STATISTICAL ANALYSIS PLAN	
Study Code	D8851C00001
Edition Number	5.0
Date	20-Sep-2021

A Phase III Randomized, Double-blind, Placebo-controlled, Multicenter Study to Determine the Safety and Efficacy of AZD7442 for the Treatment of COVID-19 in Non-hospitalized Adults

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ADA	Anti-drug-antibody
AE	Adverse event
AESI	Adverse event of special interest
AUC	Area under the serum concentration-time curve
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus 2019
CRF	Case report form
CSP	Clinical study protocol
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
FAS	Full Analysis Set
GMFR	Geometric mean fold rises
GMT	Geometric mean titer
gSD	Geometric standard deviation
ICU	Intensive care unit
IM	Intramuscular
IMP	Investigational medicinal product
IP	Investigational product
IPD	Important Protocol Deviations
IV	Intravenous
LOCF	Last observation carried forward
mAbs	monoclonal antibodies
nAb	Neutralizing antibodies
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetics
RNA	Ribonucleic acid
RR	Relative Risk or Risk Ratio
RRR	Relative Risk Reduction
SAE	Serious adverse event
SAP	Statistical analysis plan

SARS-CoV-2	Severe Acute Respiratory Syndrome-Coronavirus 2
SpO2	Oxygen saturation
WHO	World Health Organization

AMENDMENT HISTORY

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
N/A	26 Feb 2021	Initial approved SAP	Yes, version 3.0	N/A
Section 3.1	08 Mar 2021	Removed references to CSR	Yes, version 3.0	To eliminate confusion with regards to timing of CSR output development.
Section 4.2.1.7	08 Mar 2021	Added exploratory subgroup analysis for primary endpoint, to evaluate efficacy in an alternatively defined High Risk subgroup	Not a protocol defined subgroup.	To explore an alternatively defined subgroup that aligns with analyses conducted for previously approved emergency use authorizations.
Section 3.3.2	18 Mar 2021	Specified that if there is missing data for Risk Factors for Progression in EDC, then IRT reported stratifications will be used.	Yes, version 6.0	To avoid missing data for stratification variables.
Section 4.2.1.7	18 Mar 2021	Specified that an assessment of interaction cannot be conducted for the Standard of Care subgroup.	Yes, version 6.0	To make clear that an assessment of interaction cannot be conducted on Standard of Care because participants may be included in more than one category.

Section 4.2.3.2	26 Mar 2021	Specified: For Time to Usual health, if a participant has not returned to usual health by Day 29, time will be calculated as Date of Day 29 visit – date of dosing + 1. If the fever has not subsided by Day 29, then the time for the patients will be calculated as Date of Day 29 – Fever start date + 1.	Yes, version 6.0	To clarify how to derive follow-up time for events that do not occur by Day 29, to support the Wilcoxon analyses.
Section 1.2	26 Mar 2021	Updated to be consistent with Protocol v5.0. See protocol for description and justification.	Yes, version 6.0	Updated to be consistent with Protocol v5.0 and US specific amendment 1 that includes adolescents.
Section 1.3	26 Mar 2021	Updated to be consistent with Protocol v5.0. See protocol for description and justification.	Yes, version 6.0	Updated to be consistent with Protocol v5.0
Section 3.1	26 Mar 2021	Updated to be consistent with Protocol v5.0. See protocol for description and justification.	Yes, version 6.0	Updated to be consistent with Protocol v5.0
Section 3.3.1	26 Mar 2021	Updated to be consistent with Protocol v5.0. See protocol for description and justification.	Yes, version 6.0	Updated to be consistent with Protocol v5.0
Section 3.3.5	26 Mar 2021	Updated to be consistent with Protocol v5.0. See protocol for description and justification.	Yes, version 6.0	Updated to be consistent with Protocol v5.0

Section 4.2.1	26 Mar 2021	Updated to be consistent with Protocol v5.0. See protocol for description and justification.	Yes, version 6.0	Updated to be consistent with Protocol v5.0
Section 4.2.	26 Mar 2021	Updated to be consistent with Protocol v5.0. See protocol for description and justification.	Yes, version 6.0	Updated to be consistent with Protocol v5.0
Section 5	26 Mar 2021	Updated to be consistent with Protocol v5.0. See protocol for description and justification.	Yes, version 6.0	Updated to be consistent with Protocol v5.0
Section 4.2.1.6	07 Apr 2021	Added KM summary statistics to be summarized. Specified that duration of follow-up for will be summarized. Specified Efron method for ties in Cox analysis will be used.	Yes, version 6.0	KM summary estimates were added to provide more context for time to event analysis. CCI [redacted] Efron method was specified to describe how ties should be handled.
Section 4.1.10 (4.1.10.1 and 4.1.10.2)	07 Apr 2021	Added section for Duration of On-study and safety follow up to be summarized	Yes, version 6.0	CCI [redacted]
Section 4.1.1.2	07 Apr 2021	Added summary for discontinuation by age group	Yes, version 6.0	CCI [redacted]
Section 4.2.2.7, Section 4.2.3.6	15 Apr 2021	Added in subgroup analyses by serostatus at baseline	Yes, version 6.0	Added per request of clinical science team.

Section 1.1	19 Apr 2021	Update footnote to refer to CSP for definition of hospitalization. Also include Type of Hospitalization as an endpoint.	Yes, version 6.0	Updated to be in line with CSP.
Section 4.2.4	19 Apr 2021	Updated to specify summary of hospitalization through Day 29 in addition to Day 169. Also included a summary by Type of Hospitalization.	Yes, version 6.0	Updated to show hospitalizations related to the primary and key secondary endpoints separately.
Section 4.1.4.1	21 Apr 2021	Update region in Demographics section to include Latin America and Asia.	Yes, version 6.0	Updated per request of clinical.
Section 4.2.3.3	21 Apr 2021	Specify handling of partial or missing date for respiratory failure	Yes, version 6.0	Updated to ensure follow-up time can be calculated for analysis.
Section 1	16 July 2021	Updated to be consistent with Protocol v7.0. See protocol for description and justification.	Yes, version 7.0	Updated to be in line with CSP v7.0.
Figure 1.	16 July 2021	Updated to be consistent with Protocol v7.0. See protocol for description and justification.	Yes, version 7.0	Updated to be in line with CSP v7.0.
Section 1.3	16 July 2021	Updated to be consistent with Protocol v7.0. See protocol for description and justification.	Yes, version 7.0	Updated to be in line with CSP v7.0.

