STATISTICAL ANALYSIS PLAN	
Study Code	D8850C00008
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A Phase II Double-blind, Placebo-controlled Study to Evaluate the Safety and Tolerability of AZD7442 in Chinese Adults

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ADA	Anti-drug antibodies
AE	Adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	Below the lower limit of quantification
BMI	Body mass index
CI	Confidence interval
CRF	Case report form
CSP	Clinical study protocol
CSR	Clinical study report
CV	Coefficient of variation
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
gSD	Geometric standard deviation
IC80	80% maximal inhibitory concentration
ICF	Informed consent form
IP	Investigational Product
IPD	Important protocol deviation
IV	Intravenous
LLOQ	Lower limit of quantification
LOD	Limit of detection
mAb	Monoclonal antibody
MedDRA	Medical dictionary for regulatory activities
NC	Not calculated
NR	Not reportable
NS	No sample
NQ	Not quantifiable
PD	Pharmacodynamic
PK	Pharmacokinetics
PT	Preferred term
qRT-PCR	Quantitative reverse transcriptase polymerase chain reaction

SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SI	Standard international
SoA	Schedule of activities
SoC	System organ class
ULOQ	Upper limit of quantification

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	1/17/2022	Initial approved SAP	N/A	N/A
Data presentation	8/26/2022	Section 3.3.2: clarified target time can be considered as reference if time is collected.	Yes	To provide additional clarification
Data presentation	8/26/2022	Section 3.3.2: removed early discontinuation visit (EDV) from the analysis window as EDV will not be presented in summary tables	Yes	To provide additional clarification
Data presentation	8/26/2022	Section 4.2.2.2: added any IP related AESI to the AE overview; also added a summary table for most common adverse events.	Yes	Any IP related AESI and most common AE will assist safety evaluation by local team.
Data presentation	8/26/2022	Section 4.2.3: added that selected chemistry tests will also be presented in original units.	Yes	Original units for selected chemistry tests will assist safety review by local team.
Data presentation	8/26/2022	Section 4.2.3: provided reference ranges for lab tests International Normalized Ratio and Direct Bilirubin	Yes	Due to vendor system set-up, reference ranges for 2 lab tests could not be applied or transferred. Pre-specified reference ranges will be used in safety evaluation.
Data presentation	8/26/2022	Section 4.3.1.1: clarified how to present summary statistics when only one observation is ≥ LLOQ	Yes	To provide additional clarification

1 INTRODUCTION

This is the statistical analysis plan (SAP) for study D8850C00008 and outlines the analyses to be generated for the clinical study report (CSR). The SAP describes the statistical analyses specified in the latest version of the clinical study protocol (CSP) in more detail. Any changes to what is specified in the CSP will be described.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

In addition to ADA analysis set, clarifications were provided to AZD1061 ADA evaluable analysis set, AZD8895 ADA evaluable analysis set, and AZD7442 ADA evaluable analysis set.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

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

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

As safety evaluation is the primary objective and no multiplicity control is applied, ad-hoc interim analyses may be performed for additional evaluation (e.g. potential safety signal).

3.2 Analysis Populations

All participants analysis set: All participants who signed the ICF.

Randomised analysis set: All participants who were randomised in the study.

Full analysis set: All randomised participants who received any amount of AZD7442 or placebo, irrespective of their protocol adherence and continued participation in the study.

Participants will be analysed according to their randomised treatment, irrespective of whether or not they have prematurely discontinued, according to the intent-to-treat principle. Participants who withdraw consent to participate in the study will be included up to the date of their study termination

Safety analysis set: All participants who received any amount of AZD7442 or placebo.

Erroneously treated participants (eg, those randomised to intervention A but actually given intervention B) will be analysed according to the intervention they actually receive.

PK analysis set: All participants in the safety analysis set who received AZD7442 and had at least one quantifiable serum PK observation post-dose, with no important protocol deviations thought to impact the analysis of the PK data.

ADA analysis set: All participants in the safety analysis set who received any amount of AZD7442 or placebo and had a non-missing baseline ADA result and at least one non-missing post-baseline ADA result. More specifically,

- **AZD1061 ADA evaluable analysis set** consists of participants in the safety analysis set who have a non-missing baseline AZD1061 ADA result and at least one non-missing post-baseline AZD1061 ADA result.
- **AZD8895 ADA evaluable analysis set** consists of participants in the safety analysis set who have a non-missing baseline AZD8895 ADA result and at least one non-missing post-baseline AZD8895 ADA result.
- **AZD7442 ADA evaluable analysis set** consists of participants in the safety analysis set who are AZD8895 ADA evaluable and/or AZD1061 ADA evaluable.

PD analysis set: All participants in the safety analysis set who received AZD7442 or placebo and had at least one quantifiable titer observation post-dose, with no important protocol deviations thought to impact the analysis of the PD data.

Participant disposition will be reported using the all participants analysis set. Pharmacokinetics will be assessed using the PK analysis set. Pharmacodynamics will be assessed using the PD analysis set. Exploratory efficacy endpoints will be assessed using the full analysis set. Immunogenicity will be assessed using the respective ADA evaluable analysis set for AZD1061, AZD8895, and AZD7442. All remaining evaluations including safety analysis will use the safety analysis set, unless otherwise stated.

3.3 General Considerations

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

Unless otherwise noted, all data will be presented by intervention group (i.e. AZD7442 600 mg IV and placebo) using descriptive statistics. Selected outputs may be repeated by stratification factors CCI and vCCI as appropriate.

