and figures and from the statistical analysis.

The exclusion of any participants from summary tables and figures and from the statistical analysis or exclusion of 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 statistical analysis will be listed only. Concentration data for participants excluded from the statistical analysis will be presented in the individual figures of concentration versus time plots.

11.1.4. Pharmacodynamic Analysis Set

All participants in the safety analysis set who received IMP and have evaluable [redacted] data, with no important protocol deviations thought to impact the analysis of [redacted]

11.1.5. Randomized Set

The Randomized Set will consist of all participants randomized 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 SAP will be written for the study. Any deviations from the statistical methodology defined in this protocol or SAP, 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 modeling assumptions will be documented appropriately.

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

Demographic and baseline data will be summarized for all randomized participants by treatment group (Treatment Groups A, B, and C and Total). Pharmacokinetic data will be summarized by treatment group, treatment group and injection site, treatment group and bodyweight category, and treatment group, injection site, and bodyweight category. Safety and tolerability data will be summarized by treatment group (Treatment Groups A, B, and C and Total), if applicable.

Frequency counts (number of participants [n] and percentages) will be calculated 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 $n \geq 3$. 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 treatment group:

- 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.

11.2.2. Missing Data

Missing dates and times in the AE data will be handled as described in Section 10.1. Concentrations that are NQ in the PK data will be handled as described in Section 10.2.1.

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

11.2.3. Participant Characteristics

A randomization listing will be presented and include the following: each participant's randomization number, the participant's full enrollment number, the treatment to which the participant has been randomized and the country where the study Clinical Unit is located.

Participants and/or data excluded from the PK analysis set will be listed including the reason for exclusion. Participant disposition will be summarized and will include the following information: number of participants randomized 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 randomized.

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.

11.2.3.1. 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 summarized separately for all randomized participants by treatment group (Treatment Groups A, B, and C and Total). The denominator for percentages will be the number of randomized 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).

11.2.4. Prior and Concomitant Medication and Drug Administration

11.2.4.1. Prior and Concomitant Medication

Prior medications are those that started and stopped prior to the first dose of IMP; all medications taken after first dosing are considered as concomitant (including medications that started prior to dosing and continued after). Prior medications started within 3 months prior to the first dose of IMP and last dose of anti-COVID-19 vaccine received prior to randomization will be recorded also in the concomitant medication module of the EDC system.

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

The duration of the medication will be calculated as:

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

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

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.

11.2.4.2. IMP Administration

The IMP administration dates and times will be listed for each participant.

11.2.5. 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 summarized using descriptive statistics (n, mean, SD, min, median, max) by treatment group (Treatment Groups A, B, and C and Total). Categorical variables will be summarized in frequency tables (frequency and proportion) treatment group (Treatment Groups A, B, and C and Total).

The analysis of the safety variables will be based on the safety analysis set.

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

Tabulations and listings of data for vital signs and clinical laboratory tests, and listings for ECGs 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 summarized for the observed values at each scheduled assessment, together with the corresponding changes (and/or percentage change) from the baseline when baseline is defined. Clinical laboratory data will be reported in Système International units in the CSR.

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

11.2.6. Pharmacokinetics

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

11.2.6.1. Serum Concentration Data

For the individual mAbs AZD8895 and AZD1061, as well as for the sum of the individual mAbs of AZD7442 (AZD8895 + AZD1061), the serum concentrations for each scheduled time point will be summarized by treatment group, treatment group and injection site, treatment group and bodyweight category, and treatment group, injection site, and bodyweight category 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 (with injection site, and bodyweight category listed) for all participants in the safety analysis set.

11.2.6.2. Serum Pharmacokinetic Parameter Listings

All reportable PK parameters for the individual mAbs AZD8895 and AZD1061, as well as for the sum of the individual mAbs of AZD7442 (AZD8895 + AZD1061), including individual diagnostic and λz-related parameters, will be listed for each participant by treatment group (with injection site, and bodyweight category listed) based on the safety analysis set.

11.2.6.3. Serum Pharmacokinetic Parameter Descriptive Statistics

All PK parameters for the individual mAbs AZD8895 and AZD1061, as well as for the sum of the individual mAbs of AZD7442 (AZD8895 + AZD1061) will be summarized by treatment group, treatment group and injection site, treatment group and bodyweight category, and treatment group, injection site, and bodyweight category using appropriate descriptive statistics, based on the PK analysis set.

11.2.6.4. Graphical Presentation for Serum Concentration Data

Individual serum 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 by treatment group, treatment group and injection site, treatment group and bodyweight category, and treatment group, injection site, and bodyweight category, on both a linear and semi-logarithmic scale (no gSD presented), for all participants in the PK analysis set.

