STATISTICAL ANALYSIS PLAN	
Study Code	D8850C00010
Edition Number	2.0
Date	20-Nov-2023

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

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/transaminase
AST	Aspartate aminotransferase/transaminase
ATC	Anatomical therapeutic class
AUC	Area under the concentration-time curve
BLQ	Below the lower limit of quantification
BMI	Body mass index
C	Celsius
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
CSP	Clinical study protocol
CSR	Clinical study report
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EOT	End of treatment
eCRF	Electronic case report form
FAS	Full analysis set
gCV	Geometric coefficient of variation
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
gSD	Geometric standard deviation
ICF	Inform consent form
IV	Intravenously
IMP	Investigational medicinal product
IPD	Important protocol deviation
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Minimum Required Dilution
nAb	Neutralizing antibody
NR	Not Reportable
NP	Nasopharyngeal
NQ	Not Quantifiable
NS	No Sample
LLOQ	Lower limit of quantification
PD	Pharmacodynamics
PK	Pharmacokinetics
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome-coronavirus 2
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure

Abbreviation or Specialized Term	Definition
SI	Standard International
SD	Standard deviation
SoA	Schedule of Assessments
TBL	Total bilirubin
TFLs	Tables, figures, and listings
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
WHO	World Health Organization

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	8/16/2022	Initial approved SAP	N/A	N/A
Other: Study design	20Nov2023	Study is early terminated. Participants remained in the study are to complete final assessments at least 6 months after their final dose of AZD7442. No additional dose of AZD7442 will be given.	Yes	On 30 March 2023, the FDA requested that the Sponsor halt further dosing for the ENDURE Study, given that AZD7442 (EVUSHELD) is not active against > 99% of the currently circulating SARS-CoV-2 variants in the USA, the benefit risk assessment may not be favorable. After consideration of the FDAs request, the Sponsor has decided to terminate this study.
Other: Changes to CSP planned analysis	20Nov2023	Additional section added to explain the analysis set definition.	N/A	Clarify the participant inclusion / exclusion and participant visit inclusion / exclusion differences in the analysis set definition.
Other: Timing of the analyses	20Nov2023	Remove interim analysis and only final analysis is planned for the study	Yes	Due to study design change, only final analysis is needed.
Other: NLF PK analysis set	20Nov2023	Addition of NLF PK analysis set	N/A	Clarify NLF PK concentration analysis set
Other: Visit Window	20Nov2023	Remove Day 1 pre-dose time point from the visit window for Serum and NLF PK parameters.	N/A	
Other: Protocol deviation category	20Nov2023	Align protocol deviation categories with PDMP	N/A	Protocol deviation monitoring plan (PDMP) is updated, this change is to align SAP with the PDMP.
Data presentations	20Nov2023	Remove Region from the subgroup presentation	N/A	Only participants in US is enrolled.
Other: Partial date imputation	20Nov2023	Addition of partial COVID-19 vaccination date imputation method	N/A	Method to impute incomplete date that was collected for statistical analysis.
Data presentations	20Nov2023	Concomitant medication summaries will use ATC level 4 instead of level 2	N/A	To display more specific drug category

Statistical analysis method	20Nov2023	Further clarify the correlation calculation method using mixed model for repeated measurements and bootstrapping.	N/A	Clarify the statistical method used for calculation of nAb and PK concentration correlation.
Data presentations	20Nov2023	Clarify 2 assays are used for nAb titers	N/A	Two assays: one for SARS-CoV-2 authentic virus and the other peudovirus nAb are both collected.
Other: Record exclusion for analyses	20Nov2023	For serum / NLF PK and nAb analyses, clarify how the individual records will be excluded per protocol deviation occurrence	N/A	Clarify under each analysis set, due to protocol deviations that could impact the concentration and / or nAb titer values, certain data points need to be excluded from the analyses.
Other: NLF PK derivation and analysis methods	20Nov2023	Addition of NLF PK data definition, derivation and associated statistical analysis methods	N/A	Adding details on the analyses of NLF PK data
Other: COVID-19 variant analyses	20Nov2023	Addition of variant analyses	N/A	Adding details on the analyses of variants
Other: Censoring method for Symptomatic illness endpoint	20Nov2023	Addition of various censoring rules to encompass different scenarios	N/A	Further clarifying censoring method for counting incidence of illnesses.
Other: Add additional safety analyses	20Nov2023	Addition of Grade ≥3 event and embolic and thrombotic event definition and analyses	N/A	Additional safety analyses deemed necessary
Other: Lab test	20Nov2023	Adjust lab CTCAE table to align with protocol required lab tests	Yes	To align with CSP

1 INTRODUCTION

The purpose of this document is to give details for the statistical analysis of study D8850C00010 supporting the clinical study report. The reader is referred to the most recent versions of the Clinical Study Protocol (CSP) and the Case Report Form (CRF) for details of study conduct and data collection.

The term IMP (investigational medicinal product) is used throughout this SAP to refer to AZD7442, a combination product of two monoclonal antibodies (tixagevimab [AZD8895] + cilgavimab [AZD1061]). Approximately 200 participants who meet the eligibility criteria for the study will be randomized in a 1:1 ratio to one of 2 open-label AZD7442 treatment arms:

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

1.1 Objectives and Endpoints

Table 1: Objectives and Endpoints

Objective	Endpoint
Primary	
To evaluate the safety and tolerability of AZD7442	AEs, SAEs, and AESIs
To evaluate the immunogenicity of AZD7442	Incidence of ADA in serum
Secondary	
To evaluate the PK of AZD7442 in serum	• Serum AZD7442 concentrations • PK parameters
To determine anti-SARS-CoV-2 nAb levels in serum after administration of AZD7442	Changes from baseline in GMTs and GMFRs values in SARS-CoV-2 nAbs (wild-type assay or pseudo neutralization assay)
Exploratory	
To estimate the efficacy of AZD7442 for the prevention of COVID-19	• Incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness • Incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies

To estimate the efficacy of AZD7442 for the prevention of severe or critical symptomatic COVID-19	Incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness and COVID-19 deaths
To evaluate the PK of AZD7442 in nasal fluid	Nasal AZD7442 concentrations
To quantify SARS-CoV-2 viral loads in infected participants treated with AZD7442 (Illness Visits)	Viral genome copies in NP swabs at Illness Visits as determined by RT-PCR
To characterize resistance to AZD7442 (Illness Visits)	Genotypic analysis and biochemical and/or susceptibility analysis of SARS-CoV-2 variants to AZD7442
To assess additional immune responses in participants treated with AZD7442 (Illness Visits)	Other exploratory assays for humoral, mucosal, and cellular immune responses may be performed based upon emerging safety, efficacy, and pharmacodynamic data

Abbreviations: ADA = Antidrug antibody; AE = Adverse event; AESI = Adverse event of special interest; COVID-19 = Coronavirus disease 2019; GMT = Geometric mean titers; GMFR = Geometric mean fold rise; nAb =Neutralizing antibody; NP = Nasopharyngeal; PK = Pharmacokinetic; RT-PCR = Reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = Severe acute respiratory syndrome-coronavirus 2.

1.2 Study Design

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

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

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

An End of Treatment (EoT) Visit will be conducted at 15 months in both arms (3 months after the final dose of AZD7442). After the EoT Visit, the participant will enter the follow-up period. Participants will be followed for safety for an additional 9 months after the EoT Visit, i.e., through 12 months after the participant's final dose of AZD442.

Participants who discontinue IMP administration due to premature termination of the study

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

1.3 Sample Size

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

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

2 CHANGES TO PROTOCOL PLANNED ANALYSES

The CSP details record level exclusions for the nAb evaluable analysis set, following the point at which they receive an alternative COVID-19 monoclonal antibody (mAb). The purpose of an analysis set should be to exclude at the participant level. Therefore, this additional detail has been removed from the analysis set definition in Section 3.2, and record level exclusions for nAb are detailed in Section 4.2.2.4.2. These include exclusions following receipt of an alternative COVID-19 mAb by excluding nAb samples from the date a participant had a protocol deviation recorded for receiving a restricted medication, as detailed in CSP Section 6.5. Although such medications are allowed for treatment of COVID-19 or during the follow-up period (starting ≥ 3 months after the last dose of IMP), nAb samples are also excluded following the date of a positive SARS-CoV-2 RT-PCR (defined in Section 4.2.3.4.1), and nAb samples collected during illness visits are to be summarized separately to main study visits in the planned analyses. Hence this record level exclusion is in line with what was detailed in CSP.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

No interim analysis is planned for this study.

Due to the decision to halt IMP dosing in this study, there are participants who did not complete the treatment period (up to Month 15), and therefore the primary data readout (per CSP V3.0) will not be required.

The final data readout will occur once all participants have completed the follow-up period (at Month 24) or early discontinuation visit at least 6 months after final dose of IMP due to early termination of the study (see CSP section 9.4).