The following general principles will be followed throughout the study:

- Categorical variables will be summarised using frequency and percentages, where the denominator for calculation is the underlying analysis set population, unless otherwise stated. Percentages will be rounded to 1 decimal place. Rounding will be applied, except for percentages < 0.1 but > 0.0 which will be presented as '< 0.1' and percentages < 100.0 but >99.9 which will be presented as '>99.9'. Percentage for 100 is presented as 100 with no decimal. Percentages for 0 will not be presented.
- Continuous variables will be summarised with descriptive statistics including number of available observations (n), mean, standard deviation (SD), median, minimum, maximum, and quartiles as appropriate. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database, and the mean, median, lower quartile, upper quartile and SD will be reported to one more decimal place than the raw data recorded in the database, unless specified otherwise. In general, the maximum number of decimal places reported shall be 4 for any summary statistics.
- PK concentration data will be summarised using descriptive statistics, including n, n of BLQ, geometric mean, geometric coefficient of variation CV%, arithmetic mean, SD, minimum, median, and maximum values. Geometric mean, geometric SD and geometric CV% are calculated based on the log-transformed data. Geometric mean is the back-transformed mean of the log-transformed values and geometric SD is the back-transformed SD of the log-transformed values.

  $$\text{gMean} = \exp\left(\frac{\ln(y_1) + \ln(y_2) + \ldots + \ln(y_n)}{n}\right)$$

  $$\text{gSD} = \exp(SD(\ln(y_1),\ldots,\ln(y_n)))$$

  $$\text{Geometric CV (\%)} = 100 * \sqrt{\exp\left(\text{Var}\left(\ln(y_1),\ldots,\ln(y_n)\right)\right) - 1}$$

  $$= 100 * \sqrt{\exp\left(SD\left(\ln(y_1),\ldots,\ln(y_n)\right)^2\right) - 1}$$

  $$= 100 * \sqrt{\exp((\ln(gSD))^2) - 1}$$

- All PK parameters will be listed and summarised using the same descriptive statistics as for PK concentrations, with the exception that for tlast, only n, median, minimum and maximum will be reported.
- In general, PK concentration will be listed to the same number of significant figures as received from the bioanalytical laboratory (usually but not always to 3 significant figures). In general, descriptive statistics for PK concentration are presented to 4 significant figures with the exception of the min and max which are presented to 3 significant figures, while n and n of BLQ will be presented as integers. Descriptive

statistics for PK parameters are generally presented to 4 significant figures.

Pharmacokinetic parameters will be derived using non-compartmental analysis methods with Phoenix® WinNonlin® version 8.1 or higher. All descriptive and inferential statistical computations will be performed using SAS® version 9.4, or higher.

3.3.1 General Study Level Definitions

3.3.1.1 Study Period

The study consists of 3 periods:

Screening period: Days -28 through -1 (up to 28 days),

Intervention period: Day 1, randomisation and dosing,

Safety follow-up period: Days 2 through 451 (450 days).

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

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

3.3.1.2 Reference Start Date and Study Day

Study day will be calculated from the reference start date and will be used to show start/stop day of assessments and events. Reference start date is defined as the date of the first dose of study intervention i.e. Day 1.

Study day will be computed as follows:

- Study Day = date of event – date of 1st dose of study intervention + 1, if the date of event is on or after the date of 1st dose of study intervention.
- Study Day = date of event – date of 1st dose of study intervention, if the date of event is prior to the date of 1st dose of study intervention.

3.3.1.3 Baseline Definition and Change from Baseline

In general, the last available measurement prior to the first dose of study intervention will serve as the baseline. If there is no result collected prior to the first dose, then baseline value will be set to missing and will not be imputed, unless otherwise specified. In the case where the last non-missing measurement and the date and time of the dose of study intervention coincide or where time is missing, that measurement will be considered

baseline, but adverse events commencing on the date and time of the dose of study intervention will be considered post-baseline.

Change from baseline = post-baseline value – baseline value

If either the post baseline value or the baseline value is missing, then the absolute change from baseline value will also be set to missing.

3.3.2 Visit Window

Visit windows will be used for all protocol-specified assessments to allow for by-visit analyses, since not all assessments are performed on the scheduled day. Unless specified otherwise, all safety, pharmacokinetic, pharmacodynamic and immunogenicity analyses will be based on the analysis visit windows. The actual assessment from scheduled and/or unscheduled day will be mapped to the planned study visit following the analysis visit windowing rules below:

- If more than one assessment falls within a visit window, the closest non-missing assessment to the target day (or target time if assessment time available) will be used in the analysis.
- If actual dates (or datetimes) of two non-missing assessments are equidistant from the target day (or target time if assessment time available), the later visit will be used in the analysis.
- If actual dates (or datetimes) of two non-missing assessments are at the same date without time information, the assessment with worst result will be used for categorical variables and the mean will be used for continuous variables in the analysis.

The visit windows will be calculated by bisecting the scheduled visit days. The lower limit of each window will be the mean of the 2 adjacent planned study days, rounded up to the nearest integer. The upper limit of each window will be the mean of the 2 adjacent planned study days, rounded down to the nearest integer.

Table 1 Analysis windows for SARS-CoV-2 serology testing by visit

Prorocol Visit	Target Day	Analysis Visit	Analysis Window (Study Day)
Visit 2	1 (pre-dose)	Baseline	All assessments prior to the start of infusion.