11.2.6.5. Graphical Presentation for PK Parameter Data

For the individual mAbs AZD8895 and AZD1061, as well as for the sum of the individual mAbs of AZD7442 (AZD8895 + AZD1061), individual PK parameter with geometric mean (95% CI) for Cmax, AUClast, and AUCinf, will be graphically presented by treatment group, treatment group and injection site, treatment group and body weight category, and treatment group, injection site and body weight category for all participants in the PK analysis set.

11.2.6.6. Statistical Analysis for Pharmacokinetic Comparability

Pharmacokinetic comparability will be assessed between Treatment A versus Treatment B, Treatment A versus Treatment C, and Treatment B versus Treatment C based on the PK analysis set.

Analyses will be performed using a linear fixed effects analysis of variance model using the natural logarithm of primary PK parameters (eg, AUCinf, AUClast, and Cmax) for the individual mAbs AZD8895 and AZD1061, as well as for the sum of the individual mAbs (AZD8895 + AZD1061) as the response variables, treatment, injection site, anti-COVID-19 vaccination status, and continuous baseline body weight on the log scale as fixed effects and participant as a random effect. Transformed back from the logarithmic scale, geometric means together with CIs (2-sided 95%) for AUCs and Cmax will be estimated and presented. Also, ratios of geometric means together with CIs (2-sided 90%) will be estimated and presented.

11.2.7. Pharmacodynamics

11.2.7.1. CCI

CCI

11.2.8. Immunogenicity Assessment

The date and time of the blood samples collected for assessment of ADAs (samples to confirm the presence or absence of anti-AZD8895 and anti-AZD1061 antibodies from pre-dose Day 1 to Day 361, including the titer for samples confirmed positive for ADA) and neutralizing Abs will be listed. Tabulations will be provided for each treatment group. The analyses will be 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, for the number and percentage of participants with positive/negative results at each time point. The analyses will be based on the safety analysis set.

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

11.3. Protocol Deviations

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

- Inclusion/exclusion criteria deviations
- Dosing deviations (eg, incorrect treatment received, participant was not fasted as per the protocol requirements prior to and after dosing)
- Time window deviations for safety and/or PK assessments
- Participants receiving prohibited concomitant medications
- Other procedural and study conduct deviations recorded by the study Clinical Unit on a protocol deviation log

The criteria for the assessment and reporting of protocol deviations will be stipulated in a separate study specific protocol deviation specification 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 will be handled in accordance with Parexel SOPs.

For handling of protocol amendments, see Section 8.1.

11.4. Determination of Sample Size

Preliminary analysis of PK data from the first-in-human study, D8850C00001, indicated that after an IM dose of IMP (separate AZD8895 and then AZD1061 doses) at a dose of 300 mg total protein, the CV% for Cmax of the individual mAbs, AZD8895 and AZD1061 were 35.6% and 38.5%, respectively, while the CV% for AUCs of both individual mAbs, AZD8895 and AZD1061 were < 36.4%. Therefore, assuming a mean ratio of 1 between comparators, 69 participants per group will provide at least 95% power to demonstrate comparability (90% CI contained within 0.8 and 1.25).

Table 11-1 Preliminary Pharmacokinetic data from Study D8850C00001

	AZD8895	**AZD1061**
Cmax	35.6%	38.5%
AUC0-last	29.1%	30.4%
AUC0-inf	26.8%	36.4%

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 Medical Monitor. The Medical Monitor may contact the Sponsor's Lead Physician. If the Medical Monitor cannot be reached, the site's staff will contact Sponsor's Lead Physician.

Name	Role in the Study	Contact Details
PPD	Sponsor's Lead Physician	Tel: PPD E-mail: PPD

12.2. Overdose

For this study, any dose of IMP greater than the assigned dose will be considered an overdose. AstraZeneca does not recommend a specific treatment for an overdose. Symptoms of overdose should be treated as per clinical judgment.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the 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 IMP occurs in the course of the study, then the investigator 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 investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.3.1.6, and within 30 days for other overdoses.

12.2.1. Medication Error

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

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

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within one day, ie, immediately, but no later than 24 hours of when he or she becomes aware of it.

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

Medication error includes situations where an error:

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

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

- Drug name confusion.
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant.
- Drug not administered as indicated, eg, wrong route or wrong site of administration.
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet.
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature.
- Wrong participant received the medication (excluding IRT/RTSM errors).
- Wrong drug administered to participant (excluding IRT/RTSM errors).