3.2 Analysis Populations

Table 2: Populations for Analysis

Population/Analysis	Description
Enrolled	All participants who sign the ICF.
Full analysis set	All randomized participants who receive at least one dose of IMP. Participants will be assigned to their randomized treatment according to the intent-to-treat principle.
Safety analysis set	All participants who have received at least one dose of IMP. Participants will be assigned in this analysis set by the arm of treatment they actually received.
PK analysis set	All participants in the safety analysis set who received AZD7442[1] and who had at least one quantifiable serum PK observation post dose will be included in the PK analysis dataset. Participants will be assigned in this analysis set by the arm of treatment they actually received.
NLF PK analysis set	All participants in the safety analysis set who received AZD7442[1] and who had at least one quantifiable adjusted nasal lining fluid PK observation post dose will be included in the NLF PK analysis dataset. Participants will be assigned in this analysis set by the arm of treatment they actually received.
ADA evaluable analysis set	All participants in the safety analysis set who have a non-missing baseline AZD7442 ADA result and at least one non-missing post-baseline AZD7442 ADA result. This includes 2 separate evaluable analysis sets for AZD8895 and AZD1061. AZD7442 evaluable analysis set contains participants who are either AZD8895 evaluable or AZD1061 evaluable. Participants will be assigned in this analysis set by the arm of treatment they actually received.
nAb evaluable analysis set (Pseudovirus)	All participants in the safety analysis set who received AZD7442[1], and who had at least one quantifiable serum observation (pseudovirus) post dose. Participants will be assigned in this analysis set by the arm of treatment they actually received.

Population/Analysis	Description
nAb evaluable analysis set (Authentic Virus)	All participants in the safety analysis set who received AZD7442[1], and who had at least one quantifiable serum observation (authentic virus) post dose. Participants will be assigned in this analysis set by the arm of treatment they actually received.

Abbreviations: ICF, informed consent form; COVID-19, coronavirus disease 2019; IMP, investigational medicinal product.
[1]As per participant-level exclusions from the analyses identified in the most recent version of the PDMP.

3.3 General Considerations

Categorical variables will be summarized using frequency and percentages, where the denominator for calculation is the underlying analysis set population, unless otherwise stated. A row denoted as "Missing" will be included in the count tabulations where necessary to account for missing values. Summaries will be provided by treatment and visit when applicable.

Continuous variables may be summarized with descriptive statistics of number of participants with available data (n), mean, standard deviation (SD), median, the first quartile (Q1), third quartile (Q3), minimum and maximum. Summaries will be provided by treatment and visit when applicable.

For concentration data and log-transformed data, descriptive statistics (i.e., n and n < lower limit of quantification (LLOQ) [number of participants with available result and number of participants with results below the limit of quantification], geometric mean, geometric SD, arithmetic mean, SD, co-efficient of variation, median, min and max) will be presented by treatment group and visit, when applicable.

3.3.1 General Study Level Definitions

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 first day of the dose of IMP i.e., Day 1.

Study Day will be computed as follows:

- *Study Day = (Date of assessment/event – Date of first dose of IMP) + 1 if the date of the assessment/event is on or after the date of the first dose of IMP.*

- *Study Day = (Date of assessment/event – Date of first dose of IMP) if the date of the assessment/event is prior to the date of the first dose of IMP.*

In general, when the assessment/event date is partial or missing, Study Day and any corresponding durations will be displayed as missing in the listings.

For illness visits, an illness study day will be calculated. The reference start date is defined as the day of first illness assessment, i.e., illness visit Day 1. This will be calculated separately for each illness episode.

Illness Study Day will be computed as follows:

- *Illness Study Day = (Date of assessment/event – Date of illness visit Day 1) + 1.*

Baseline

In general, baseline is defined as the last non-missing measurement taken prior to the first dose of IMP. If the last non-missing measurement is taken at same date and time of the dose of IMP, this measurement will be considered baseline, with the exception of adverse events (AEs) and non-IMP medications commencing on the date and time of the dose of IMP, these assessments will be considered post-baseline.

Illness Visit baseline is defined as the first non-missing measurement taken on Illness Visit Day 1. If there is no non-missing measurement available on Illness Visit Day 1, Illness Visit baseline is considered as missing. For instances, where Illness Visit Day 1 occurs on the same day as a main study Visit, and Illness Visit Day 1 measurements are missing, then the measurements from the main study Visit will be used as Illness Visit baseline. Otherwise, if there is still no available measurement for Illness Visit Day 1, Illness Visit baseline is considered as missing.

Change from baseline will be calculated as *(post-baseline visit – baseline visit)*.

Change from baseline for Illness Visits will be calculated as:

- *Change from baseline at Illness Visit Day 1 = Test value at Illness Visit Day 1 – Baseline value*
- *Change from baseline at Illness Visits after Illness Visit Day 1 = Test value at post Illness Visit – Illness Visit baseline value*

3.3.2 Visit Window

A windowing convention will be used to determine the analysis value for a given study visit for visit-based assessments, which are as follows:

- Serum sample for SARS-CoV-2 serology (anti-nucleocapsid testing)
- Serum sample for AZD7442 PK assessments
- Serum sample for AZD7442 ADA
- Serum sample for SARS-CoV-2 nAbs levels (pharmacodynamics [PD])
- Serum sample exploratory biomarkers
- Nasal lining fluid sample for AZD7442 PK assessments
- Clinical chemistry, hematology, coagulation, and urinalysis
- Vital signs
- Electrocardiogram (ECG)
- Illness visits for COVID-19 symptom assessment, vital signs, immunogenicity, PD, PK, coagulation, serum sample for exploratory assessments

The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls halfway between the two visits (the lower limit of the first post-baseline visit will be Day 2). If an odd number of days exists between two consecutive visits, then the upper limit will be taken as the midpoint value minus 1 day.

One or more results for a particular variable may be obtained in the same visit window. In such an event, the result with the date closest to the expected visit date will be used in the analysis. In the event that two observations are equidistant from the expected visit date, the later observation will be used in the analysis.

The visit windows are defined in the following tables.

Table 3: Analysis windows for serum sample for SARS-CoV-2 serology, ADA and SARS-CoV-2 nAbs levels

Arm A

Visit	Day Relative to First Dose	Visit Window (Study Day)
Day 1	≤ 1	≤ 1
Day 29	29	2 – 60
Day 92	92	61 - 106
Day 121	121	107 - 152
Day 183	183	153 - 197
Day 212	212	198 - 242
Day 274	274	243 - 319
Day 365	365	320 - 410
Day 456	456	≥411 [for serology and SARS-CoV-2 nAbs] 411 – 592 [for ADA assessment]
Day 729 (Follow-up)	729	≥593 [for ADA assessment]

Arm B

Visit	Day Relative to First Dose	Visit Window (Study Day)
Day 1	≤ 1	≤ 1
Day 29	29	2 – 60
Day 92	92	61 - 137
Day 183	183	138 - 197
Day 212	212	198 - 242
Day 274	274	243 - 319
Day 365	365	320 - 410
Day 456	456	≥411 [for serology and SARS-CoV-2 nAbs] 411 – 592 [for ADA assessment]
Day 729 (Follow-up)	729	≥593 [for ADA assessment]

Table 4: Analysis windows for serum sample for AZD7442 PK assessment, NLF sample for mucosal response

Arm A

Visit	Day Relative to First Dose	Visit Window (Study Day)
Day 3	3	2 – 6 [subset of 20 participants, PK and NLF assessment]
Day 11	11	7 – 19 [subset of 20 participants, PK and NLF assessment]
Day 29	29	20 – 60 [subset of 20 participants, PK and NLF assessment] 2 – 60 [otherwise]
Day 92	92	61 - 106
Day 121	121	107 - 152
Day 183	183	153 - 197
Day 212	212	198 - 242
Day 274	274	243 - 319
Day 365	365	320 - 410
Day 456	456	≥411

Arm B

Visit	Day Relative to First Dose	Visit Window (Study Day)
Day 1, Post-dose	1	1, > 1st IMP dose time
Day 3	3	2 – 6 [subset of 20 participants, PK and NLF assessment]

Visit	Day Relative to First Dose	Visit Window (Study Day)
Day 11	11	7 – 19 [subset of 20 participants, PK and NLF assessment]
Day 29	29	20 – 60 [subset of 20 participants, PK and NLF assessment] 2 – 60 [otherwise]
Day 92	92	61 - 137
Day 183	183	138 - 197
Day 212	212	198 - 242
Day 274	274	243 - 319
Day 365	365	320 - 410
Day 456	456	≥411

Table 5: Analysis windows for cardiac/thrombosis biomarkers

Visit	Day Relative to First Dose	Visit Window (Study Day)
Day 1	≤ 1	≤ 1
Day 29	29	2 - 60
Day 92	92	61 - 137
Day 183	183	138 - 228
Day 274	274	229 - 319
Day 365	365	320 - 410
Day 456	456	411 - 592
Day 729 (Follow-up)	729	≥593

Table 6: Analysis windows for clinical chemistry, hematology, coagulation, and urinalysis

Visit	Day Relative to First Dose	Visit Window (Study Day)
Day 1	≤ 1	≤ 1
Day 92	92	2 - 137
Day 183	183	138 - 228
Day 274	274	229 - 319
Day 365	365	320 - 410
Day 456	456	411 - 592
Day 729 (Follow-up)	729	≥593