Visit 7	181	Day 181	All assessments after the start of first administration of investigational product to 270
Visit 9	361	Day 361	>=271

Table 2 Analysis windows for serum PK concentration by visit

Protocol Visit	Target Day	Analysis Visit	Analysis Window (Study Day)
Visit 2	1 (pre-dose)	Baseline	All assessments prior to the start of infusion
Visit 2	1 (post-dose)	Day 1, End of Infusion	start of infusion to day 4
Visit 3	8	Day 8	5 to 19
Visit 4	31	Day 31	20 to 45
Visit 5	61	Day 61	46 to 75
Visit 6	91	Day 91	76 to 135
Visit 7	181	Day 181	136 to 225
Visit 8	271	Day 271	226 to 315
Visit 9	361	Day 361	>=316

Table 3 Analysis windows for serum ADA assessment by visit

Protocol Visit	Target Day	Analysis Visit	Analysis Window (Study Day)
Visit 2	1 (pre-dose)	Baseline	All assessments prior to the start of infusion.
Visit 4	31	Day 31	Start of infusion to day 60
Visit 6	91	Day 91	61 to 135
Visit 7	181	Day 181	136 to 270
Visit 9	361	Day 361	>=271

Table 4 Analysis windows for serum SARS-CoV-2 nAbs assessment by visit

Protocol Visit	Target Day	Analysis Visit	Analysis Window (Study Day)
Visit 2	1 (pre-dose)	Baseline	All assessments prior to the start of infusion
Visit 3	8	Day 8	Start of infusion to 19

Visit 4	31	Day 31	20 to 45
Visit 5	61	Day 61	46 to 75
Visit 6	91	Day 91	76 to 135
Visit 7	181	Day 181	136 to 225
Visit 8	271	Day 271	226 to 315
Visit 9	361	Day 361	>=316

Table 5 Analysis windows for vital signs

Protocol Visit	Target Day	Analysis Visit	Analysis Window (Study Day)
Visit 2	1 (pre-dose)	Baseline	All assessments prior to the start of infusion
Visit 2	1 (post-dose)	Day 1, end of infusion	Start of infusion to 15 mins after infusion completed
Visit 2	1 (post-dose)	Day 1, 30 mins post-dose	16 mins to 45 mins after infusion completed
Visit 2	1 (post-dose)	Day 1, 60 mins post-dose	46 mins to 75 mins after infusion completed
Visit 2	1 (post-dose)	Day 1, 90 mins post-dose	76 mins to 105 mins after infusion completed
Visit 2	1 (post-dose)	Day 1, 120 mins post-dose	106 mins after infusion completed to day 4
Visit 3	8	Day 8	5 to 19
Visit 4	31	Day 31	20 to 45
Visit 5	61	Day 61	46 to 75
Visit 6	91	Day 91	76 to 135
Visit 7	181	Day 181	136 to 225
Visit 8	271	Day 271	226 to 315
Visit 9	361	Day 361	>=316

Table 6 Analysis windows for ECG

Protocol Visit	Target Day	Analysis Visit	Analysis Window (Study Day)
Visit 1	Day -28 to Day -1	Baseline	All assessments prior to the start of infusion
Visit 4	31	Day 31	Start of infusion to day 105
Visit 7	181	Day 181	106 to 270

Visit 9	361	Day 361	>=271

Table 7 Analysis windows for clinical laboratory by visit

Protocol Visit	Target Day	Analysis Visit	Analysis Window (Study Day)
Visit 2	1(pre-dose)	Baseline	All assessments prior to start of infusion
Visit 3	8	Day 8	Start of infusion to 19
Visit 4	31	Day 31	20 to 105
Visit 7	181	Day 181	106 to 270
Visit 9	361	Day 361	>=271

3.3.3 Handling of Unscheduled Visits

Measurements collected from unscheduled visits or early study discontinuation visits may also be considered in the analysis visit window. In the case of a missing value at a scheduled visit, which is then followed by a non-missing value at an unscheduled assessment within the same visit window, the non-missing value at the unscheduled assessment will be used. Data collected at unscheduled assessments might be included in baseline definitions, and in any definitions of maximum value, minimum value where appropriate.

3.3.4 Multiplicity/Multiple Comparisons

No statistical hypotheses will be evaluated based on formal statistical tests. Consequently, no correction for multiplicity will be used.

3.3.5 Handling of Protocol Deviations in Study Analysis

An IPD, per ICH definition is “a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant’s rights, safety, or wellbeing.”

The study specific IPDs are provided and classified in the AstraZeneca Protocol Deviation Plan. The IPDs include but are not limited to Inclusion/Exclusion Criteria Deviations, Investigational Product Deviations, Excluded Medications taken, and Deviations to study procedure. Refer to PD Plan document for all details of IPD.

Additionally, all protocol deviations and issues related to COVID-19 (such as missed visit, procedure not performed at visit etc.) will be captured for reporting.

3.3.6 Handling of Missing data

3.3.6.1 Imputation of Missing Date about Prior/Concomitant Medications

Partial or completely missing dates of prior and/or concomitant medications will be handled as described in APPENDIX 1.

3.3.6.2 Imputation of Missing Information related to AE

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.

• AE with a (complete or partial) missing onset date will be treated as post dose and will be presented in AE summaries, unless the stop date (or partial onset date) indicates otherwise.

There will be no imputation of AE data for the data listings and key subject information.

3.3.6.3 Imputation for PK, PD and ADA Endpoints

Serum PK concentration that are Not Quantifiable (NQ), Not Reportable (NR), or No Sample (NS) will be handled as described in Section 4.3.1.1.

ADA titer values below the minimum required dilution (MRD) will be handled as described in Section 4.4.2.

For neutralizing antibody against SARS-CoV-2, titer values below the lower limit of quantification (LLOQ) or above the upper limit of quantification (ULOQ) will be handled as described in Section 4.5.1.1.

4 STATISTICAL ANALYSIS

4.1 Study Population

This section will cover subject disposition, analysis sets, protocol deviations, demographics and baseline characteristics, prior and concomitant medication, and medical/surgical history.

4.1.1 Subject Disposition and Completion Status

Number and percentage of participants in the following categories will be presented in a summary table for each intervention group (i.e. AZD7442 600 mg IV and placebo) and study total: participants enrolled, screen failures, participants randomized, participants not randomized (including reasons), participants who received any dose of study intervention,

participants who did not receive treatment (including reasons), participants with on-going study follow-up, participants who completed the study, participants discontinued from study (including reasons), participants who became unblinded (including reasons).

Separate listings including all standardized disposition terms will be also provided for participants who were discontinued from the study as well as for participants who completed the study.