Section 3.1	16 July 2021	Updated to be consistent with Protocol v7.0. See protocol for description and justification.	Yes, version 7.0	Updated to be in line with CSP v7.0.
Section 3.2	16 July 2021	Updated to be consistent with Protocol v7.0. See protocol for description and justification.	Yes, version 7.0	Updated to be in line with CSP v7.0.
Section 3.3.2	16 July 2021	Added clarification on using Smoking History eCRF page to support High Risk derivation	Yes, version 7.0	Updated to provide clarity to programming team, and to account for potential missing data on symptom eCRF page CCI [redacted]
Section 3.3.5	16 July 2021	Updated to be consistent with Protocol v7.0. See protocol for description and justification.	Yes, version 7.0	Updated to be in line with CSP v7.0.
Sections 4.1.1.2 and 4.1.4.1	16 July 2021	Removed <18 years category	Yes, version 7.0	Adolescents are no longer being enrolled into study
Sections 4.1.4.2, 4.1.6.2, 4.1.7.2, 4.1.8.2, 4.1.10.2	16 July 2021	Added mFAS as a repeat table	Yes, version 7.0	Included repeat tables in mFAS to report baseline characteristics in primary analysis population
Section 4.1.5.1	16 July 2021	Added BMI as a categorical variable, and smoking history.	Yes, version 7.0	Left out inadvertently in previous SAP version

Section 4.2	16 July 2021	Updated to be consistent with Protocol v7.0. See protocol for description and justification.	Yes, version 7.0	Updated to be in line with CSP v7.0.
Section 4.2.1.2	16 July 2021	Updated to be consistent with Protocol v7.0. See protocol for description and justification.	Yes, version 7.0	Updated to be in line with CSP v7.0.
Section 4.2.1.5	16 July 2021	Updated to be consistent with Protocol v7.0. See protocol for description and justification.	Yes, version 7.0	Updated to be in line with CSP v7.0.
Section 4.2.1.6	16 July 2021	Updated to include non-responder sensitivity analysis, and updated multiple imputation method to be consistent with CMH method	Yes, version 7.0	Non-responder analysis was left out inadvertently in previous version.
Section 4.2.1.8	16 July 2021	Update to CMH. Removed subgroup for Vitamin D based on normal range. Remove exploratory analysis for alternatively defined High Risk population.	Yes, version 7.0	Normal range for Vitamin D does not exist in data. CCI [redacted]
Section 4.2.2	16 July 2021	Updated to be consistent with Protocol v7.0. See protocol for description and justification.	Yes, version 7.0	Updated to be in line with CSP v7.0.

Section 4.2.3	16 July 2021	Updated to specify relevant analyses will be conducted in mFAS, instead of FAS.	Yes, version 7.0	Updated analysis set to be aligned with primary analysis population.
Section 4.2.3.4	16 July 2021	Updated to specify CMH will be used for binary endpoint	Yes, version 7.0	Updated to align with primary analysis method
Section 4.2.3.6	16 July 2021	Updated to specify CMH will be used	Yes, version 7.0	Updated to align with primary analysis method
Section 4.2.4.1	16 July 2021	Updated to clarify the reporting the hospitalizations, and duration of hospitalizations. Updated to specify use of mFAS.	Yes, version 7.0	Updated to provide clarity on how to identify and report unique hospitalization events.
Section 4.5.4.2	16 July 2021	Updated to clarify patients will be summarized by their worst observed value	Yes, version 7.0	Updated to clarify patients will be summarized by their worst observed value
Section 3.3.3	25 August 2021	Updated to include visit window definition for all visit-based assessments	Yes, version 7.0	Updated to include visit window definition for all visit-based assessments
Section 4.2	25 August 2021	Table 11. was updated to be consistent with text. The second and third estimands were incorrect.	Yes, version 7.0	Table 11. was updated to be consistent with text. The second and third estimands were incorrect.
Section 4.5	31 August 2021	Indicate that Safety outputs will be repeated in High Risk patients	Yes, version 7.0	Safety outputs will be repeated in High Risk patients
Section 4.2.2.7	17 September 2021	Removed text specifying that an interaction p-value will be presented	Yes, version 7.0	Text should’ve been removed in previous SAP amendment.

Section 4.2.3.1	17 September 2021	Updated to specify analysis duration will start at date of dosing. And updated to indicate analysis will only be for participants with documented fever at baseline.	Yes, version 7.0	Analysis updated to be aligned with logic used for time to return to usual health. Additionally, to clarify participant population analysis should occur in.
Section 4.2.3.2	17 September 2021	Updated to include imputation of half the LLOQ for viral load analysis	Yes, version 7.0	Confirmed with translation science, and updated to support programming derivations.
Section 4.5.5	17 September 2021	Updated to specify highest baseline ECG value would be used for shift table	Yes, version 7.0	Clarification for programming activities.

1 INTRODUCTION

The purpose of this document is to give details for the statistical analysis of study D8851C00001 supporting the clinical study report. The reader is referred to 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 include both treatment groups (AZD7442 600 mg and placebo). AZD7442 is specified when referring to participants who received active intervention.

1.1 Objectives and Endpoints

Table 1

Objective	Estimand Description/Endpoint
Primary	
To estimate the efficacy of AZD7442 in the prevention of the composite endpoint of either severe COVID-19 or death from any cause through study Day 29	**Population:** Modified Full Analysis Set
	Endpoint: A composite of either severe COVID-19 or death from any cause through Day 29. Severe COVID-19 is characterized by a minimum of either pneumonia (fever, cough, tachypnea, or dyspnea, AND lung infiltrates) or hypoxemia (SpO_2 < 90% in room air and/or severe respiratory distress) and a WHO Clinical Progression Scale score of 5 or higher (Protocol Appendix F).
	Intercurrent events: The set of intercurrent events for this estimand consists of participants who receive COVID-19 treatment product prior to Day 29 without already having met the primary efficacy endpoint. The set of intercurrent events will be handled following the treatment policy strategy.
	Summary measure: Relative risk reduction of severe COVID-19 or death from any cause in participants taking AZD7442 compared to those taking placebo during the 28-day post-dose period (Day 1 to Day 29).
To evaluate safety and tolerability of a single IM dose of AZD7442 compared to placebo.	AEs, SAEs, and AESIs through end of study.
Key Secondary	
To estimate the efficacy of AZD7442 in the prevention of the composite endpoint of either death or hospitalization[a] for COVID-19 complications or sequelae through Day 169	**Population:** Modified Full Analysis Set
	Endpoint: A composite of either death from any cause or hospitalization[a] for COVID-19 complications or sequelae during the 168-day post-dose period (Day 1 to Day 169).
	Intercurrent events: The set of intercurrent events for this estimand consists of receipt of COVID-19 treatment product or becoming unblinded to properly consider vaccination for COVID-19, prior to Day 169 without already having met the key secondary efficacy endpoint. The set of intercurrent events will be handled following the treatment policy strategy.