Table 7: Analysis windows for Vital signs

Arm A

Visit	Day Relative to First Dose	Visit Window (Study Day)
Screening	<1	<1
Day 1, Pre-dose	1	1, ≤ 1st IMP dose time
Day 1, Post-dose	1	1, > 1st IMP dose time
Day 29	29	2 - 60
Day 92, Pre-dose	92	61 – 106, ≤ 2nd IMP dose time
Day 92, Post-dose	92	61 – 106, > 2nd IMP dose time
Day 121	121	107 - 151
Day 183, Pre-dose	183	152 – 197, ≤ 3rd IMP dose time
Day 183, Post-dose	183	152 – 197, > 3rd IMP dose time
Day 212	212	198 - 242
Day 274, Pre-dose	274	243 – 319, ≤ 4th IMP dose time
Day 274, Post-dose	274	243 – 319, > 4th IMP dose time
Day 365, Pre-dose	365	320 – 410, ≤ 5th IMP dose time
Day 365, Post-dose	365	320 – 410, > 5th IMP dose time
Day 456	456	411 - 592
Day 729 (Follow-up)	729	≥593

Arm B

Visit	Day Relative to First Dose	Visit Window (Study Day)
Screening	<1	<1
Day 1, Pre-dose	1	1, ≤ 1st IMP dose time
Day 1, During Dose, 15 mins	1	>1st IMP dose time - ≤ 22 minutes 30 seconds post 1st IMP dose time
Day 1, During Dose, 30 mins	1	>22 minutes 30 seconds post 1st IMP dose time - ≤ 37 minutes 30 seconds minutes post 1st IMP dose time
Day 1, During Dose, 45 mins	1	>37 minutes 30 seconds post 1st IMP dose time - ≤ 52 minutes 30 seconds post 1st IMP dose time
Day 1, During Dose, 60 mins	1	> 52 minutes 30 seconds post 1st IMP dose time - ≤ 67 minutes 30 seconds post 1st IMP dose time
Day 1, Post-dose	1	1, >67 minutes 30 seconds post 1st IMP dose time
Day 29	29	2 - 60
Day 92	92	61 - 137
Day 183, Pre-dose	183	138 – 197, ≤ 2nd IMP dose time
Day 183, Post-dose	183	138 – 197, > 2nd IMP dose time

Visit	Day Relative to First Dose	Visit Window (Study Day)
Day 212	212	198 - 242
Day 274	274	243 - 319
Day 365, Pre-dose	365	320 – 410, ≤ 3rd IMP dose time
Day 365, Post-dose	365	320 – 410, > 3rd IMP dose time
Day 456	456	411 - 592
Day 729 (Follow-up)	729	≥593

Table 8: Analysis windows for ECG

Arm A

Visit	Day Relative to First Dose	Visit Window (Study Day)
Screening	<1	<1
Day 1	1	1
Day 92	92	2 - 137
Day 183	183	138 - 228
Day 274	274	229 - 319
Day 365	365	320 - 410
Day 456	456	≥411

Arm B

Visit	Day Relative to First Dose	Visit Window (Study Day)
Screening	<1	<1
Day 1	1	1
Day 183	183	2 - 273
Day 365	365	274 - 410
Day 456	456	≥411

Table 9: Analysis windows for immunogenicity, PD, PK, coagulation, serum sample for exploratory assessments (Illness visit schedule)

Visit	Day Relative to Illness	Visit Window (Study Day)
Illness Day 1	≤ 1	≤ 1
Illness Day 14	14	≥2

Table 10: Analysis windows for COVID-19 symptom assessment, SARS-CoV-2 RT-PCR sequencing NP swab, and vital signs (for Confirmed Illness visit schedule)

Visit	Day Relative to Illness	Visit Window (Study Day)
Illness Day 1	≤ 1	≤ 1

Visit	Day Relative to Illness	Visit Window (Study Day)
Illness Day 5	5	2- 5
Illness Day 7	7	6 - 10
Illness Day 14	14	≥11 (for Vital signs) 11 – 20 (for Covid-19 symptoms)
Illness Day 28	28	21 – 58 (for Covid-19 symptoms)
Illness Day 90	90	≥59 (for Covid-19 symptoms)

For assessments occurring during the Illness Visit Schedule, windows are applied only to illness episodes with laboratory confirmed positive RT-PCR test results. One or more results for a particular human biological samples variable may be obtained in the same visit window. In such an event, the result with the date closest to the expected visit date will be used in the analysis. In the event that two observations are equidistant from the expected visit date, the later observation will be used in the analysis.

3.3.3 Handling of Unscheduled Visits

Unscheduled, retest (same visit number assigned), and early discontinuation measurements will contribute to the summaries. Visits for visit-based data will follow a windowing convention as described in Section 3.3.2. If there are multiple observations collected at the same date and time, unscheduled visit record will be considered last.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

3.3.4 Multiplicity/Multiple Comparisons

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

3.3.5 Handling of Protocol Deviations in Study Analysis

A detailed list of possible Important Protocol Deviations (IPDs), and the process for reviewing them by the Clinical Study Team is discussed in the most recent version of the IQVIA Protocol Deviation Management Plan (PDMP).

The following categories of protocol deviations will be reviewed by the medical and statistical team members prior to Clinical Database Lock:

- Deviations relating to informed consent and process, inclusion and exclusion criteria
- Participants who fail to completely or correctly have a required laboratory assessment performed

- Participants who experience deviations related to planned study procedures and safety
- Participants who receive concomitant use of restricted medications per CSP Section 6.5
- Participants who experience an investigational product deviation
- Deviations from the responsibility of the principal investigator
- Deviations relating to improper source documents and management of the documents
- Deviations relating to regulatory requirement
- Deviations relating to facilities/equipment

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivation, and analysis/data presentation by domain.

4.1 Study Population

The domain study population covers participant disposition, analysis sets, protocol deviations, demographics and baseline characteristics, disease characteristics, medical history, prior and concomitant medication, and study drug compliance.

4.1.1 Subject Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Treatment groups are reported based on randomized treatment. The Enrolled Participant Analysis Set as defined in Section 3.2 is used for reporting disposition and screening failures. Disposition information can be directly obtained from the eCRF.

4.1.1.2 Presentation

The disposition table of participants will include the number of participants with informed consent, and screen failure. Numbers and percentages will be presented by treatment and total for the following. Note: Percentages are based on total randomized participants.

- Randomized participants
- Participants randomized but not dosed
- Participants who completed the end of treatment visit
- Participants who discontinued early from treatment
    - Reason for discontinuing early from treatment

- Participants who completed the study
- Participant who discontinued early from study
    - Reason for discontinuing early from study

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

Analysis sets are defined in Section 3.2.

4.1.2.2 Presentation

Number of participants will be reported by treatment for Full Analysis Set (FAS), Safety Analysis Set, PK Analysis Set, NLF PK Analysis Set, ADA evaluable analysis set (separated by ADA of AZD8895, ADA of AZD1061, and ADA of AZD7442), and nAb evaluable analysis sets (Pseudovirus, Authentic virus). For each analysis set, number of participants excluded and number for each reason will be reported by treatment.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

Protocol deviations (IPDs) are identified in the most recent version of the protocol deviation management plan for the following categories:

- Deviations related to informed consent and process
- Deviations from inclusionary criteria
- Deviations from exclusionary criteria
- Deviations related to laboratory assessments
- Restricted medication taken per CSP Section 6.5
- Deviations related to study procedures
- Deviations impacting safety
- IMP deviations
- Deviations related to principal investigator responsibility
- Deviations to source documentation
- Deviations to regulatory compliance
- Deviations to facilities/equipment

4.1.3.2 Presentation

Number and percentage of participants with IPDs will be provided by treatment group and total for each category of protocol deviations. The summary will be based on the Safety Analysis Set.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Demographics are categorized as follows:

- Age group:
  - ≥ 12 to < 18 years, ≥ 18 to < 65 years, ≥ 65 to < 75 years, ≥ 75 to <80 years and ≥ 80 years.
- Sex: Male, Female
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islanders, White

4.1.4.2 Presentation

The summary of demographics characteristics will be provided for the Safety Analysis Set, summarized by actual treatment groups. Other analysis sets will be summarized if deemed necessary.

Demographics will be summarized by treatment group and total using descriptive statistics for age and number and percentage of participants for age group, sex, race, and ethnicity.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Baseline characteristics include the following:

- Weight (kg)
- Height (cm)
- Body Mass Index (BMI) (kg/m^2) = weight (kg)/ [height $(m)^2$] as a continuous variable
- BMI as a categorical variable (<25, 25 - <30, 30 - <35, ≥35)
- Smoking History (Current, Former, Never); average pack-year for Current/Former smokers
- Screening result from NP swab for SARS-CoV-2 RT-PCR (Positive, Negative)

- Previous COVID-19 vaccination status (Vaccinated [within 3 months prior to first IMP dose], Not Vaccinated [or latest vaccination more than 3 months prior to first IMP dose])

- Time since previous COVID-19 vaccination (days) calculated as (Date of first IMP Dose) - (Date of latest COVID-19 vaccination prior to first IMP dose) + 1

Partial dates for latest COVID-19 vaccination prior to first IMP dose will be imputed as follows:

- If year and month are available and day is missing, then impute at the last day for the respective month. If this results in a date that is after first IMP dose, then set to the day prior to first IMP dose.

- If year is available and month and day are missing, then impute as missing. In this case, previous COVID-19 vaccination status and time since previous COVID-19 vaccination (days) will also be missing.