Randomization code and actual kit numbers used will also be listed.

The number and percentage of participants with one or more disruption(s) due to COVID-19 pandemic will be presented by intervention group (i.e. AZD7442 600 mg IV and placebo) and study total. A listing of all participants affected by the COVID-19 related study disruption will be produced. COVID-19 related study disruptions may include:

- Visit related (if a study visit is impacted by global/country situation, then contact mode will be specified);
- Study intervention related;
- Withdrawal from study (if primary reason for ending study is related to global/country situation).

4.1.2 Analysis Sets

See section 3.2 for the definitions of analysis set.

The number of participants belonging to each analysis set will be presented in a summary table by intervention group (i.e. AZD7442 600 mg IV and placebo) and study total.

Listing of all participants excluded from any analysis set and reason for exclusion from respective analysis set will also be provided.

4.1.3 Protocol Deviations

The number and percentage of participants with at least one IPD, including COVID-19 related IPD, will be summarised following categories specified in Protocol Deviation Plan, for each intervention group and study total based on the Safety Analysis Set.

All COVID-19 related issues regardless of whether the issue is considered as a protocol deviation or not, will be listed separately.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Demographics includes but is not limited to age, sex, race and ethnic group.

All demographic data will be summarized using descriptive statistics based on the Safety Analysis Set for each intervention group and study total. Age will be summarised as a continuous variable and also as a categorical variable (i.e. CCI).

All demographic data will be listed based on the Safety Analysis Set.

4.1.5 Baseline Characteristics

Baseline characteristics includes but is not limited to height (cm), weight (kg), body mass index (BMI) (kg/m²), COVID-19 vaccination status (i.e. yes, no).

BMI (kg/m²) will be calculated from the height (in meters) and weight (in kilograms) as follows: BMI = weight / (height^2).

All baseline characteristics data will be summarized using descriptive statistics based on the Safety Analysis Set for each intervention group and study total.

All baseline characteristics will be listed based on the Safety Analysis Set.

4.1.6 Disease Characteristics

Study population includes healthy participants as well as participants with stable medical conditions. For participants with stable medical conditions, their concomitant disease will be collected as an on-going condition in medical history. Details will be discussed in Section 4.1.7.

4.1.7 Medical/Surgical History and Concomitant Disease

Medical/Surgical history will be coded in Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or higher .

Medical history will be presented descriptively by System Organ Class (SOC) and Preferred Term (PT) for each intervention group and study total. Number and percentages of participants by each SOC/PT will be summarized based on the Safety Analysis Set.

Surgical history will be presented similarly in a separate table.

4.1.8 Prior and Concomitant Medications

The WHO-DD March 2021 B3 Global or higher is used to classify medications by WHO Anatomical Therapeutic Chemical (ATC) classification of ingredients.

Prior medications are defined as any medication that started and stopped prior to enrolment (exclusive).

Concomitant medications are defined as:

- any medication that started on or after enrolment;
- any medication that started before enrolment AND was ongoing at the time of enrolment or ended on the enrolment date

Medications with completely missing stop date are classified as concomitant. Handling method of partial/complete missing date about prior/concomitant medications is described in Section 3.3.6.1. Medications will be classified as either prior or concomitant (but not both) accordingly.

The number and percentage of participants receiving prior or concomitant medication, including COVID-19 vaccine, will be presented by intervention group and study total using the Safety Analysis Set.

All medications will also be listed.

4.1.9 Study Drug Compliance

Compliance will not be calculated as this is a single dose study. Dose administration details such as whether a participant completed study intervention per protocol will be presented as exposure, which is discussed in Section 4.2.1.

4.2 Safety and Tolerability

The study primary objective is to evaluate the safety and tolerability of a single dose of 600 mg AZD7442 administered IV among Chinese participants (including those with stable medical conditions). Safety assessments, including AEs, SAEs, AESIs, safety laboratory parameters (haematology, clinical chemistry, coagulation, and urinalysis); 12-lead ECG; vital signs (blood pressure, pulse rate, body temperature, and respiratory rate) will be presented based on Safety Analysis Set.

4.2.1 Exposure

Exposure for the following categories will be summarised descriptively with the number and percentages of participants in Safety Analysis Set: number of participants received administration, administration per protocol (Yes/No), and if not per protocol, reasons and action taken.

Exposure details, such as administration date and time, will be listed based on Safety Analysis Set.

4.2.2 Adverse Events

4.2.2.1 Definitions

Definitions of an AE or SAE can be found in Appendix B of the study protocol. Adverse Events of Special Interest (AESIs) is defined in section 8.3.4 of the study protocol.

The AESIs for AZD7442 include:

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

AEs and SAEs will be collected from the time of signing the informed consent form throughout the study up to and including the last visit. AEs and SAEs with an onset date/time >= date/time of dosing will be summarized by actual intervention group based on Safety Analysis Set. AEs will be coded with MedDRA version 24.0 or higher.

4.2.2.2 Analysis and Presentation

An overview of AEs will be presented by actual intervention group and study total based on Safety Analysis Set. It will summarize the number and percentage of participants reporting at least one event (i.e., multiple occurrences of an AE for a participant will only be counted once) and number of events where appropriate (i.e., accounting for multiple occurrences of the same event in a participant) for the following categories:

- Any AE
- Any SAE
- Any SAE with outcome death
- Any AE leading to discontinuation of IP
- Any AE leading to dose interruption
- Any AE leading to withdrawal from study
- Any AESI
- Any IP related AE
- Any IP related SAE
- Any IP related AESI

AE overview may be repeated by CCI [redacted] and CCI [redacted] as appropriate.

Adverse events, AEs with outcome of death, SAEs and AE leading to IP discontinuation/interruption will be summarised by SOC, and PT assigned to the event by MedDRA. For each PT, the number and percentage of patients reporting at least one

occurrence will be presented, i.e., for a patient multiple occurrences of an AE will only be counted once.