Other Secondary	
To determine if AZD7442 will prevent respiratory failure through study Day 29	The incidence of participants with respiratory failure, defined as requirement for mechanical ventilation, ECMO, non-invasive ventilation, or high flow nasal cannula oxygen delivery.
To determine whether AZD7442 reduces participants' severity of participant-reported COVID-19 symptoms through Day 29	COVID-19 symptom severity assessments based on symptom severity scores over time during the 28-day period from and including the day of the dose of AZD7442 or placebo. Each symptom is scored from 0 to 4.
To determine if AZD7442 reduces the progression of participant-reported COVID-19-associated symptoms through Day 29	Progression through Day 29 of one or more COVID-19-associated symptoms to a worse status than recorded in the participant-reported symptom diary at study entry, prior to start of AZD7442 or placebo.
To determine if AZD7442 reduces SARS-CoV-2 detection or levels of RNA in nasal swabs through Day 29.	Detection (detectable versus undetectable), level, and change from baseline of SARS-CoV-2 RNA from nasal swabs through Day 29.
To evaluate differences in symptom duration between the AZD7442 and placebo treatment groups through Day 29	• Time to return to usual (pre-COVID-19) health through Day 29. • Duration of fever through Day 29 defined as the last day in the participant-reported symptom diary on which a temperature greater than 37.8°C was recorded or a potentially antipyretic drug, such as acetaminophen or ibuprofen, was taken.
To evaluate the single-dose PK of AZD7442	Serum concentration and PK parameters.
To evaluate the ADA responses to AZD7442 in serum	Incidence of ADA to AZD7442 in serum over time.
CCI [redacted]	
CCI [redacted]	[redacted]
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[redacted]	[redacted]
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a. Hospitalization is defined as ≥ 24 hours of acute care, in a hospital or similar acute care facility, including Emergency Rooms or temporary facilities instituted to address medical needs of those with severe COVID19 during the COVID-19 pandemic. See also Appendix I in the CSP for further guidance on the definition of hospitalization.

ADA Anti-drug-antibody; AE Adverse event; AESI Adverse event of special interest; COVID-19, Coronavirus disease 2019; ECMO Extracorporeal membrane oxygenation; CCI ICU Intensive care unit; IM, intramuscular; IMP Investigational medicinal product; CCI PK Pharmacokinetic; RNA Ribonucleic acid; SAE Serious adverse event; SARS-CoV-2 Severe acute respiratory syndromecoronavirus-2; SpO2 Oxygen saturation; WHO World Health Organization.

1.2 Study Design

This is a Phase III, randomized, double-blind, placebo-controlled study assessing the safety and efficacy of a single 600 mg IM dose of AZD7442 compared to placebo for the treatment of COVID-19.

Participants will be outpatient adults (≥ 18 years) with a documented positive SARS-CoV-2 molecular test (antigen or nucleic acid) from a sample collected ≤ 3 days prior to study entry and with ≤ 7 days of symptoms of COVID-19 at study entry, plus the presence of select symptoms within 24 hours prior to Day 1.

At least 60% of participants will meet the protocol definition of being at high risk of progression to severe COVID-19, which is defined in Protocol Section 4.1.

Randomization will be stratified (using centralized blocked randomization) by:

- Time from symptom onset (≤ 5 days versus > 5 days)
- High risk versus low risk of progression to severe COVID-19

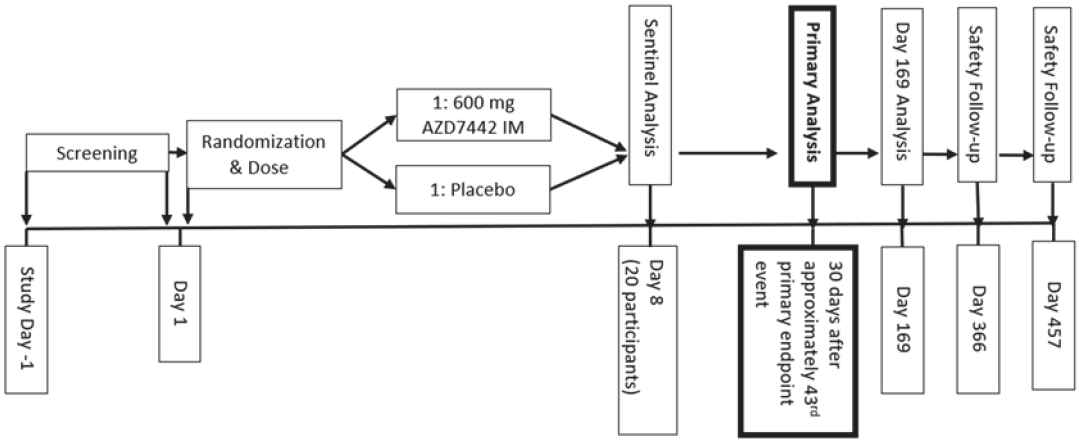
Up to approximately 1700 participants will be randomized in a 1:1 ratio to receive a single IM dose of 600 mg of AZD7442 (n = up to approximately 850) or placebo (n = up to approximately 850) on Day 1. The first 20 participants to be dosed (approximately 10 allocated to the AZD7442 group and 10 allocated to placebo) will form a sentinel group. After the entire sentinel group has been dosed, further enrollment will pause until the sentinel group's safety data through Day 8 has been reviewed by the DSMB (Data Safety Monitoring Board) in order to provide a recommendation to the AstraZeneca Unblinded Review Committee to continue or to halt dosing of additional participants. For DSMB, see Protocol Section 9.6.

Participants will be enrolled into one of 2 independent cohorts:

- Cohort 1 (n ≈ 300), which will include the sentinel group, will undergo more intensive testing to characterize their virological and immunological status, and to correlate that status with clinical outcomes.
- Cohort 2 (n up to ≈ 1400) will be followed for clinical outcomes.

After administration of the dose of study intervention on Day 1, participants will undergo 28 days of intensive follow-up, followed by limited follow-up through Day 457. See Figure 1.

Figure 1. Study Design



1.3 Sample Size

Up to approximately 1700 participants will be randomized in a 1:1 ratio to receive a single IM 600 mg dose of AZD7442 (n up to ≈ 850) or placebo (n up to ≈ 850) on Day 1.

This is an event-driven study with a primary analysis initiated 30 days after approximately 43 primary endpoints have been confirmed in the primary analysis population. The study has at least CCI to detect a relative reduction of CCI in the incidence of severe COVID-19/death between the study groups (AZD7442 vs placebo), using the following assumptions:

- CCI

2 CHANGES TO PROTOCOL PLANNED ANALYSES

There is no change of planned analyses.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

The primary analysis will be initiated 30 days after 43 primary endpoint events have been confirmed in the primary analysis population. The number of events may be higher if the event accrual rate is different than expected at this time. All data during this 30 day interval, including additional primary endpoint events, will be evaluated. A Day 169 analysis (Key Secondary Analysis and safety) will be conducted when all participants have

been followed through Day 169. A final analysis will be conducted when all participants have completed the study.