4.1.5.2 Presentation

Baseline characteristics will be summarized with demographics, as specified in Section 4.1.4.2.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

Disease characteristics include the following at baseline:

- Active treatment for solid tumor and hematologic malignancies (Yes/No);
- Receipt of solid-organ transplant and taking immunosuppressive therapy (Yes/No);
- Receipt of chimeric antigen receptor T-cell or hematopoietic stem cell transplant; moderate or severe primary immunodeficiency (Yes/No);
- Moderate or severe primary immunodeficiency (Yes/No);
- Advanced or untreated HIV infection (Yes/No);
- Active treatment with systemic high-dose corticosteroids, alkylating agents, antimetabolites, tumor necrosis factor blockers and other biologic agents that are immunosuppressive or immunomodulatory (Yes/No);
- Serum for SARS-CoV-2 Serology (Positive, Negative);
- Other (Yes/No)

4.1.6.2 Presentation

Disease characteristics will be summarized by treatment group and total using descriptive statistics for continuous variables and number and percentage of participants for categorical variables.

Summary of disease characteristics will be provided for the Safety Analysis Set, presented with actual treatment groups.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical/surgical history and concomitant disease will be coded using Medical Dictionary for Regulatory Activities (MedDRA) 26.0 or higher.

Medical/surgical history are defined as any medical or surgical or condition/disease that started and stopped before the first dose of IMP. Concomitant diseases are defined as any medical condition/disease that started before the first dose of IMP and were ongoing at the time of the dose of IMP or ended on date of dose.

4.1.7.2 Presentation

Medical and surgical history and concomitant disease will be summarized by System Organ Class (SOC) and Preferred Term (PT) by actual treatment groups and total for participants in the Safety Analysis Set.

A participant having more than one condition/disease within the same SOC or PT will be counted only once for that SOC or PT.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

All medications will be coded using the World Health Organization (WHO) Drug Global dictionary, version B3 March 2023 or a more recent version.

A medication will be regarded as prior if it was stopped prior to the first dose of IMP. A medication will be regarded as concomitant if the start date is on or after the date of the first dose of IMP, or if it started on or prior to the first dose of IMP and ongoing after the dose of IMP.

The handling of partial/missing dates is detailed in Appendix A 1.

4.1.8.2 Presentation

Prior and concomitant medications will be summarized by Anatomical Therapeutic Class (ATC) Level 4 and preferred drug name by treatment and total based on the Safety Analysis

Set. A participant having more than one medication within the same ATC Level 4 or preferred drug name will be counted only once for that ATC Level 4 or preferred drug name.

4.1.9 Study Drug Compliance

4.1.9.1 Definitions and Derivations

Treatment compliance will be calculated as follows:

Treatment compliance (%) = (Total number of actual dosing occasions/total number of expected dosing occasions) x *100%*

Treatment compliance is categorized as: ≤ 80%, > 80% to ≤ 100%, > 100% to ≤ 120%, > 120%.

In order to allow for participants who discontinue IMP early in the compliance calculation, the number of expected dosing occasions will be calculated as the number of scheduled dosing visits up to and including the last available dosing visit for that participant.

4.1.9.2 Presentation

Treatment compliance, and total number of dosing occasions will be summarized by treatment group, using descriptive statistics for participants in the Safety Analysis Set. Additionally, the categorical summary of treatment compliance defined in Section 4.1.9.1 will be shown.

4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary, secondary, other endpoints.

Statistical category	Endpoint	Population	Intercur-rent event strategy	Population level summary (analysis)	Details in section
Objective 1: To evaluate the safety, and tolerability of AZD7442 in adult and pediatric participant ≥ 12 years of age.					
Primary	Incidence and exposure adjusted incidence of AEs, SAEs, and AESIs	Safety analysis set	N/A	Descriptive	Section 4.3.2
Objective 2: To evaluate the immunogenicity of AZD7442 in adult and pediatric participant ≥ 12 years of age.					
Primary	Incidence of ADA to AZD7442	ADA evaluable analysis set	N/A	Descriptive	Section 4.2.1
Objective 3: To evaluate the PK of AZD7442 in adult and pediatric participant ≥ 12 years of age.					

Secondary	Serum AZD7442 (tixagevimab and cilgavimab) concentrations PK parameters	PK analysis set	N/A	Descriptive	Section 4.2.24.2.1
Objective 4: To determine anti-SARS-CoV-2 nAb levels in serum after administration of AZD7442 in adult and pediatric participant ≥ 12 years of age.					
Secondary	Changes from baseline in GMTs and GMFRs values in SARS-CoV-2 nAbs (wild-type assay or pseudo neutralization assay)	nAb evaluable analysis sets	N/A	Descriptive	Section 4.2.2
Objective 5: Exploratory – See Section 4.2.3					

4.2.1 Primary Endpoints – Immunogenicity

This section describes immunogenicity derivations and analyses. The definitions, and presentation of adverse events are given in Section 4.3.2.

4.2.1.1 Definition

ADA assessments of serum samples will be conducted utilizing a tiered approach (screen, confirm, titer), and ADA data will be collected at scheduled visits shown in Protocol Section 1.3. ADA results from each sample will be reported as either positive or negative. If the sample is positive, the ADA titer will be reported as well. In addition, the presence of neutralizing ADA may be tested for all ADA-positive samples. The neutralizing ADA results will be reported as positive or negative. A participant is defined as being ADA-positive if the participant is ADA evaluable and a positive ADA result is available at any time, including baseline and all post-baseline measurements; otherwise, the participant is defined as ADA negative.

4.2.1.2 Derivations

The number and percentage of ADA-evaluable participants in the following ADA categories in each treatment group will be determined. The number of ADA-evaluable participants in the treatment group will be used as the denominator for percentage calculation. Note that, ADA responses will be summarized for AZD8895, AZD1061, and AZD7442 separately.

- ADA positive at any visit (at baseline and/or post-baseline). AZD7442 is ADA positive if either AZD8895 or AZD1061 is ADA positive. The percentage of these participants in a population is known as ADA prevalence.
- Treatment-induced ADA positive (ADA negative at baseline and ADA positive at ≥1 post-baseline assessment with ADA titer ≥ 2 × MRD [minimum required dilution]). In a situation that one of the components AZD8895 and AZD1061 is treatment-induced ADA positive, and the other component is treatment-boosted

ADA positive (as defined below), AZD7442 will be counted in the worst case (i.e., treatment-induced ADA positive).

- Treatment-boosted ADA positive (baseline ADA titer that was boosted by ≥4-fold following drug administration). AZD7442 is treatment-boosted ADA positive if either AZD8895 or AZD1061 is treatment-boosted ADA positive, except in the situation described in the treatment-induced bullet above.
- Treatment-emergent ADA positive (either treatment-induced ADA positive or treatment-boosted ADA positive). The percentage of these participants in a population is known as ADA incidence.
- ADA positive post-baseline and positive at baseline.
- ADA positive at baseline and not detected post-baseline.
- Treatment-emergent ADA (TE-ADA) persistently positive for AZD8895 and AZD1061, is defined as treatment-emergent ADA positive participants having at least 2 post-baseline ADA positive measurements with titer ≥ 2 × MRD at least 16 weeks (112 days) between the first and last positive measurement, or an ADA positive result at the last available assessment. AZD7442 is persistently positive if one of AZD8895 and AZD1061 is persistently positive.
- Treatment-emergent ADA (TE-ADA) transiently positive for AZD8895 and AZD1061, is defined as treatment-emergent ADA positive participants having at least one post-baseline ADA positive measurement with titer ≥ 2 × MRD and not fulfilling the conditions for TE-ADA persistently positive. AZD7442 is transiently positive if the participant is treatment-emergent ADA positive, but neither AZD8895 nor AZD1061 is not fulfilling persistently positive ADA response.
- Non-treatment emergent ADA positive, defined as participants being ADA positive and not fulfilling the conditions for TE-ADA positive.

In addition, the following ADA category may be summarized.

- Neutralizing ADA (to AZD8895, AZD1061, or AZD7442) positive at any time.

4.2.1.3 Primary Analysis of ADA

A summary of the number and percentage of participants who developed detectable ADA to AZD7442 (ADA results to AZD8895 and AZD1061 will be reported separately) by ADA categories (Section 4.2.1.2) in different treatment arms will be presented based on the ADA evaluable analysis set. ADA assessments collected post-dose on the days of IMP administration will be excluded. In addition, descriptive statistics of the maximum titer will

be presented by ADA category. ADA results and titers will be summarized by visit and treatment group.

ADA results will be listed for all participants in the Safety Analysis Set regardless of ADA-evaluable status. ADA titer will be presented, and neutralizing ADA data may be presented for samples confirmed positive for the presence of ADA to AZD7442. AEs in ADA positive participants by ADA positive category will be listed.

The effect of ADA on PK, and safety will be examined by descriptive summaries, if data allow. Descriptive summaries of PK concentration on participants in both the ADA evaluable analysis set and PK analysis set, number of participants having AEs in different categories, and number of participants with AEs by System Organ Class (SOC) and preferred term (PT) will be provided by ADA response: Treatment-emergent ADA positive, non-treatment emergent ADA positive, and ADA negative, and by treatment groups.

4.2.1.4 Sensitivity Analyses of the Primary Endpoint

No sensitivity analysis will be formed for primary endpoint.

4.2.1.5 Supplementary Analyses of the Primary Endpoint

No supplementary analysis will be formed for primary endpoint.

4.2.1.6 Subgroup Analyses

No subgroup analyses will be formed for primary endpoint.