A summary of all AEs will be presented by PT. Most common adverse events (frequency of >5% in any treatment group) as well as AESI will also be summarised by PT. Summary of AEs will be broken down further by investigator's causality assessment (related vs not related) and maximum intensity. If a patient reports multiple occurrences of the same AE within the same study period, the maximum intensity will be taken as the highest recorded maximum intensity (the order being mild, moderate, and severe).

Details of all AEs and SAEs, including those reported during screening, will be listed based on the Safety Analysis Set.

4.2.3 Clinical Laboratory

Chemistry, haematology, coagulation, and urinalysis will be taken at scheduled visits indicated in the SoA (Section 1.3) of CSP. Safety laboratory assessments are defined in the CSP Table 12 in section 8.2.4.

Quantitative laboratory parameters reported as "< X", i.e. below the lower limit of quantification or "> X", i.e. above the upper limit of quantification, will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following summaries will be provided by actual intervention group based on the Safety Analysis Set for each of chemistry, haematology, coagulation, and urinalysis laboratory parameter where appropriate:

- Observed and change from baseline in Standard International (SI) units by visit (for quantitative parameters). Additionally, some chemistry assessments including alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase, alkaline phosphatase, and creatine kinase will also be presented in original units.
- Number and percentage of participants in each laboratory parameter category by visit (for categorical parameters)
- Shift tables from baseline to the maximum and/or minimum post-baseline observed value according to normal range criteria (e.g., low, normal, high)

In addition, the post-baseline maximum of ALT and AST by the post-baseline maximum of total bilirubin may be presented as appropriate.

All clinical laboratory data will be listed.

Note: During the study blinded data review before the clinical database lock , a data transfer issue was identified that the reference range for International Normalized Ratio and Direct Bilirubin were not applied in vendor database set-up. The following reference ranges will be pre-specified and used in safety evaluation:

- International Normalized Ratio:
  - Patient not taking oral anticoagulant: 0.8 - 1.2
  - Patient taking oral anticoagulant: 2.0 - 3.0
- Direct Bilirubin: 0-0.4 mg/dL

4.2.4 Vital Signs

Vital signs assessments (body temperature, diastolic blood pressure (DBP), systolic blood pressure (SBP), pulse rate and respiratory rate) will be performed at the visits indicated in the SoA (Section 1.3) of CSP.

Additionally, vital sign values will be classified as normal (between the lower and upper limits), low (below the lower limit), and high (above the upper limit) according to the reference ranges:

Table 8 Vital sign reference ranges

Parameter	Standard Unit	Lower limit	Upper limit
Body temperature	°C		37.8
DBP	mmHg	60	90
SBP	mmHg	90	140
Pulse rate	beats/min	60	100
Respiratory rate	breath/min	12	20

The following summaries will be provided by actual intervention group based on the Safety Analysis Set where appropriate:

- Observed values and change from baseline in vital sign parameters by visit;
- Shift tables from baseline to the maximum and/or minimum post-baseline observed value according to reference range (e.g., low, normal, high)

All vital sign data will be listed, and vital sign status compared to the reference range (low, normal, high) will be indicated.

4.2.5 Electrocardiogram

Twelve-lead electrocardiogram (ECG) will be performed at timepoints as specified in the SoA (Section 1.3) of CSP. The following ECG variables will be collected:

- Heart rate (bpm)
- PR interval (msec)
- RR interval (msec)
- QRS duration (msec)
- QT interval (msec)
- QTcF interval (msec)
- Overall ECG interpretation (Investigator's judgement)
  - Normal
  - Abnormal, not clinically significant
  - Abnormal, clinical significant

Markedly abnormal quantitative ECG parameters will be identified in accordance with the following predefined markedly abnormal criteria:

- Observed values for QTcF interval will be classified as:
  - > 450 msec;
  - > 480 msec;
  - > 500 msec
- Change from baseline for QTcF interval will be classified as:
  - >30 msec increase from baseline
  - >60 msec increase from baseline

It is to be noted that the previous categories are not mutually exclusive, but cumulative. For example, if a participant's worst post-baseline QTcF post-baseline observed value is 490 mmHg, then this participant will be reported once under QTcF > 450 msec and once under QTcF > 480 msec.

The following summaries will be provided by actual intervention group based on the Safety Analysis Set for ECG parameters where appropriate:

- Observed and change from baseline by visit (for quantitative parameters);

- A shift table of categorical ECG interpretation (from best to worst: normal, abnormal - not clinically significant, abnormal - clinically significant) at baseline versus worst post-baseline observation

- Number and percentages of participants with at least one markedly abnormal post-baseline observed.

Individual ECG results and abnormalities in ECG will be listed.

4.2.6 Other Safety Assessments

Other assessments such as Pregnancy Testing will be listed where appropriate.

4.3 Pharmacokinetics

One of the study secondary objectives is to evaluate pharmacokinetics of AZD8895, AZD1061, and AZD7442 after a single dose of 600 mg AZD7442 IV.

Serum samples will be collected for measurements of AZD8895 and AZD1061 concentrations as well as AZD7442 concentration (i.e. sum of AZD8895 and AZD1061) at time points specified in the SoA (Section 1.3) of CSP.

PK analyses will be based on the PK Analysis Set, and may be repeated by CCI and CCI as appropriate. Any PK data excluded from summary tables or mean plots will be flagged in participant listing.

4.3.1 Serum Concentration

Serum PK concentrations of each mAb (AZD8895 and AZD1061) and AZD7442 (i.e. sum of AZD8895 and AZD1061) will be listed and tabulated as appropriate.