3.2 Analysis Populations

Table 2 Populations for Analysis

Population/Analysis Set	Description
All participants analysis set	All participants screened for the study, to be used for reporting disposition and screening failures.
Full analysis set	All randomized participants who received IMP, irrespective of their protocol adherence and continued participation in the study. Participants will be analyzed according to their randomized treatment, irrespective of whether or not they have prematurely discontinued, according to the intent-to-treat principle. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination.
Modified full analysis set	All participants in the full analysis set who received IMP ≤ 7 days from symptom onset and were not hospitalized at baseline (≤ Day 1) for isolation purpose.
Early Intervention Analysis Set	All participants in the modified full analysis set who received IMP ≤ 5 days from symptom onset.
Seronegative Analysis Set	All participants in the modified full analysis set who were seronegative at baseline.
Safety analysis set	The safety analysis set consists of all participants who have received IMP. Erroneously-treated participants (eg, those randomized to treatment A, but were actually given treatment B) are accounted for in this analysis set by assigning them to the treatment they actually received.
PK analysis set	Dosed participants for whom an adequate (measurable drug concentration) PK profile has been obtained. All participants who received AZD7442 and from whom PK blood samples are assumed not to be affected by factors such as protocol violations, and who had at least one quantifiable serum PK observation post dose, will be included in the PK analysis dataset.
Virology analysis set	The Virology analysis set consists of all participants in Cohort 1, who undergo more intensive virologic and immunologic assessments. Participants will be analyzed according to their received treatment.
ADA evaluable analysis set	The ADA evaluable analysis set contains 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 analysis set is not defined in the CSP but is required for analysis.
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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 will 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 [number of participants with available data], n < lower limit of quantification (LLOQ) [number of participants with results below the limit of quantification], geometric mean, arithmetic mean, SD, co-efficient of variation, median, min and max will be presented by treatment group and visit, when applicable.

3.3.1 Statistical Hypothesis

The primary efficacy endpoint is a binary response whereby a participant is classified as either having severe COVID-19 symptoms or death from any cause, or not. Efficacy will be calculated as the relative risk reduction (RRR), defined as 1−Relative Risk. The null hypothesis is the RRR of severe COVID-19 or death from any cause through Day 29 in participants on AZD7442 compared with those on placebo is equal to zero. The alternative hypothesis is that the RRR is not equal to zero.

The primary efficacy endpoint will be formally assessed at timepoints as described in Section 3.1. The type I error rate will be controlled by a 2-sided alpha = 0.05. The primary estimand, supportive estimands, and key secondary endpoints will be tested at an alpha level of 5%. The methodology used to conserve alpha is detailed in Section 3.3.5.

All point estimates will be presented with a 95% CI, unless otherwise stated. P-values, corresponding to a 2-sided test, will be presented for comparisons between treatments.

3.3.2 General Study Level Definitions

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

Change from baseline will be calculated as (post-baseline visit – baseline visit). Percent change from baseline will be calculated as (change from baseline/baseline*100).

For any presentation for or by strata, or for any analysis requiring the adjustment of strata as covariates, variables will be derived from the eCRF data captured in the RAVE EDC.

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3.3.4 Handling of Unscheduled Visits, Retest, and Early Discontinuation

Unscheduled, retest (same visit number assigned), and early discontinuation measurements will not be included in by-visit summaries but may contribute to the baseline and/or maximum value, where applicable (e.g. shift table). Visits for visit-based data will follow a windowing convention as described in Section 3.3.3.

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3.3.6 Handling of Important 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 AZ R&I Non-Compliance Handling Plan.

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

- Participants who do not meet inclusion criteria
- Participants who meet any of the exclusion criteria

- Participants who are identified as developing an issue worthy of study withdrawal, but are not withdrawn
- Participants who experience an investigational product deviation
- Participants who receive concomitant use of disallowed medications
- Participants who experience deviations related to planned study procedures
- Other important deviations that may impact safety or violate study Suspension/Termination rule per CSP Section 7.4.

4 STATISTICAL ANALYSIS

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

4.1 Study Population

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

4.1.1 Participant Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Treatment groups are reported based on randomized treatment. The All Participant Analysis Set (PAS) as defined in Section 3.2 is used for reporting disposition and screening failures.

4.1.1.2 Presentation

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 ongoing in study (for primary analysis only)
- Participant who completed the study
- Participant who discontinued early from study
    - Reason for discontinuing early from study
- Participants 18 to 64 years who discontinued early from study
    - Reason for discontinuing early from study

- Participants >= 65 years 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), modified Full Analysis Set (mFAS), Early Intervention Analysis Set (EIAS), Seronegative Analysis Set (SNAS), Safety Analysis Set, PK Analysis Set, Virology Analysis Set, ADA evaluable analysis set, and nAB evaluable analysis set. For each analysis set, number of participants excluded and number for each reason will be reported by treatment.

4.1.3 Important Protocol Deviations

4.1.3.1 Definitions and Derivations

IPDs will be identified by the study team in a blinded fashion before database lock.

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 FAS.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Demographics are categorized as follows:

- Age group:
    - ≥ 18 to < 65 years, ≥ 65 to < 75 years, ≥ 75 to <80 years and ≥ 80 years.
    - < 65 years vs ≥ 65 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
- Region: US, Europe, Latin America, Asia, Other

4.1.4.2 Presentation

The summary of demographics characteristics will be provided for the FAS and mFAS. If there are major differences between the FAS and the Safety Analysis Set, the summaries will be repeated and presented by actual treatment for the Safety Analysis Set.

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, ethnicity, and region.

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)
- Time from Symptom Onset as a continuous variable
- Time from Symptom Onset (≤ 5 days, > 5 days)
- Risk Group (High, Low)
- Smoking History (Current, Former, Never)

4.1.5.2 Presentation

Baseline characteristics will be summarized with demographics.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

Disease characteristics include the following:

- COVID-19 co-morbidities (at least one co-morbidity, no co-morbidity)

  Note: Comorbidity = Risk factors in CRF: SARS-CoV-2 Progression risk to COVID-19, excluding the risk factor “Person aged >=65 year”.
- Serum for SARS-CoV-2 Serology (Positive, Negative)
- Nicotine Use (Current, Former, Never)
- WHO Clinical Progression Scale score (ordinal 2 – 3 based on inclusion criteria)

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 FAS and mFAS. If there are major differences between the FAS and the Safety Analysis Set, the summaries will be repeated and presented by actual treatment for the Safety Analysis Set.

COVID-19 co-morbidities for adult and pediatric participants will be summarized separately.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical history and concomitant disease will be coded using Medical Dictionary for Regulatory Activities (MedDRA) 23.1 or higher.

Medical history is defined as any medical 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 history and concomitant disease will be summarized by System Organ Class (SOC) and Preferred Term (PT) by treatment and total based on the FAS and mFAS.

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 2020, or a more recent version.

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

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

4.1.8.2 Presentation

Prior and concomitant medications will be summarized by Anatomical Therapeutic Class (ATC) level 2 and preferred drug name by treatment and total based on the FAS and mFAS. A participant having more than one medication within the same ATC Level 2 or preferred drug name will be counted only once for that ATC Level 2 or preferred drug name.

4.1.9 Study Drug Compliance

4.1.9.1 Definitions and Derivations

Compliance will not be calculated since participants will receive a single dose (2 IM injections) within clinic.

4.1.9.2 Presentation

Not applicable.

4.1.10 Duration of On-Study and Safety Follow-up

4.1.10.1 Definitions and Derivations

On-study follow-up will be calculated as Time = max(Date of Last Safety Assessment/Study Discontinuation/Death/Study Completion) – Date of dosing + 1.

Safety follow-up will be calculated as Time = Date of Last Safety Assessment – Date of dosing + 1.

4.1.10.2 Presentation

Duration of on-study and safety follow-up time will be summarized using descriptive statistics: n, mean, SD, Q1, median, Q3, min, and max, which will be presented for both the FAS and mFAS.