4.2.2 Secondary Endpoints

4.2.2.1 Pharmacokinetic Data

4.2.2.1.1 Definition

Serum samples will be collected for measurement of serum concentrations of AZD8895 and AZD1061 at scheduled visits as per Protocol Section 1.3. Serum concentrations of AZD7442 is calculated as the sum of AZD8895 and AZD1061. For a subset of 20 participants, samples will be additionally collected at Day 3 and Day 11. Analysis of relevant PK parameters may be performed by the Sponsor and reported in a separate report. Three observations > LLOQ are required as a minimum for a PK parameter to be summarized.

4.2.2.2 SARS-CoV-2 Neutralizing Antibodies

4.2.2.2.1 Definition

Titer and fold ratio in SARS-CoV-2 nAbs will be collected and calculated for each arm and will be summarized at each scheduled visit as per Protocol Section 1.3.

4.2.2.2.2 Derivations

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

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

For each treatment group the correlation and 95% confidence interval between log2 transformed titers and log2 transformed serum concentration will be bootstrapped using the mixed model approach proposed by Hamlett, Ryan and Wolfinger (2004).

```
proc mixed data=<data> method=ml covtest asycov asycorr;
   class <subject> <visit> <response identifier>;
   model <response> = <response identifier>/ solution
   ddfm=kr;
   random <response identifier>/ type=un subject=<subject> v
   vcorr;
   repeated <response identifier>/ type=un
   subject=<visit>(<subject>);
run;
```

The above mixed model will be fitted separately to each treatment group, where response identifier is a classifier variable for either the log2 transformed titers or log2 transformed serum concentrations, and response is the respective value for this variable. Two random effect terms are defined for the two levels of the response classifier for each participant. The repeated statement defines the covariance structure for the residuals for visits nested within participant for each level of the response classifier. Both are given an unstructured covariance.

Data is resampled with replacement 10,000 times at the participant level with equal probability fixing the number of participants in each resample to that of the original dataset. Each duplicate participant selected will be treated as a separate individual. The mixed model is fitted to each sample i and the correlation between log2 titer and log2 serum concentration is calculated based on converged models as

$$\widehat{\rho_i} = \frac{Cov_{subject}(2,1)_i + Cov_{visit(subject)}(2,1)_i}{\sqrt{\left(\left(Cov_{subject}(1,1)_i + Cov_{visit(subject)}(1,1)_i\right) \times \left(Cov_{subject}(2,2)_i + Cov_{visit(subject)}(2,2)_i\right)\right)}},$$

where Cov represents the covariance term at participant level (subject) and visit nested within participant [visit(subject)]. The same correlation estimate, $\hat{\rho}$ will be fit to the full data (i.e. not resampling) and the mean bias adjusted factor will be derived as

$$\hat{b} = \frac{\sum_{i=1}^{n}(\hat{\rho}_i - \hat{\rho})}{n},$$

where n is the number of converged models. The median, 2.5th and 97.5th percentiles will be taken over $\hat{\rho}_i - \hat{b}$ to give the bias-adjusted bootstrapped correlation coefficient and 95% CI. Convergence (%) will be defined as percentage of converged models with respect to the number of bootstraps run. This correlation analysis is based on paired quantifiable records from both PK and nAb samples (on the same sample collection date). Samples from illness visits or samples having values <LLOQ are also to be excluded.

4.2.2.3 Handling of Dropouts and Missing Data

PK and PD analyses will be based on participants with data available. However, the following imputation methods will be used for descriptive analyses of PK and PD, respectively.

Pharmacokinetics data

Individual concentrations below the LLOQ of the bioanalytical assay will be reported as Not Quantifiable (NQ) in the listings with the LLOQ defined in the footnotes of the relevant tables, figures, and listings (TFLs). Serum concentrations that are NQ or not reported (NR) will be handled as follows for the provision of descriptive statistics:

- Any values reported as NR 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 mean, SD, geometric mean, gSD and geometric coefficient of variation (gCV%) will be set to Not Computed (NC). 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 mean, minimum, median, and maximum will be reported as NQ and the gCV% and geometric mean and gSD as NC.
- The number of values below LLOQ (n < LLOQ) will be reported for each time point together with the total number of collected values (n).

- If only two observations are > LLOQ then the minimum and maximum are presented with the other summary statistics as NC.

SARS-CoV-2 Neutralizing Antibodies

The analysis of neutralizing antibody GMT and GMFR 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.

4.2.2.4 Primary Analysis of Secondary Endpoints

4.2.2.4.1 Pharmacokinetics Data

PK analysis will be based on actual treatment in the PK Analysis Set.

If a participant has any protocol deviation which is identified as a record-level exclusion for the PK analysis in Table 5 of the most recent version of the PDMP, then the PK samples of both compounds collected after the date of deviation and the corresponding derived total concentrations for AZD7442 will be excluded from the analyses.

Due to the change in dosing schedules between CSP V3.0 (dated 09 December 2022) and CSP V4.0 (dated 06 June 2023), there may be visits with a mixture of participants who received and participants who did not receive IMP in previous visit. Therefore, any PK samples from participants who did not receive IMP according to the SoA of CSP V3.0, irrespective of the visit date being before or after the effective date of CSP V4.0 implementation, will be excluded from analyses at all subsequent visits.

PK assessments scheduled for collection pre-dose, but instead collected post-dose at a visit where dosing is done, will be excluded from the analyses. Similarly, PK assessments scheduled for collection post-dose, but collected pre-dose will also be excluded from the analyses.

Individual AZD7442 (AZD8895 and AZD1061) serum concentrations data will be listed and tabulated by mAb component, along with descriptive statistics for the PK analysis set for each treatment group.

Figures of serum concentrations by mAb component and treatment group will also be presented. The figures will include the subset of 20 participants with additional PK measurements.

Potential correlation between PK exposure and safety response may optionally be explored. PK analysis may be performed by the Sponsor and reported in a separate report. The analysis is not covered in this SAP.

4.2.2.4.2 SARS-CoV-2 Neutralizing Antibodies

SARS-CoV-2 nAb analysis will be based on actual treatment in nAb Evaluable Analysis Set. Two (2) assays will be used to provide titers for authentic virus and pseudovirus nAb.

If a participant has any protocol deviation which is identified as a record-level exclusion for the immunogenicity analysis in Table 5 of the most recent version of the PDMP, then their SARS-CoV-2 nAb samples collected after the date of deviation will be excluded from the analyses.

Due to the change in dosing schedules between CSP V3.0 (dated 09 December 2022) and CSP V4.0 (dated 06 June 2023), there may be visits with a mixture of participants who received and participants who did not receive IMP in previous visit. Therefore, any SARS-CoV-2 nAb samples from participants who did not receive IMP according to the SoA of CSP V3.0, irrespective of the visit date being before or after the effective date of CSP V4.0, will be excluded from analyses at all subsequent visits.

SARS-CoV-2 nAb assessments scheduled for collection pre-dose, but instead collected post-dose at a visit where dosing is done, will be excluded from the analyses.

For participants who receive a COVID-19 vaccine after the first dose of IMP, data collected after receipt of the vaccine will also be excluded. Furthermore, for participant who receive a positive SARS-CoV-2 RT-PCR (defined in Section 4.2.3.4.1), data collected after infection will also be excluded, except in the case that SARS-CoV-2 nAb samples were collected during an illness visit.

Descriptive statistics for titer and fold rise will include number of participants, geometric mean, geometric standard deviation (gSD), 95% confidence interval (CI), minimum and maximum. This will be reported separately for nAbs collected during treatment period and illness visits (the illness visits where the series corresponds to positive RT-PCR test, as defined in Section 4.2.3.4.1, will be used in the summary).

A scatter plot of log2 transformed titers with log2 transformed serum concentration for each treatment arm, along with the bias-adjusted bootstrapped correlation coefficient, 95% CI and convergence (%) (see Section 4.2.2.2.1).

Summaries will also be split by the previous COVID-19 vaccination status (as defined in Section 4.1.5.1). Samples from 2 separate assays will be analysed using the same methods as described here.

4.2.2.5 Sensitivity Analyses of the Secondary Endpoint

No sensitivity analyses will be performed for secondary endpoints (PK and PD).

4.2.2.6 Subgroup Analyses

No subgroup analyses will be performed for secondary endpoints (PK and PD).

4.2.3 Other Endpoints – Exploratory

4.2.3.1 Definition

The exploratory endpoints are:

- SARS-CoV-2 RT-PCR-positive symptomatic illness (including COVID-19 hospitalization or death)
- Post-treatment response for SARS-CoV-2 nucleocapsid antibodies
- SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness, defined for SARS-CoV-2 RT-PCR-positive symptomatic illness and met the severe criteria, and COVID-19 deaths
- PK of AZD7442 in Nasal Fluid (NLF)

Similar to serum PK samples, NLF samples will be collected following the same schedule as for the serum samples. NLF raw concentrations of AZD7442 is calculated as the sum of raw NLF concentrations for AZD8895 and AZD1061. For a subset of 20 participants, samples will be additionally collected at Day 3 and Day 11. Adjusted (by ratio of serum and NLF urea) NLF concentrations as well as ratio of serum PK concentration and NLF PK concentration (i.e., Serum:NLF partition ratio) will be calculated using the following formula:

*Adjusted NLF concentration = Raw NLF concentration [ng/mL] * (1000*Serum Urea[mmol/L])/(NLF Urea [umol/L])*

Serum:NLF Partition Ratio (%) =100%(0.001* Adjusted NLF concentration[ng/mL])/(Serum concentration[ug/mL])*

When Raw NLF concentration <LLOQ for either AZD8895 or AZD1061, replace it with LLOQ for the calculation.