4.3.1.1 Handling Rule for BLQ Serum Concentrations

Serum concentrations that are below the LLOQ (i.e. Not Quantifiable [NQ]), or reported as NR (Not Reportable) or NS (No Sample) will be handled as follows for the provision of descriptive statistics:

- Any values reported as NR or NS will be excluded from the summary tables and corresponding figures.
- At a time point where less than or equal to 50% of the concentration values are NQ, all NQ values will be set to the LLOQ, and all descriptive statistics will be calculated accordingly.
- At a time point where more than 50% (but not all) of the values are NQ, the gmean, gSD, gCV%, arithmetic mean and SD will be set to NC (Not Calculated). The maximum value will be reported from the individual data, and the minimum and median will be set to NQ.

- If all concentrations are NQ at a time point, no descriptive statistics will be calculated for that time point. The gmean, arithmetic mean, minimum, median and maximum will be reported as NQ, and the gCV%, gSD and SD will be reported as NC.
- The number of values below LLOQ will be reported for each time point together with the total number of collected values (n).

Three observations ≥ LLOQ are required as a minimum for a serum concentration or PK parameter (e.g. Cmax, Cmin, Clast) to be summarized. When only one or two observations ≥ LLOQ , minimum and maximum will be presented , and will be presented as the only available value in case of one observation ≥ LLOQ, with the other summary statistics as NC.

For mean figures, concentrations that are NQ will be handled as described for the descriptive statistics. If this handling results in a geometric mean of "NQ", then the value plotted at that time point will be set to missing for both linear and semi-logarithmic plots.

For individual figures, concentrations that are NQ will be regarded as missing, with the exception that NQ prior to the first quantifiable sample should all be set to 0 (linear scale).

4.3.1.2 Presentation of PK Concentration

The PK concentrations will be summarized in tabular and graphical forms, as appropriate, according to the latest version of the AstraZeneca standards.

Serum concentrations for each scheduled time point will be summarized for each mAb component and AZD7442 based on the PK Analyses Set using the following descriptive statistics: number of participants included in analysis (n), n below lower limit of quantification (LLOQ), arithmetic mean, SD, geometric mean, geometric CV%, median, minimum, and maximum. This summary may be repeated by CCI and CCI as appropriate.

Serum concentrations above cut-offs (i.e. minimum protective concentration) may be considered to have functional inhibition. Functional inhibition data may be summarized as appropriate.

A listing of concentration-time data including PK scheduled timepoints, actual sample collection times, sample actual relative times, as well as derived sampling time deviations will be presented using the PK Analysis Set.

Combined individual serum concentrations versus actual times grouped by mAb component will be plotted on both linear and semi-logarithmic scales using the PK Analysis Set. Geometric means of concentration data will be plotted over time on both linear and

semi-logarithmic scales as appropriate. Additional geometric mean plots by age and vaccination status may be provided. Nominal sampling time points relative to dosing will be used for mean plots. Actual sampling time points relative to dosing will be used for individual plots.

4.3.2 PK Parameters

Pharmacokinetic parameters will be derived using non-compartmental analysis methods, if data permit.

4.3.2.1 Derivation of PK Parameters

Where possible, the following key PK parameters in Table 9 will be estimated for each individual mAb (AZD8895, AZD1061) and AZD7442, if data permit.

Table 9 Key PK Parameters

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

The following PK diagnostic parameters will also be calculated for for individual mAb (AZD8895, AZD1061) and AZD7442, if data permit.

Table 10 PK Diagnostic Parameters

λz lower	Lower (earlier) t used for λz determination
λz upper	Upper (later) t used for λz determination
λz, N	Number of data points included in the log-linear regression analysis
λz span ratio	Time period over which λz was determined as ratio of $t_{½λz}$
Rsq_adj	Statistical measure of fit for the regression used for λz determination adjusted for the number of used data points (n obs)
λz	Terminal elimination rate constant
AUCextr	Extrapolated area under the curve from tlast to infinity, expressed as percentage of AUCinf

PK analysis will, where data allow, be carried out using actual elapsed times determined from the PK sampling times and the dosing time recorded in the database. If actual elapsed times are missing, nominal times may be used. Nominal sampling times may be used for any agreed interim PK parameter calculations if required.

For day 1, concentrations below the lower limit of quantification (BLQ) from the time of pre-dose sampling up to the time of the first quantifiable concentration will be set to a value of 0. After this point, BLQ concentrations will be set to missing for all concentration profiles. If 2 or more consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, the profile will be deemed to have terminated and therefore these quantifiable values will be set to missing for the calculation of the PK parameters unless there is a scientific rationale not to do so. If an entire concentration-time profile is BLQ, the profile is excluded from the PK analysis.

Area under the concentration curve will be calculated using trapezoidal methods when concentrations are increasing and logarithmic trapezoidal method when concentrations are decreasing.

Three concentrations higher than the lower limit of quantification are required as a minimum for the AUC parameter to be summarised, with at least one of these concentrations following Cmax.

4.3.2.2 Presentation of PK Parameters

Where possible, all PK parameters (except tlast) in Table 9 will be summarised for each mAb component and AZD7442 based on the PK Analysis Set using the following descriptive statistics: n, geometric mean, geometric CV%, arithmetic mean, SD, median, minimum, and maximum. For tlast, only n, median, minimum, and maximum will be presented. This summary may be repeated by CCI and CCI as appropriate.

All PK parameters, including PK diagnostic parameters, will be listed if data permit.

4.4 Immunogenicity

Blood samples for determination of anti-drug antibodies (ADA) in serum will be assessed at day 1 (pre-dose), visit 4, visit 6, visit 7, visit 9 as shown in the SoA (Section 1.3) of CSP.

Baseline is defined as the last available ADA assessment prior to the first study intervention. Post-baseline includes all ADA assessments after study intervention during the study period.

ADA results to AZD8895, AZD1061 and AZD7442 will be reported separately using the respective ADA Evaluable Analysis Set as defined in Section 3.2. In the evaluation of ADA results to AZD7442, if a component mAb (i.e. AZD8895 or AZD1061) is not ADA evaluable, all results from the component would be treated as missing.