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

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error.
- Participant accidentally missed drug dose(s), eg, forgot to take medication.
- Accidental overdose (will be captured as an overdose).
- Participant failed to return unused medication or empty packaging.
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product.

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

12.3. Pregnancy

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

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

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal 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 anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly) should be followed up and documented even if the participant was discontinued from the study.

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see 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 from the day of the IMP administration up to 90 days later.

In case of pregnancy of the partner of a male participant, the partner's pregnancy should be reported on the pregnancy form (consent from the partner must be obtained before the pregnancy form is completed) following the same timeframe and routing as described for any participant's pregnancy. Pregnancy of the participant's partner is not considered to be an AE. These pregnancies will also be followed up, and the outcome of the pregnancy (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly) 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 authorized 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 investigator. The investigator 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 IRB 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. REFERENCE LIST

Griffin et al 2017
Griffin MP, Khan AA, Esser MT, Jensen K, Takas T, Kankam MK et al. Safety, tolerability, and pharmacokinetics of MEDI8897, the respiratory syncytial virus prefusion F-targeting monoclonal antibody with an extended half-life, in healthy adults. Antimicrob Agents Chemother. 2017;61(3):e01714-16.

Li 2016
Li F. Structure, Function, and Evolution of Coronavirus Spike Proteins. Annu Rev Virol. 2016;3(1):237-61.

US CDC 2021
Centers for Disease Control and Prevention. New variants of the virus that causes COVID-19. Available from: https://www.cdc.gov/coronavirus/2019-ncov/transmission/variant.html. Accessed 14 February 2021.

US CDC 2022
Centers for Disease Control and Prevention. What you need to know about variants. Available from: https://www.cdc.gov/coronavirus/2019-ncov/variants/about-variants.html. Accessed 28 January 2022.

US CDC 2022
Centers for Disease Control and Prevention. Vaccine Administration. Available from: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/administration.html. Accessed 28 January 2022.

WHO 2021
WHO Coronavirus disease (COVID-19) Situation Report. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed 19 February 2021.

Zhou et al 2020
Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-3.

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

Hospitalization

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

Important Medical Event or Medical Intervention

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

Simply stopping the suspect drug does not mean that it is an Important Medical Event; medical judgment must be used.

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

A Guide to Interpreting the Causality Question

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

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

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

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

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

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

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

Appendix B International Airline Transportation Association 6.2 Guidance Document

Labeling 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 Dangerous Goods Regulations (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 human immunodeficiency virus (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

Introduction

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

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

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

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

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

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

Definitions

Potential Hy's Law

Aspartate aminotransferase (AST) or ALT ≥ 3 x upper limit of normal (ULN) **together with** TBL ≥ 2 x ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)

Aspartate aminotransferase or ALT ≥ 3 x ULN **together with** TBL ≥ 2 x 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.

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:

- Aspartate aminotransferase ≥ 3 x ULN
- Alanine aminotransferase ≥ 3 x ULN
- Total bilirubin ≥ 2 x ULN

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

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

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

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

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

Follow-Up

<u>Potential Hy's Law Criteria not met</u>

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

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

Potential Hy's Law Criteria met

If the participant does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study intervention (see Section 6 of this appendix)
- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of PHL; serious criteria "Important Medical Event" and causality assessment "yes/related" according to CSP process for SAE reporting
- For participants that met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change[1] in the participant's condition
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data
  - Subsequent to this contact the Investigator will:
    - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
    - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the HL laboratory kit should be used (if applicable).
    - Complete the three liver CRF modules as information becomes available.

Review and Assessment of Potential Hy's Law Cases

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

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

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

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

Where There is an Agreed Alternative Explanation for the 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 an 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.

Laboratory Tests

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

Hy's Law Laboratory Kit for Central Laboratories (18 December 2018)

Additional standard biochemistry and coagulation tests	GGT (gamma glutamyl transpeptidase (transferase)) LDH (lactate dehydrogenase) Prothrombin time INR (international normalized ratio)	
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA	IgG anti-HCV HCV RNA [a] 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	

[a] HCV RNA is only tested when anti HCV is positive or inconclusive.

REFERENCES

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

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Document Name: d8850c00009-csp-amendment-2		
Document Title:	D8850C00009 Clinical Study Protocol Amendment 2	
Document ID:	Doc ID-004620080	
Version Label:	4.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
15-Jun-2022 19:29 UTC	PPD	Content Approval
16-Jun-2022 21:45 UTC	PPD	Content Approval
15-Jun-2022 20:09 UTC	PPD	Content Approval

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