4.2.3.2 Derivations

Categorical and continuous endpoints are shown in Section 4.2.3.1.

4.2.3.3 Handling of Dropouts and Missing Data

Unless otherwise specified, missing data will not be imputed. NLF PK analyses will be based on participants with data available. However, the following imputation methods will be used for descriptive analyses of NLF PK.

NLF PK data

Individual concentrations that are <LLOQ will be reported as <LLOQ in the listings for AZD8895 and AZD1061. Value of LLOQ will be used for both raw and adjusted AZD8895 and AZD1061 concentrations in summaries of AZD8895 and AZD1061 concentrations. AZD7442 concentration is sum of AZD8895 and AZD1061 concentrations, calculated after setting <LLOQ to LLOQ. Adjusted AZD7442 concentration is same as raw AZD7442 concentration in such cases.

4.2.3.4 Analysis of Exploratory Endpoints

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

The incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness will be summarized with descriptive statistics in the FAS at the final data readout only. The number and percentage of participants who have the events will be provided overall and before Day 183, or Day 365.

Participants will be included as an event if they have RT-PCR-confirmed SARS-CoV-2 prior to Day 183, or Day 365, after first IMP dose and present with at least one of the qualifying symptoms as defined in the CSP. A positive SARS-CoV-2 RT-PCR will be defined based on the central laboratory result whenever both central and local laboratory results are available for NP swabs, or if only a central lab NP swab result is available. If only a local NP swab laboratory result is available, then the local laboratory result will be used. If no SARS-CoV-2 RT-PCR results are available, the participant will be considered as not having a RT-PCR-positive symptomatic event. Data from the eCRF will be used to determine if the participant met the qualifying symptoms. If a participant's first case of SARS-CoV-2 RT-PCR positive symptomatic illness occurs on or after Day 183, or Day 365, the participant will be considered as not having an event, respectively. Death due to COVID-19 or hospitalization due to COVID-19 can contribute to this endpoint when a qualifying symptom assessment is not observed.

- For participants with an event after first IMP dose, before Day 183, or Day 365, the date of event will be defined as the earliest symptom onset date from those which triggered an illness visit, where COVID-19 was confirmed with a positive SARS-CoV-2 RT-PCR laboratory test. In the case of death due to COVID-19 or hospitalization due to COVID-19, the date of event is the earliest date of death/date of hospital admission when a qualifying symptom is not observed.

If any of the following censoring reasons are met, the censoring date will be defined as follows:

- Participants who had SARS-CoV-2 RT-PCR positive test prior to first IMP dose will be censored at date of first IMP dose.
- Participants who receive a COVID-19 vaccination after first IMP dose, and prior to having an event before Day 183, or Day 365 will be censored at the date of vaccination.
- Participants who have a protocol deviation for receiving restricted medication after first IMP dose, and prior to having an event before Day 183, or Day 365 will be censored at the date of the deviation.
- Participants who have a record-level exclusionary protocol deviation for PK samples (see Table 5 in most recent version of PDMP) after first IMP dose, and prior to having an event before Day 183, or Day 365 will be censored at the date of the deviation.
- Participants who discontinue early from the study after first IMP dose, and prior to having an event before Day 183, or Day 365 will be censored at date of end of study or date of last assessment, whichever is later. For participants who continue to participate in the study at the time of the analysis, the data cut off (DCO) date will be used as their last assessment date. For participants with no post-baseline visit data available, the date of the first IMP administration will be used i.e., follow-up will be 1 day.

The follow up time will be calculated as the minimum of the date of censoring, date of event, and date of Day 183 or Day 365 – date of first IMP dose + 1. When the minimum of the date of censoring and date of Day 183 or Day 365 is prior to date of event, then participants will be censored at their defined end of follow up time. Otherwise, participants will be identified as having an event at this time.

Time to the first SARS-CoV-2 RT-PCR-positive symptomatic illness episode will be analyzed using Kaplan-Meier (KM) method and quartiles will be presented. Proportion of participants who experience event, participants who are censored, breakdown of events, and reasons for censoring will be presented by treatment group at Day 183 or Day 365. KM plot will also be generated by treatment groups.

A listing will be provided for all COVID-19 symptom assessments and NP swabs assessed by RT-PCR (both local laboratory and central laboratory samples) regardless of RT-PCR result.

4.2.3.4.2 Post-treatment Response for SARS-CoV-2 Nucleocapsid Antibodies

The incidence of participants who have a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies will be summarized using FAS by treatment group overall and before Day 183, or Day 365 at the final data readout only. Same censoring criteria as described in Section 4.2.3.4.1 will be applied.

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

The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness and COVID-19 deaths will be summarized using FAS at the final data readout only. The number and percentage of participants who have the events will be provided overall and before Day 183, or Day 365. Same censoring criteria as described in Section 4.2.3.4.1 will be applied. SARS-CoV-2 RT-PCR-positive symptomatic illness Kaplan-Meier estimates, similar to Section 4.2.3.4.1, may be produced if the data allow.

4.2.3.4.4 PK of AZD7442 in Nasal Fluid

NLF PK analysis will be based on actual treatment in the NLF PK Analysis Set. Same record exclusion criteria as explained in previous section 4.2.2.4.1 will be applied.

Individual AZD7442 (AZD8895 and AZD1061) adjusted NLF concentrations data and serum to NLF partition ratio will be listed and tabulated by mAb component, along with descriptive statistics for the NLF PK analysis set for each treatment group.

Figures of adjusted NLF concentrations and serum to NLF partition ratio by mAb component and treatment group will also be presented. The figures will include the subset of 20 participants with additional NLF PK measurements.

4.2.3.4.5 Viral Genome Copies in NP Swabs (Illness Visits Only)

Observed and change from baseline for Illness Visits (as defined in Section 3.3.1) in viral load will be summarized by planned treatment group and time points for the Illness Visits in the FAS and may be reported outside of the Clinical Study Report (CSR). For values reported as lower than LLOQ, a value equal to half of the limit of quantification will be imputed in viral quantitation summaries. Missing values will not be imputed in viral quantitation summaries.

A listing will be provided for all viral genomes copy data, regardless of RT-PCR result. Indicators will be included in listings of illness visits to distinguish those with positive RT-PCR results from those with negative RT-PCR results.

4.2.3.4.6 Genotypic Analysis and Biochemical and/or Susceptibility Analysis of SARS-CoV-2 Variants to AZD7442 (Illness Visits Only)

An exploratory efficacy endpoint is the genotypic analysis and biochemical and/or susceptibility analysis of SARS-CoV-2 from NP swabs collected at Illness Visit baseline.

The genotypic analysis of the SARS-CoV-2 variants observed in illness NP swabs participants during illness visits will be evaluated using a qualified NGS sequencing assay, performed by Monogram Biosciences (South San Francisco, CA). The number and percentages of participants for each treatment group by Day 183 and by Day 365 will be summarized for the following items:

- Detected SARS-CoV-2 spike-based lineages
- SARS-CoV-2 spike-based lineages detected at illness (>=25% sensitivity) at the time of the first SARS-CoV-2 RT-PCR-positive symptomatic illness
- SARS-CoV-2 spike co-occurring substitutions detected at illness (>=3% and <25% sensitivity) at the time of the first SARS-CoV-2 RT-PCR-positive symptomatic illness
- SARS-CoV-2 spike co-occurring substitutions detected at illness (>=25% sensitivity) at the time of the first SARS-CoV-2 RT-PCR-positive symptomatic illness
- SARS-CoV-2 spike “individual” substitutions detected at illness (>=3% and <25% sensitivity) at the time of the first SARS-CoV-2 RT-PCR-positive symptomatic illness
- SARS-CoV-2 spike “individual” substitutions detected at illness (>=25% sensitivity) at the time of the first SARS-CoV-2 RT-PCR-positive symptomatic illness

In addition, SARS-CoV-2 variants data will be listed together with the first SARS-CoV-2 RT-PCR-positive symptomatic and PK concentrations.

Susceptibility results for the SARS-CoV-2 variants identified by the genotypic analysis may not be part of the tables and may not be included in the final CSR.

4.2.3.4.7 Biomarkers of AZD7442

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

4.2.3.5 Additional Analyses of Exploratory Endpoints

No sensitivity analysis will be performed for the exploratory endpoints.

4.2.3.6 Subgroup Analyses

No subgroup analysis will be performed for the exploratory efficacy endpoints.

4.3 Safety Analyses

The domain safety covers exposure, adverse events, clinical laboratory, vital signs, ECG, and physical examination. Tables are provided for the safety set; listings are provided for the safety set depending on the availability of data.

4.3.1 Exposure

4.3.1.1 Definitions and Derivations

Exposure to IMP is defined as the number of days between the date of first dose of IMP and the date of last dose of IMP inclusive, that is:

Exposure (days) = Date of last dose of IMP - date of first dose of IMP + 1

This calculation does not consider any gaps in exposure caused by the participant missing one or more intermediate scheduled doses. Such cases will be identified in the CSR if they occur but will not explicitly be accounted for in any analysis.

4.3.1.2 Presentation

The exposure information including number of dose(s) and exposure (days) will be summarized by treatment for the Safety Analysis Set.

A listing of exposure will be provided at the time of the final analysis.

4.3.2 Adverse Events

4.3.2.1 Definitions and Derivations

All Adverse events (AEs) will be coded using the MedDRA dictionary, version 25.0 or higher.