4.4.1 ADA Definitions

ADA result from each sample will be reported as either positive or negative. If the sample is positive, the ADA titer will be reported as well. ADA-positive samples may also be further tested for characterization of the ADA response.

ADA detection at sample level:

- For each mAb component AZD1061 and AZD8895, a sample is considered to be ADA positive if the titer is greater than or equal to the respective minimum required dilution (MRD) of the assay.
- For a sample at a particular visit, AZD7442 is positive for that visit if either AZD1061 and/or AZD8895 is positive.
- A sample is considered to be ADA negative if the titer is < MRD of the assay.

ADA status at participant level:

ADA positive:

- A participant is considered ADA-positive to a mAb component AZD1061 or AZD8895 if having a positive ADA result to the respective mAb at any visit, including baseline and all post-baseline measurements.
- A participant is considered ADA-positive to AZD7442 if having a positive ADA result to AZD8895 and/or AZD1061 at any visit, including baseline and all post-baseline measurements.
- A participant is considered ADA negative to a mAb component AZD1061 or AZD8895 if having negative ADA results to the respective mAb at all visits, including baseline and all post-baseline measurements.
- A participant is considered ADA negative to AZD7442 if having negative ADA results to both AZD8895 and AZD1061 at all visits, including baseline and all post-baseline measurements.

The proportion of ADA-positive participants in a population is known as ADA prevalence.

Treatment-induced ADA positive:

- For each mAb component AZD1061 and AZD8895, a participant is treatment-induced ADA positive if ADA negative at baseline and ADA positive at ≥ 1 post-baseline assessments with ADA titer ≥ 2 folds of the respective MRD.

- For AZD7442, A participant is treatment-induced ADA positive if either AZD8895 and/or AZD1061 is treatment-induced ADA positive.

Treatment-boosted ADA positive:

- For each mAb component AZD1061 and AZD8895, a participant is treatment-boosted ADA positive if ADA positive at baseline and the baseline titer is boosted by ≥ 4 folds at ≥1 post-baseline timepoint.
- For AZD7442, a participant is treatment-boosted ADA positive if either AZD8895 and/or AZD1061 is treatment-boosted ADA positive.

Treatment-emergent ADA positive:

- For each mAb component AZD1061 and AZD8895, a participant is treatment-emergent ADA positive if the component is either treatment-induced positive or treatment-boosted positive.
- For AZD7442, a participant is treatment-emergent ADA positive if either AZD8895 and/or AZD1061 is treatment-emergent ADA positive.

The proportion of treatment-emergent ADA-positive participants in a population is known as ADA incidence.

Non-treatment-emergent ADA positive:

• For each mAb component AZD1061 and AZD8895, a participant is non-treatment-emergent ADA positive if the participant is ADA-positive for the respective mAb but not fulfilling the criteria for being treatment-emergent ADA positive.

• For AZD7442, a participant is non-treatment-emergent ADA positive if at least one component is positive, and

  – If one component is positive, the positive component is non-treatment-emergent ADA positive.

  – If both components are positive, both components are non-treatment-emergent ADA positive.

Persistently ADA positive:

- For each mAb component AZD1061 and AZD8895, a participant is persistently ADA positive if the participant is treatment-emergent ADA positive, and having at least 2 ADA post-baseline positive with titer ≥ 2 folds of the respective MRD (with ≥ 16 weeks

between first and last positive) or positive with ADA titer ≥ 2 folds of MRD at last post-baseline assessment.
- For AZD7442, a participant is persistently ADA positive if either AZD8895 and/or AZD1061 is persistently ADA positive.

Transiently ADA positive:

- For each mAb component AZD1061 and AZD8895, a participant is transiently ADA positive, if the participant is treatment-emergent ADA positive, and having at least one post-baseline ADA positive assessment with titer ≥ 2 folds of the respective MRD, and not fulfilling the conditions of persistently positive.
- For AZD7442, a participant is transiently ADA positive if AZD7442 is treatment-emergent ADA positive and not fulfilling the conditions of persistently positive.

4.4.2 Handling Rule for Negative or Borderline ADA data

The analysis of serum ADA data will use the following imputation method: ADA titer values below the MRD are negative results, hence they are not imputed and are excluded from calculation of summary statistics. Titer values of borderline positive ADA samples reported as ≤ MRD are imputed as MRD in the calculation of summary statistics on ADA titer.

4.4.3 ADA Analysis and Presentation

For AZD1061, AZD8895 and AZD7442, respectively, number and percentage of participants in each of the following ADA categories in different treatment groups will be summarized descriptively based on the respective ADA Evaluable Analysis Sets:
- Participants who are ADA positive at any time during the study, including baseline and/or post-baseline.
- Participants who are ADA positive at baseline only.
- Participants who are ADA positive at baseline and at least one post-baseline assessment.
- Participants who are treatment-emergent ADA positive, reported overall and separately as treatment-induced and treatment-boosted participants.
- Participants who are non-treatment-emergent ADA positive.
- Participants who are persistently ADA positive.
- Participants who are transiently ADA positive.

Summary of ADA responses during the study with number and percentage of participants in each category will be provided in different treatment groups. Summary statistics of maximum ADA titers in each category, displaying min, Q1, median, Q3 and max, will be provided by intervention group and study total based on respective ADA evaluable analysis set for AZD1061, AZD8895, and AZD7442.

For ADA summaries at a single time point (e.g., baseline ADA or by visit) the corresponding titer summary of either AZD8895 or AZD1061 will be based on the reported titer of the positive sample for that particular visit. For AZD7442, the titer will be the titer result of the positive component (i.e. either AZD1061 or AZD8895); if a participant has titer results to both AZD1061 and AZD8895, the higher titer result will be used. For proportions summarized across visits (e.g., ADA positive at any time) the corresponding titer summaries will be based on the maximum titer of all positive samples for each participant.