4.2 Endpoint Analyses

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

Table 11. Overview of Efficacy Estimands

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 1: To estimate the efficacy of AZD7442 in the prevention of the composite endpoint of either severe COVID-19 or death from any cause through study Day 29					
Primary	A composite of either severe COVID-19 or death from any cause through Day 29: Binary Event/Non-event	mFAS	Data collected after an intercurrent event will be analyzed as observed.	Relative risk reduction of AZD7442 vs. placebo during the 28-day post-dose period (Cochran-Mantel-Haenszel Test)	4.2.1.4
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Supplementary	Time-to-event	mFAS	Same as primary	Cumulative incidence, Hazard ratio, Absolute risk reduction (Kaplan-Meier Method, Stratified Log-rank Test, Cox Regression)	4.2.1.7
Subgroup	Same as primary	mFAS	Same as primary	Same as primary	4.2.1.8
Objective 2: To estimate the efficacy of AZD7442 in the prevention of the composite endpoint of either death or hospitalization for COVID-19 complications or sequelae through Day 169					
Key secondary	A composite of either death from any cause or hospitalizationa for COVID-19 complications or sequelae during the 168-day post-dose period: Binary Event/Non-event	mFAS	Same as primary	Relative risk reduction of AZD7442 vs. placebo during the 168-day post-dose period (Cochran-Mantel-Haenszel Test)	4.2.2.5
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Supplementary	Time-to-event	mFAS	Same as primary	Cumulative incidence, Hazard ratio, Absolute risk reduction (Kaplan-Meier Method, Stratified Log-rank Test, Cox Regression)	4.4.4.7
Objective 3: Other secondary – See Section 4.2.3					
CCI [redacted]					

4.2.1 Primary Efficacy Endpoint

All analyses for the primary efficacy endpoint will be based on mFAS.

4.2.1.1 Definition

The primary efficacy endpoint is a composite of either severe COVID-19 or death from any cause through Day 29. Severe COVID-19 is characterized by a minimum of either pneumonia (fever, cough, tachypnea, or dyspnea, and lung infiltrates) or hypoxemia (SpO2 < 90% in room air and/or severe respiratory distress) and a WHO Clinical Progression Scale score of 5 or higher (see Protocol Appendix F).

4.2.1.2 Derivations

Binary response

The primary efficacy endpoint is a binary response, for which participants who have either severe COVID-19 or death from any cause through Day 29 will be coded as "Yes" (Event), otherwise "No" (Non-event) or "Missing" depending on the analysis method being used.

Missing data

For the primary analyses using the Cochran-Mantel-Haenszel (CMH) method, participants who withdraw from the study or are lost to follow-up prior to Day 29 for the primary endpoint will be considered as missing and will be excluded from the primary efficacy analyses. See Section 4.2.1.3 for handling of missing data.

CCI

[redacted]

Follow-up time

Follow-up time or the time-to-event (T) will be the response in the supplementary time-to-event analyses (Section 4.2.1.6). Calculation of T and definition of censoring are as follows:

- For participants who have an event on or before the primary assessment timepoint:

  T = Date of event – Date of dosing + 1

- For participants who do not have an event on or before the primary assessment timepoint:

  T = 29 days

  The participants will be censored at Day 29 for the supplementary analysis.

- For participants who discontinue or are lost to follow-up prior to Day 29, they will be censored at the last known status before Day 29. The follow-up time will be calculated as follows:

  T = Date of last known status before Day 29 – Date of dosing + 1

4.2.1.3 Handling of Dropouts and Missing Data

This section is regarding missing response data as defined in Section 4.2.1.2

For the primary analysis of the primary endpoint, missing data will not be imputed and will be treated as missing. For the sensitivity analysis, missing data will be imputed as indicated in Section 4.2.1.6. For the supplementary analysis, missing data will be included and censored at the date of last known status.

4.2.1.4 Primary Estimand Analysis of Primary Efficacy Endpoint

For the binary endpoint described in Section 4.2.1.2, the CMH method will be used to investigate treatment effect stratified by the 2 stratification factors as described in Sections 1.2 and 3.3.2. If the test results in a warning due to sparse data in a specific stratum, then a stratification factor will be dropped.

The efficacy will be estimated by the common relative risk, or risk ratio (RR) from the CMH method. The relative risk reduction RRR = 100 x (1−RR) represents the percent reduction in incidence of severe COVID-19 or death from any cause in the AZD7442 group relative to the placebo group.

The CMH method will be implemented by using the SAS PROC FREQ procedure using the CMH option. The null hypothesis will be rejected by a General Association p-value <0.05. The 2-sided 95% CI will be presented. The Breslow-Day test p-value will be presented to evaluate homogeneity of the RRR across strata.

If the CMH test continues to produce a warning due to sparse data after dropping a stratification factor as specified above, the Chi-squared method will be used to perform the primary analysis. The RRR, the 95% CI, and p-value will be reported. This analysis will be performed without any imputation of missing data.

CCI [redacted]

CCI

[redacted]

- CCI [redacted]

4.2.1.7 Supplementary Analyses of the Primary Efficacy Estimand

For the supplementary analysis, the response is time-to-event, which is defined in Section 4.2.1.2.

Kaplan-Meier analyses, including median survival time and survival probability estimates for Day 29, will be summarized, and curves for time to severe COVID-19 or death from any cause during the first 28 days of follow-up will be generated for each randomized group. The duration of follow-up for the primary endpoint will be summarized using the reverse Kaplan-Meier method.

A stratified Log-Rank test with the two stratification factors will be conducted to assess the difference between the curves. A Cox-Proportional Hazards model will be performed to obtain the hazard ratio and the 95% CI. The Cox model will include terms of treatment and the two stratification factors. The Efron method will be used to handle ties.

Additionally, the absolute risk reduction of AZD7442 with respect to placebo in preventing severe COVID-19 or death from any cause at Day 29, will be presented, along with the 2-sided 95% CI using the stratified Miettinen and Nurminen's score method (Miettinen and Nurminen 1985).

4.2.1.8 Subgroup Analyses

CCI [redacted]

Subgroups are listed and categorized as below:

- Age: 18 - <65 vs ≥ 65; < 75 vs ≥ 75; < 80 vs ≥ 80
- Sex: Male vs Female

- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islanders, White
- Ethnicity: Hispanic vs Not Hispanic
- Region: US, Europe, Other
- Time from Symptom Onset:
  - ≤ 5 days vs >5 days
  - ≤ 3 days vs >3 days
  - Quartile: 25%, 50%, 75%
- Risk Group: High vs Low
- COVID-19 co-morbidities: at least one co-morbidity vs. no co-morbidity
- Baseline Vitamin D
  - < 30 ng/mL vs ≥ 30 ng/ml
- Baseline Zinc: < 100 ug/dl vs ≥ 100 ug/dl
- Standard of Care: Antiviral Therapy, Antiviral Therapy, not active against COVID, Immune-Based Therapy, Corticosteroids, Adjunctive Therapy, Antibiotic, Other , None

  (Note: The clinical team will review concomitant medications given to treat disease under study, and will classify each to one of the above categories prior to database lock.)