The safety of AZD7442 will be assessed by:

- Incidence of AEs
- Incidence of Serious Adverse Events (SAEs)
- Incidence of adverse events of special interest (AESIs)

AEs and SAEs

AEs will be recorded from the time of the first IMP administration throughout the study up to and including the last visit. SAEs are those events recorded as "Serious" on the AE page of the eCRF. SAEs will be recorded from the time of signing the informed consent form. The definition of AEs and SAEs can be found in Protocol Appendix B.

Listings of AEs and SAEs will be provided. Events prior to the first dose of IMP will only be presented in the listings. For events with partial dates, if the known part of the date indicates that the event stopped before the first dose of IMP, it will be considered as an event prior to the first dose of IMP. Otherwise, it will be considered as an event post first dose of IMP.

AESIs

AESIs are events of scientific and medical interest, specific to the further understanding of the IMP safety profile, and require close monitoring and rapid communication by the investigators to the Sponsor. An AESI can be serious or non-serious. All AESIs will be recorded in the eCRF. AESIs for AZD7442 include the following:

- Anaphylaxis and other serious hypersensitivity reactions, including confirmed diagnosis of immune complex disease
- Injection site reactions (IM administration) and infusion-related reactions (IV administration)
- Cardiovascular and thromboembolic events
- Multisystem inflammatory syndrome – pediatric participants

Deaths

If any participants die during the study as recorded on the "Death Details" page of the eCRF, the number and percentage of participants with death related to COVID-19 and those with other deaths will be summarized by actual treatment group based on the Safety Analysis Set.

Severity

Summary of AEs and SAEs post the first dose of IMP will be broken down further by maximum severity. Severity, adapted from the CTCAE v5.0 (see Appendix A 2), will be classified as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening or disabling), and Grade 5 (death) by using grading for AEs. Severity for AEs will be collected on "Adverse Events" form of eCRF. Should a participant experience multiple events within a SOC or PT, only the participant's worst severity grade will be counted for that SOC or PT.

Relationship to IMP/Study Procedure

Relationship to IMP/ study procedure, as indicated by the Investigator, will be classified as not related or related. Should a participant experience multiple events within a SOC or PT, the participant will be counted as related for that SOC or PT if the event is related to either IMP or study procedure.

Exposure adjusted rate

Exposure adjusted rate is calculated as number of participants with AEs in categories divided by total participant-year follow-up for each treatment group. Participant years is determined by summing the total number of follow-up days of each participant, and then dividing by 365.25. The exposure period is calculated from time of first dose to end of study, or the current data cut-off, whichever is earlier.

4.3.2.2 Presentation

AEs will be presented for actual treatment for the Safety Analysis Set in categories as below.

- AEs
- SAEs
- AEs with outcome death
- AEs leading to IMP discontinuation
- AEs leading to study discontinuation
- AESIs
- Related AEs
- Related SAEs
- Related AESIs
- Grade 3 or higher AEs
- Grade 3 or higher AESIs
- Related Grade 3 or higher AEs
- Related Grade 3 or higher AESIs

Summaries will include the number and percentage of participants reporting at least one event, and exposure adjusted rates, where appropriate.

An overview table of AEs will be presented for actual treatment, including the number and percentage of participants for each category.

Moreover, each category will be presented by SOC and PT. Specifically, for AESI summaries these will be presented by the AESI category and PT. For Grade 3 or higher summaries, a breakdown of participants with grades ≥3, 3, 4 and 5 will be presented for each PT (taking the worst grading if a participant experiences multiple events within a PT). Should a participant experience multiple events within a category, the participant will be counted only once for that category.

Summaries of the most common AEs (occurring in >1%, and >5% of participants in any treatment group) will be presented by PT. SAEs causing discontinuation of the study treatment and SAEs causing discontinuation from the study will also be summarized by PT.

AEs will be summarized by maximum intensity. If a participant 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, severe, potentially life-threatening, and fatal).

In addition, participants with adjudicated cardiovascular events will be summarized by the following categories and overall:

- Cardiac ischemia
- Cardiovascular death
- Heart failure
- Stroke
- Thrombotic Event

Summary statistics will be presented for time to onset for adjudicated cardiovascular events, calculated as (Date of Onset) – (Date of first IMP Dose) + 1. Date of Onset is defined as the start date of the adverse event or laboratory assessment that leads to adjudication.

The number and percentage of participants assessed for adjudication will be presented with categories for confirmed and unconfirmed.

Serious adverse events with a preferred term identified by the standardized MedDRA query (SMQ) for embolic and thrombotic events (Appendix A 4) will be summarized by SOC and PT. Furthermore, a separate summary of serious adverse events for those identified by the same SMQ or with SOC of cardiac disorders will be presented by SOC and PT.

4.3.3 Clinical Laboratory, Blood Sample and Urinalysis

4.3.3.1 Definitions and Derivations

Hematology, serum clinical chemistry, coagulation, cardiac biomarker, and urinalysis will be performed as per the schedule of events (refer to Protocol Sections 1.3 and 8.2.4 for

schedule and lists of parameters). A urine pregnancy test will be performed at screening and per the schedule of events (refer to Protocol, Section 1.3). If urine tests positive or indeterminate, a serum test will be performed for confirmation.

Quantitative laboratory parameters reported as "< X", i.e. below the lower limit of quantification (BLQ) or "> X", i.e. above the ULOQ, 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.

Quantitative laboratory parameters will be compared with the relevant central laboratory normal ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory normal range.
- Normal: Within the laboratory normal range (upper and lower limit included).
- High: Above the upper limit of the laboratory normal range.

Quantitative laboratory parameters with available Common Terminology Criteria for Adverse Events (CTCAE) toxicity grades will be categorized as follows where higher grades representing a more severe toxicity (refer to Appendix A 2) for each parameter toxicity grade criteria):

- Grade 1 (i.e., mild);
- Grade 2 (i.e., moderate);
- Grade 3 (i.e., severe);
- Grade 4 (i.e., life-threatening);
- Grade 5 (i.e., death).

Although not defined in the CTCAE toxicity grading system, version 5, non-missing laboratory parameter results not meeting any of the 5 grades defined in the CTCAE toxicity grading system will be categorized as 'No Event' for the purpose of the shift from baseline summaries.

4.3.3.2 Presentations

The following summaries will be provided by actual treatment group for laboratory parameters:

- Observed and change from baseline in Standard International (SI) units by visit (for quantitative parameters).
- Observed and change from baseline for Illness Visits as defined in Section 3.3.1 (for coagulation parameters) in SI units by Illness Visit (the Illness Visits where the

series corresponds to positive RT-PCR test, as defined in Section 4.2.3.4.1, will be used in the summary).

- Number and percentage of participants in each laboratory parameter category by visit (for categorical parameters).
- Maximum post-baseline ALT/AST observed value categorized as < 3 x upper limit of normal (ULN), ≥ 3 to < 5 x ULN, ≥ 5 to < 10 x ULN or ≥ 10 ULN by maximum post-baseline total bilirubin (TBL) observed value categorized as < 2 x ULN or ≥ 2 x ULN.
- Heatmap of the maximum post-baseline observed value in ALT value by the maximum post-baseline observed value in TBL value, both expressed as multiple of ULN.
- Heatmap of the maximum post-baseline observed value in AST value by the maximum post-baseline observed value in TBL value, both expressed as multiple of ULN.
- A listing of participants with at least one observed value in ALT value ≥ 3 x ULN, AST value ≥ 3 x ULN or TBL value ≥ 2 x ULN will be provided.
- Listing of participants with at least one abnormal laboratory observed value outside the normal range criteria (refer to Section 4.3.3.1).

The following further summaries may be provided by actual treatment group for laboratory parameters:

- Shift from baseline to the worst post-baseline observed value according to the CTCAE toxicity grades (for quantitative parameters with available CTCAE toxicity grades; refer to Section 4.3.3.1).
- Shift from baseline to the maximum/minimum post-baseline observed value according to normal range criteria (for quantitative parameters without available CTCAE toxicity grades; refer to Section 4.3.3.1).

4.3.4 Vital Signs

4.3.4.1 Definitions and Derivations

Vital signs will be performed at time points specified in Protocol Section 1.3, including the following parameters:

- Systolic blood pressure (SBP) (mmHg)
- Diastolic blood pressure (DBP) (mmHg)
- Pulse rate (beats per minute [bpm])

- Body temperature (C)
- Respiratory rate (breaths/min)
- Oxygen saturation (%)

4.3.4.2 Presentations

For severity grades of abnormal Vital Signs refer to Appendix A 3.

The following summaries will be provided by actual treatment group for each vital sign parameter:

- Observed and change from baseline by visit
- Observed and change from baseline for Illness Visits (as defined in Section 3.3.1) by Illness Visit (the illness visits where the series corresponds to positive RT-PCR test, as defined in Section 4.2.3.4.1, will be used in the summary).
- Number and percentages of participants with at least one abnormal post-baseline observed value (refer to Appendix A 3)
    - Participants will be summarized by the worst severity observed.

All vital sign data will be listed. Indicators will be included for illness visits to distinguish those with positive RT-PCR results from those with negative RT-PCR results.