All ADA data will be listed for all participants in the safety analysis set regardless of ADA-evaluable status.

Individual plots of serum PK concentrations over time by ADA category (i.e. ADA negative, treatment-emergent ADA positive, non-treatment-emergent ADA positive) may be provided. Additional analysis to evaluate the potential impact of immunogenicity on pharmacokinetics and/or safety may be assessed when appropriate.

4.5 Pharmacodynamics

One of the study exploratory objectives is to evaluate the neutralising responses against SARS-CoV-2 in serum. Serum samples will be collected for neutralising responses at time points specified in the SoA (Section 1.3) of CSP.

4.5.1 Serum Neutralising Responses Against SARS-CoV-2

4.5.1.1 Handling Rule for Unquantifiable Neutralizing Titer

The analysis of neutralizing antibody titers and fold rises will use the following imputation method: a titer value measured below the LLOQ will be imputed to a value that is half of the LLOQ in summaries and analyses but will be listed as reported in the raw data. Titer values measured as above the upper limit of quantification (ULOQ) will be imputed at the ULOQ value.

4.5.1.2 Analysis and Presentation

If data permit, neutralizing antibody titers and fold rises will be summarized by interventional group at each scheduled visit based on PD Analysis Set. This analysis may be repeated by stratification factors age and vaccination status against COVID-19 at screening as appropriate. All neutralizing antibody data will be listed.

Descriptive statistics for neutralizing antibody titers and fold rises may include number of participants in the analysis, geometric mean, geometric standard deviation (GSD), 95% CI, minimum and maximum

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

The titer fold rise is calculated as the ratio of the post-dose titer level to the pre-dose titer level. The geometric mean fold rise will be calculated as anti-logarithm of Σ (log2 transformed (post-dose titer/ pre-dose titer)/n). The GSD and 95% CIs for fold rises will be calculated similarly to those for titer values.

Results of the neutralizing response against SARS-CoV-2 may be reported separately from the CSR.

4.6 Other Exploratory Analyses

One of study exploratory analyses is to evaluate the efficacy of a single dose of AZD7442 compared to placebo, administered IV, for the prevention of SARS-CoV-2 infection. Exploratory efficacy analyses will be based on Full Analysis Set.

4.6.1 SARS-CoV-2 qRT-PCR Test

Monitoring of COVID-19 symptoms will be performed as per the schedule of events (refer to CSP Section 1.3). A SARS-CoV-2 qRT-PCR test could be performed at the discretion of the investigator if the participant met the qualifying symptoms (refer to CSP Table 11).

The incidence ofCOVID-19 will be the proportion of participants with a positive SARS-CoV-2 qRT-PCR test result occurring after IP dosing. If data permit, the incidence of COVID-19 will be summarized by intervention group and study total using appropriate descriptive statistics.

Available SARS-CoV-2 qRT-PCR data and participants with qualifying symptoms may be listed.

4.6.2 SARS-CoV-2 Serology Test

Serum samples will be collected (if feasible) as per the schedule of events (refer to CSP Section 1.3) for SARS-CoV-2 serology test to monitor participants for infection. To be considered positive in the endpoint analysis, the positive result should be tested from a validated assay performed at the central laboratory.

A participant is considered to have a post-treatment response if serology result is negative at baseline and positive at ≥ 1 post-baseline. All available serology data prior to COVID-19 vaccination (if applicable) during the study will be included in analysis.

If data permit, the proportion of participants with a post-treatment response will be summarized by intervention group and study total.

Available serology results may be listed as appropriate.

5 INTERIM ANALYSIS

Please refer to section 3.1 for analyses timing. In general, scope of analyses will be similar in all planned analyses or ad-hoc interim analyses (if applicable). If data permit, additional analysis may be considered as appropriate. No early stopping decision will be made for futility or superiority at the primary or ad-hoc interim analyses (if applicable).

6 REFERENCES

Not applicable

7 APPENDIX

APPENDIX 1. Date Conventions for Prior/Concomitant Medications

START DATE	STOP DATE	ACTION
Known	Known or ongoing	If medication stop date < enrolment date, assign as prior; If medication start date < enrolment date and medication stop date ≥ enrolment date , assign as concomitant; If enrolment date ≤ medication start date, assign as concomitant.
	Partial	If known components of medication stop date show that medication stopped before enrolment date, assign as prior; If medication start date < enrolment date and (known components of medication stop date show that

		medication stopped on or after enrolment date), assign as concomitant; If enrolment date ≤ medication start date, assign as concomitant.
	Missing, not ongoing	If medication stop date is missing, then it can never be assigned as prior only; If medication start date < enrolment date, assign as concomitant; If enrolment date ≤ medication start date, assign as concomitant.
Partial	Known or ongoing	If medication stop date < enrolment date, assign as prior; If (known components of medication start date show that medication started before enrolment date) and (medication stop date ≥ enrolment date), assign as concomitant; If known components of medication start date show that medication started on or after enrolment date, assign as concomitant.
	Partial	If known components of medication stop date show that medication stopped before enrolment date, assign as prior; If (known components of medication start date show that medication started before enrolment date) and (known components of medication stop date show that medication stopped on or after enrolment date), assign as concomitant; If known components of medication start date show that medication started on or after enrolment date, assign as concomitant.

	Missing, not ongoing	Cannot be assigned as prior only; If known components of medication start date show that medication started before enrolment date, assign as concomitant; If known components of medication start date show that medication started on or after enrolment date, assign as concomitant.
Missing	Known or ongoing	If medication stop date < enrolment date, assign as prior; If medication stop date >= enrolment date, assign as concomitant.
	Partial	If known components of medication stop date show that medication stopped before enrolment date, assign as prior; If known components of medication stop date show that medication stopped on or after enrolment date, assign as concomitant.
	Missing, not ongoing	Assign as concomitant