  Participants may be assigned to multiple Standard of Care categories, therefore, an assessment for interaction will not be conducted for this subgroup.
- Baseline Serum for SARS-CoV-2 Serology: Positive vs Negative
- Depending on the availability of data, efficacy by virus variant strain may be explored.

4.2.2 Key Secondary Efficacy Endpoint

All analyses for the key secondary efficacy endpoint will be based on mFAS.

4.2.2.1 Definition

The key secondary endpoint is a composite of either death from any cause or hospitalization for COVID-19 complications or sequelae during the 168-day post-dose period (Day 1 to Day 169).

4.2.2.2 Derivations

Binary response

The key secondary endpoint is a binary response, for which participants who have either death from any cause or hospitalization for COVID-19 complications or sequelae during the 168-day post-dose period will be coded as "Yes" (Event), otherwise "No" (Non-event) or "Missing" depending on the analysis method being used.

Missing data

For the analysis using the Cochran-Mantel-Haenszel (CMH) method, participants who withdraw from the study or are lost to follow-up prior to Day 169 for the key secondary endpoint will be considered as missing and will be excluded from the key secondary efficacy analyses. See Section 4.2.2.3 for handling of missing data.

CCI

[redacted]

Follow-up time

Follow-up time or time-to-event (T) will be the response in the supplementary analysis (Section 4.2.2.6). Calculation of T and definition of censoring are as follows:

- For participants who have an event on or before Day 169:

  T = Date of event – Date of dosing + 1

- For participants who do not have an event on or before Day 169:

  T = 169 days

  The participants will be censored at Day 169 for the supplementary analysis.

- For participants who discontinue or are lost to follow-up, they will be censored at the last known status before date of dosing + 168. The follow-up time will be calculated as follows:

  T = Date of last known status before Day 169 – Date of dosing + 1.

  Date of last known status will be either the date of study discontinuation visit or the

last assessment before Date of dosing + 168 for the key secondary endpoint, for those who are lost to follow-up.

4.2.2.3 Handling of Dropouts and Missing Data

This section is regarding missing response data as defined in Section 4.2.2.2.

For the analysis of the key secondary endpoint, missing data will not be imputed and will be treated as missing. No assumptions will be made about data not collected after discontinuation. For the supplementary analysis missing data will be included and censored at the date of last known status.

4.2.2.4 Analysis of the Key Secondary Efficacy Endpoint

Being consistent with the primary analysis of primary endpoint, CMH test will be used. The RRR and its 95% CI will be calculated at Day 169. The same methods will be used as described for the analysis of the primary endpoint.

To control for multiplicity of the primary estimand, supportive estimands, and key secondary endpoint, see Section 3.3.5 for a hierarchical approach. If the significance of the primary efficacy estimands and supportive estimands is not achieved, then the p-value for testing the key secondary efficacy endpoint will be considered nominal.

Similar to that in Section 4.2.1.4, a Chi-square test will be used instead of the CMH if it fails.

CCI [redacted]

4.2.2.6 Supplementary Analyses of the Key Secondary Efficacy Endpoint

For the supplementary analyses, the response will be time-to-event through Day 169, which is defined in Section 4.2.2.2.

Similar to the supplementary analyses of the primary endpoint (Section 4.2.1.6), Kaplan-Meier summaries and curves will be reported. A stratified Log-Rank test will be conducted to assess the difference between the curves. The Cox-Proportional Hazards model will be used to obtain hazard ratios and their respective 95% CIs. The absolute risk reduction will be calculated similarly as for the primary efficacy endpoint. Sensitivity analyses related to unblinding for vaccination apply.

4.2.2.7 Subgroup Analysis

A subgroup analysis of the Key Secondary efficacy endpoint will be conducted using serostatus (positive/negative) at baseline. No other subgroups will be evaluated for the Key Secondary endpoint. No forest plot will be presented.

4.2.3 Other Secondary Endpoint

Analysis for time to undetectable of SARS-CoV-2 RNA from nasal swabs will be based on virology analysis set.

All other analyses will be based on mFAS.

4.2.3.1 Definition

Endpoints with binary outcome:

- The incidence of participants with respiratory failure, through Day 29, defined as a requirement for mechanical ventilation, ECMO, non-invasive ventilation, or high flow cannula oxygen delivery.

  Participants will be coded as "Yes" if there is respiratory failure through Day 29; otherwise, "No".

- The incidence of participants with progression, through Day 29, of one or more COVID-19-associated symptoms to worse status (increasing in severity scale by ≥ 1) than recorded in the participant-reported symptom diary entry prior to start of AZD7442 or placebo.

  Participants will be coded as "Yes" if there is progression through Day 29; otherwise, "No". Participants with severity score of 4 on every scale at baseline will be excluded.

Endpoints with time-to-event outcome:

- Time to undetectable of SARS-CoV-2 RNA from nasal swabs through Day 29.
- Time to return to usual (pre-COVID-19) health through Day 29.

Endpoints with continuous outcome:

- Change from baseline in COVID-19 symptom severity assessments (SARS-CoV-2 Daily Symptoms Questionnaire) based on symptom severity scores over time during the 28-day period.

  Each symptom is scored from 0 to 4: Shortness of Breath Severity, Difficulty Breath Severity, Chills Severity, Cough Severity, Fatigue Severity, Muscle Aches Severity, Body Aches Severity, Headaches Severity, Lost of Taste Severity, Lost of Smell

Severity, Sore Throat Severity, Congestion Severity, Runny Nose Severity, Nausea Severity, Vomiting Severity, Diarrhea Severity.

- Change from baseline of SARS-CoV-2 RNA from nasal swabs through Day 29.
- Duration of fever from date of dosing through Day 29 defined as the last day in the participant-reported symptom diary on which a temperature greater than 37.8°C was recorded or a potentially antipyretic drug, such as acetaminophen or ibuprofen, was taken. This analysis will be conducted on participants who have a documented fever at baseline.

The following endpoints are detailed in Section 4.4.

- Serum concentration and PK parameters.
- Incidence of ADA to AZD7442 in serum over time.

4.2.3.2 Derivations

Follow-up time: For endpoints with binary or time-to-event outcome, follow-up time will be derived similarly to those for the primary endpoint (Section 4.2.1.2).

For time to return to usual health, if a participant has not returned to usual health by Day 29, time will be imputed as Day 29.

For duration of fever, if the fever has not subsided by Day 29, time will be imputed as Day 29.

For analyses of SARS-CoV-2 RNA, "Not Detected" results will be imputed with a value half of the LLOQ. Values measured as above the upper limit of quantification (ULOQ) will be imputed at the ULOQ value.

The time-weighted average change in $\log_{10}$ SARS-CoV-2 RNA from baseline (Day 1) to Day 6 and 29 is defined as:

$$\frac{\sum_{i=a}^{b-1} \{0.5 \times (Y_i + Y_{i+1}) \times (t_{i+1} - t_i)\}}{(t_b - t_a)}$$

where *Y*i is the change from baseline in $\log_{10}$ SARS-CoV-2 RNA at Visit *i*, *t* is the time at the specified timepoint (the actual study day), *a* is the baseline assessment at Day 1, and *b* is the last assessment at or prior to Day 6 and 29, respectively. Sensitivity analysis will be performed for this derived endpoint – see Section 4.2.3.5.