4.3.5 Electrocardiogram

4.3.5.1 Definitions and Derivations

The following ECG parameters will be measured for this study as per the schedule of events (see Protocol Section 1.3):

- PR interval (msec)
- QRS duration (msec)
- QT interval (msec)
- QTc interval (msec)
- QTcB interval (msec)
- QTcF interval (msec)
- RR interval (msec)
- ECG mean heart rate (beats/min)

The overall interpretation of the ECG results will be classified as normal, abnormal not clinically significant, or clinically significant abnormal by the investigator.

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

- Observed values for QTc, QTcF, and QTcB intervals will be classified as:
  - > 450
  - > 480
  - > 500 msec
- Change from baseline for QTc, QTcF, and QTcB intervals 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 QTc post-baseline observed value is 490 mmHg, then this participant will be reported once under QTc > 450 msec and once under QTc > 480 msec.

4.3.5.2 Presentations

The following summaries will be provided by actual treatment group for each ECG parameter:

- Number and percentages of participants with at least one markedly abnormal post-baseline observed value/change from baseline (for quantitative parameters; refer to Section 4.3.5.1)
- Listing of participants with at least one markedly abnormal observed value/change from baseline
- Shift from baseline in overall ECG interpretation to the worst post-baseline assessment; the hierarchy order of clinically significant abnormal, not clinically significant abnormal, and normal from worst abnormal to normal will be followed
- Listing of participants with at least one abnormal overall ECG interpretation, including the finding(s) for each participant

All individual measurements will be listed.

4.3.6 Other Safety Assessments

4.3.6.1 Physical Examination

Physical examinations (completed and targeted) will be conducted as per the schedule of events (refer to Protocol Section 1.3). Clinically significant abnormal findings at screening

will be recorded in the Medical History, while clinically significant abnormal findings following vaccination will be recorded as AEs.

5 INTERIM ANALYSIS

No interim analysis is planned for this study.

6 REFERENCES

NIH. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50. Published 2017. Accessed 10 February 2022.

FDA. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. Available from: https://www.fda.gov/media/73679/download Published September 2007.

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7 APPENDIX

A 1 Partial Date Conventions

Algorithm for Prior / Concomitant Medications

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

START DATE	STOP DATE	ACTION
	Missing, not ongoing	If medication stop date is missing, then it can never be assigned as prior only; If medication start date < date of first dose of IMP, assign as concomitant; If date of first dose of IMP ≤ medication start date, assign as concomitant.
Partial	Known or ongoing	If medication stop date < date of first dose of IMP, assign as prior; If (known components of medication start date show that medication started before date of first dose of IMP) and (medication stop date ≥ date of first dose of IMP), assign as concomitant; If known components of medication start date show that medication started on or after date of first dose of IMP, assign as concomitant.
	Partial	If known components of medication stop date show that medication stopped before date of first dose of IMP, assign as prior; If (known components of medication start date show that medication started before date of first dose of IMP) and (known components of medication stop date show that medication stopped on or after date of first dose of IMP), assign as concomitant; If known components of medication start date show that medication started on or after date of first dose of IMP, assign as concomitant.
	Missing, not ongoing	Cannot be assigned as prior only; If known components of medication start date show that medication started before study drug start date, assign as concomitant; If known components of medication start date show that medication started on or after date of first dose of IMP, assign as concomitant.
Missing	Known or ongoing	If medication stop date < date of first dose of IMP, assign as prior; If medication stop date ≥ date of first dose of IMP, assign as concomitant.
	Partial	If known components of medication stop date show that medication stopped before date of first dose of IMP, assign as prior; If known components of medication stop date show that medication stopped on or after date of first dose of IMP, assign as concomitant.
	Missing, not ongoing	Assign as concomitant.

A 2 CTCAE Toxicity Grade, Version 5.0

CTCAE Term	Laboratory test	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	Hemoglobin (g/dL)	<LLN - 10.0	<10.0 - 8.0	<8.0	-
Eosinophilia[2]	Absolute eosinophils	>ULN and >baseline	-	-	-
Leukocytosis	White blood cells (x 10E9/L)	-	-	>100	-
Cardiac troponin I increased	Troponin I (high sensitivity) ng/L	> 19.8 - <100 (males) >13.6 - <100 (females)	-	>= 100	-

CTCAE Term	Laboratory test	Grade 1	Grade 2	Grade 3	Grade 4
Activated partial thromboplastin (aPTT) time prolonged	aPTT (sec)	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN	-
Alanine aminotransferase (ALT) increased[1]	ALT (U/L)	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Alkaline phosphatase (ALP) increased[1]	ALP (U/L)	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Aspartate aminotransferase (AST) increased[1]	AST (U/L)	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if	>20.0 x ULN if baseline was normal; >20.0 x baseline if

CTCAE Term	Laboratory test	Grade 1	Grade 2	Grade 3	Grade 4
		baseline was abnormal	baseline was abnormal	baseline was abnormal	baseline was abnormal
Blood bilirubin increased[1]	Total bilirubin (µmol/L)	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Cholesterol high	Cholesterol (mmol/L)	>ULN - 7.75	>7.75 - 10.34	>10.34 - 12.92	>12.92
Creatine phosphokinase (CPK) increased	Creatine kinase (U/L)	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN
Creatinine increased[2]	Creatinine	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN

CTCAE Term	Laboratory test	Grade 1	Grade 2	Grade 3	Grade 4
Gamma glutamyl transferase (GGT) increased[1]	GGT (U/L)	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Hemoglobin increased	Hemoglobin (g/dL)	Increase from ULN in >0 - 2	Increase from ULN in >2 - 4	Increase from ULN in >4	-
International normalized ratio (INR) increased[3]	INR	>1.2 – 1.5	>1.5 – 2.5	>2.5	-
Lymphocyte count decreased	Absolute lymphocytes count (x 10E9/L)	<LLN – 0.8	<0.8 – 0.5	<0.5 – 0.2	<0.2
Lymphocyte count increased	Absolute lymphocytes count (x 10E9/L)	-	>4 – 20	>20	-
Neutrophil count decreased	Absolute neutrophils count (x 10E9/L)	<LLN – 1.5	<1.5 – 1.0	<1.0 – 0.5	<0.5

CTCAE Term	Laboratory test	Grade 1	Grade 2	Grade 3	Grade 4
Platelet count decreased	Platelet count (x10E9/L)	<LLN – 75.0	<75.0 – 50.0	<50.0 – 25.0	<25.0
White blood cell (WBC) decreased	WBC (x 10E9/L)	<LLN – 3.0	<3.0 – 2.0	<2.0 – 1.0	<1.0
Hypercalcemia[4]	Corrected serum calcium (mmol/L)	>ULN – 2.9	>2.9 – 3.1	>3.1 – 3.4	>3.4
Hyperkalemia	Potassium (mmol/L)	>ULN – 5.5	>5.5 – 6.0	>6.0 – 7.0	>7.0
Hypernatremia	Sodium (mmol/L)	>ULN - 150	>150 - 155	>155 - 160	>160
Hypoalbuminemia	Albumin (g/dL)	<LLN - 3	<3 - 2	<2	-
Hypocalcemia[4]	Corrected serum calcium (mmol/L)	<LLN - 2.0	<2.0 – 1.75	<1.75 – 1.5	<1.5

CTCAE Term	Laboratory test	Grade 1	Grade 2	Grade 3	Grade 4
Hypoglycemia	Glucose (mg/dL)	<LLN - 55	<55 - 40	<40 - 30	<30
Hypokalemia	Potassium (mmol/L)	_	<LLN - 3.0	<3.0 - 2.5	<2.5
Hyponatremia	Sodium (mmol/L)	<LLN - 130	125-129	120-124	<120
Chronic kidney disease	Estimated glomerular filtration rate (eGFR) (ml/min/1.73m2)	<LLN - 60	59 - 30	29 - 15	<15
Proteinuria	Urine protein	1+ proteinuria	**Adult:** 2+ and 3+ proteinuria	**Adult:** 4+ proteinuria	-

[1] Baseline grades, or post-baseline grades where no baseline visit available, follow the criteria defined for normal baseline results.
[2] Baseline grades, or post-baseline grades where no baseline visit available, do not follow criteria based on baseline results.
[3] Derived only for participants not receiving anticoagulation medication.
[4] Corrected serum calcium (mmol/L) derived (0.02 * (40 g/L - albumin g/L)) + serum calcium (mmol/L).
Additional laboratory test may be collected if clinically indicated, at the discretion of the Investigator.
Source: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

A 3 Clinical Abnormalities: Vital Signs

Vital Signs Parameter	Vital Signs Grade			
	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) (°F)	37.9-38.4 100.1-101.1	38.5-38.9 101.2-102.0	39.0-40 102.1-104	> 40 > 104
Tachycardia (beats/minute)	101-115	116- 130	> 130	NA
Bradycardia (beats/minute) c	50-54	45-49	< 45	NA
Hypertension; systolic (mmHg)	141-150	151-155	> 155	NA
Hypertension; diastolic (mmHg)	91-95	96-100	> 100	NA
Hypotension; systolic (mmHg)	85-89	80-84	< 80	NA
Respiratory rate (breaths/minute)	17-20	21-25	> 25	NA

Hg = mercury. NA = not applicable.
Source: https://www.fda.gov/media/73679/download

A 4 Standardized MedDRA Query: Embolic and Thrombotic Events

It includes 3 sub standardized MedDRA queries:

- Embolic and thrombotic events, arterial (SMQ)
- Embolic and thrombotic events, venous (SMQ)
- Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ)

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