4.2.3.3 Handling of Dropouts and Missing Data

Absence of data following participants' withdrawal/lost to follow-up prior to cut-off time of analysis will be treated as missing.

For the endpoints with binary outcome, missing data will not be imputed. For the endpoints with time-to-event outcome, missing data will be included and censored at the date of last known status.

For continuous endpoints with change from baseline to Day 6 or Day 29, missing Day 6 or Day 29 data will be imputed using last-observation-carried-forward (LOCF) method for ANCOVA. There will be no imputation for the Mixed Model for Repeated Measures (MMRM).

For respiratory failure, the following imputation rules will be used for missing or partial dates, if mechanical ventilation, non-invasive ventilation, ECMO, or high flow nasal cannula is indicated as being given to a participant"

- If 'Day" is missing AND the "Month" is after the Month in which the Day 29 visit occurs, then the participant will be censored as not having Respiratory Failure at the date of the Day 29 visit.
- Otherwise, impute partial or missing date as Day 1 visit date.

4.2.3.4 Analysis of Other Endpoints

All CIs and p-values will be considered nominal for analysis of other endpoints. Unless otherwise noted, the mFAS will be used.

Endpoints with binary outcome will be analyzed using CMH model as in the primary efficacy analysis in Section 4.2.1.4.

Endpoints with time-to-event outcome will be analyzed using only Kaplan-Meier analysis, which is described in Section 4.2.1.6.

Note: For time to undetectable of SARS-CoV-2 RNA from nasal swabs, an analysis will be conducted in the virology analysis set.

Endpoints with continuous outcome:

For SARS-CoV-2 RNA, the observed and change from baseline values at each visit, will be summarized using descriptive statistics on the original and $\log_{10}$ scale.

For Cohort 1 (Virology Analysis Set), $\log_{10}$ change from baseline to all post-baseline values will be analyzed using an MMRM, which will include $\log_{10}$ baseline value, the 2 stratification factors, treatment, visit, and treatment by visit interaction in the model. The LS Mean, standard error and 95% CI will be reported at each visit by treatment. The LS Mean difference, it's 95% CI, and p-value, will be reported for each visit.

For the MMRM, an unstructured (UN) correlation matrix will be used to model within subject autocorrelation [repeated statement within SAS]. If this model fails to converge, simpler correlation structures will be considered, e.g. AR(1), CS.

Figures for $\log_{10}$ LS mean change from baseline over time (mean ± SD) will be provided.

For all participants pooled, i.e., combined Cohort 1 and Cohort 2 (modified Full Analysis Set), treatment groups will be compared with respect to log_{10} change from baseline to Day 6, and change from baseline to Day 29, using an Analysis of Covariance (ANCOVA) model. Log_{10} baseline, treatment, and the 2 stratification factors will be included in the model. LS mean and 95% CI by treatment will be reported. Missing values at Day 6 and Day 29 will be imputed using LOCF as indicated in Section 4.2.3.3.

The analyses above (both the Cohort 1 and Pooled analyses), including figures, will be repeated based on viral load at baseline. The analyses will be repeated for participants with baseline viral load: $>10^4$ copies/ml, $>10^5$ copies/ml, $>10^6$ copies/ml, and $>10^7$ copies/ml.

For each COVID-19 symptom severity assessment during the 28-day period, the observed and change from baseline values at each visit, will be summarized using descriptive statistics.

To assess treatment difference over time, change from baseline to all post-baseline values will be analyzed using an MMRM analysis, which will include baseline severity score, the 2 stratification factors, treatment, visit, and treatment by visit interaction in the model. This analysis is similar to that of SARS-CoV-2 RNA as shown above, which has more details.

For each symptom, shift tables will be used to show the proportion of participants shifting from baseline severity score to maximum post-baseline severity score, and baseline severity score to last recorded post-baseline severity score, through Day 29.

Additionally, for each symptom, the proportion of participants who experience a reduction in severity >= 1 from baseline to worst post-baseline value, will be tabulated.

A tornado plot for each symptom, by treatment, will be produced to describe the presence of each symptom and proportions of severity scores, by visit.

For time to return to usual health through Day 29 and **duration of fever,** descriptive statistics by treatment will be provided. Treatment groups will be compared using a 2-sided Wilcoxon Rank Sum test at an alpha level of 5%. The Hodges-Lehmann estimate and its 95% CI for the location shift between the AZD7442 and placebo groups will be reported.

CCI [redacted]

4.2.3.6 Subgroup Analyses

A subgroup analysis by serostatus (positive/negative) at baseline will be conducted on the following previously described secondary endpoint: Incidence of Respiratory Failure, Incidence of Symptom Progression, Time to Return to Usual Health, and SARS-CoV-2 RNA viral load.

CCI

[redacted]

CCI

[redacted]

- CCI [redacted]

CCI

4.3 Pharmacodynamic Endpoint

Not Applicable.

4.4 Pharmacokinetics and ADA Endpoints

4.4.1 Serum AZD7442 Concentrations

Individual AZD7442 (AZD8895 and AZD1061) serum concentration data will be listed and tabulated by mAb component, along with descriptive statistics for the PK analysis set. A figure of serum concentrations by mAb component will also be presented.

Pharmacokinetic exposure (i.e., AUCs) and other PK parameters may be estimated using non-compartmental analysis; this will be optional if data permit. Potential correlation between PK exposure and efficacy/safety response may optionally be explored. Population

PK analysis may be performed by the Sponsor and reported in a separate report. The analysis is not covered in this SAP.

4.4.2 Immunogenicity

4.4.2.1 The Incidence of ADA to AZD7442 In Serum

4.4.2.1.1 ADA Variables

Serum samples for ADA assessments 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 nAb will be tested for all ADA-positive samples. The nAb results will be reported as positive or negative. A participant is defined as being ADA-positive if a positive ADA result is available at any time, including baseline and all post-baseline measurements; otherwise the participant is defined as ADA negative.

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.

- ADA positive at any visit (at baseline and/or post-baseline). The percentage of these participants in a population is known as ADA prevalence.
- Treatment-induced ADA positive (positive post-baseline and not detected at baseline).
- Treatment-boosted ADA positive (baseline ADA titer that was boosted by ≥4-fold following drug administration).
- 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, defined as treatment-emergent ADA positive participants having at least 2 post-baseline ADA positive measurements with at least 16 weeks (112 days) between the first and last positive measurement, or an ADA positive result at the last available assessment.
- Treatment-emergent ADA (TE-ADA) transiently positive, defined as treatment-emergent ADA positive participants having at least one post-baseline ADA positive measurement and not fulfilling the conditions for TE-ADA persistently positive.

- nAb (to AZD7442) positive at any visit (at baseline and/or post-baseline).

4.4.2.1.2 ADA Analysis

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 4.4.2.1.1) in different treatment arms will be presented based on the ADA evaluable analysis set. Summaries will be repeated for participants in the treatment group, and will be presented by those vaccinated, unvaccinated, and total.

ADA results will be listed for all participants in the safety analysis set regardless of ADA-evaluable status. ADA titer and nAb data will 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, safety, and efficacy will be examined by descriptive summaries if data allow.

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

4.4.4 Handling of Missing Data

The PK descriptive analyses of serum AZD7442 concentrations (Section 4.4.1) will use the following imputation methods: 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). Individual serum concentrations that are Not Reportable (NR) will be reported as NR and those that are

missing will be reported as No Sample (NS) in the listings. Serum concentrations that are NQ, NR, or NS 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 geometric mean, 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 geometric mean, minimum, median, and maximum will be reported as NQ and the gCV% and geometric mean ± 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).

Three observations > LLOQ are required as a minimum for a serum concentration or PK parameter (e.g. Cmax, Cmin, Clast) to be summarized. Two observations > LLOQ are presented as minimum and maximum with the other summary statistics as NC.

The analysis for the incidence of ADA to AZD7442 in serum will use the following imputation method: ADA titers values below the limit of detection (LOD) are negative results, hence they are not imputed and are excluded from calculation of summary statistics. Titer values of positive ADA samples reported as ≤ LOD are imputed as LOD in the calculation of summary statistics on ADA titer.

CCI

[redacted]

4.5 Safety Analyses

The domain safety covers exposure, adverse events, clinical laboratory, vital signs, and ECG.

Tables are provided for the Safety Analysis Set; listings are provided for All participants or the Safety Analysis Set depending on the availability of data. Safety tables will be repeated in the High Risk population.

4.5.1 Exposure

4.5.1.1 Definitions and Derivations

Due to the simplicity of dosing for this study, exposure is summarized in the participant disposition table.

4.5.1.2 Presentation

Not applicable.

4.5.2 Adverse Events

4.5.2.1 Definitions and Derivations

All Adverse events (AEs) will be coded using the MedDRA dictionary, version 23.1 or higher.

The safety of AZD7442 will assessed by:

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

AEs and SAEs

AEs will be recorded from the time of IMP administration throughout the study up to and including the last visit. Serious adverse events (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. SAEs prior to the dose of IMP and AEs will only be presented in the listings. For SAEs with partial dates, if the known part of the date indicates that SAE stopped before the dose of IMP, it will be considered as SAE prior to the dose of IMP. Otherwise, it will be considered as SAE post 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 immune complex disease
- Injection site reactions

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 dose of IMP will be broken down further by maximum severity and relationship to study intervention. Severity will be classified as mild, moderate, severe, life-threatening or disabling, and 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 system organ class (SOC) or preferred term (PT), only the participant's worst severity grade will be counted for that SOC or PT.

Relationship to IMP

Relationship to IMP/other medication/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 one of those is related.

Exposure adjusted rate

Exposure adjusted rate is calculated as number of participants with AEs in categories divided by total participant-year exposure to investigational study intervention. 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 dose to end of study.

4.5.2.2 Presentation

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

- AEs
- SAEs
- SAEs with outcome death
- AEs leading to IMP discontinuation
- AEs leading to study discontinuation
- AESIs

Summaries will include the number and percentage of participants reporting at least one event, number of events, 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. Should a participant experience multiple events within a category, the participant will be counted only once for that category.

AEs that occur after unblinding due to vaccination will be presented and tabulated separately.

4.5.3 Clinical Laboratory, Blood Sample and Urinalysis

4.5.3.1 Definitions and Derivations

Hematology, serum clinical chemistry, coagulation, 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 upper limit of quantification (ULQ), 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 CTCAE toxicity grades will be categorized as follows where higher grades representing a more severe toxicity (refer to Appendix 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.

4.5.3.2 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).
- 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.
- Scatter plots 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.
- Scatter plots 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.
- Shift from baseline to the worst post-baseline observed value according to the Common Terminology Criteria for Adverse Events (CTCAE) toxicity grades (for quantitative parameters with available CTCAE toxicity grades; refer to Section 4.5.3.1).
- Shifts from baseline to the maximum/minimum post-baseline observed value according to normal range criteria (for quantitative parameters without CTCAE toxicity grades; refer to Section 4.5.3.1).
- Listing of participants with at least one abnormal laboratory observed value outside the normal range criteria (refer to Section 4.5.3.1).

4.5.4 Vital Signs

4.5.4.1 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 (%)

4.5.4.2 Presentations

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

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

- Observed and change from baseline by visit
- Number and percentages of participants with at least one abnormal post-baseline observed value (refer to Appendix 3)
    - Participants will be summarized by the worst severity observed.

4.5.5 Electrocardiogram

4.5.5.1 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)
- QTcB interval (msec)
- QTcF interval (msec)
- RR interval (msec)
- ECG maximum heart rate (beats/min)
- ECG mean heart rate (beats/min)

Since triplicate ECGs will be performed for this study, the mean of the 3 measurements collected on a visit will be used in the by-visit summaries for that visit, but the highest of the 3 measurements collected at baseline and the highest among all post-baseline measurements will be used for the shift from baseline summaries. Should one or two of the

triplicate measurements be missing at a specific visit, the mean of the available measurements will be used in the by-visit summaries for that visit.

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 but ≤ 480 msec
  - > 480 but ≤ 500 msec
  - > 500 msec
- Change from baseline for QTc, QTcF, and QTcB intervals will be classified as:
  - ≥ 30 to 60 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.

4.5.5.2 Presentations

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

- Observed and change from baseline by visit (for quantitative parameters)
- Number and percentages of participants with at least one markedly abnormal post-baseline observed value/change from baseline (for quantitative parameters; refer to Section 4.5.5.1)
- 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
- Listing of participants with at least one abnormal overall ECG interpretation, including the finding(s) for each participant

All individual measurements will be listed.

4.5.6 Other Safety Assessments

4.5.6.1 Definitions and Derivations

Not applicable.

4.5.6.2 Presentations

Not applicable.

5 INTERIM ANALYSIS

No interim analysis will be conducted.

6 REFERENCES

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Wilson, E.B., Hilferty, M.M. The distribution of chi-squared. Proceedings of the National Academy of Sciences, Washington; 1931, 684-688.

Zou, G. A Modified Poisson Regression Approach to Prospective Studies with Binary Data. Am J Epidemiol 2004; 159:702–706.

7 APPENDIX

Appendix 1. Partial Date Conventions

Algorithm for Prior / Concomitant Medications

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

START DATE	STOP DATE	ACTION
	Partial	If known components of medication stop date show that medication stopped before date of dose of IMP, assign as prior; If (known components of medication start date show that medication started before date of dose of IMP) and (known components of medication stop date show that medication stopped on or after date of dose of IMP), assign as concomitant; If known components of medication start date show that medication started on or after date of 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 dose of IMP, assign as concomitant.
Missing	Known or ongoing	If medication stop date < date of dose of IMP, assign as prior; If medication stop date ≥ date of dose of IMP, assign as concomitant.
	Partial	If known components of medication stop date show that medication stopped before date of dose of IMP, assign as prior; If known components of medication stop date show that medication stopped on or after date of dose of IMP, assign as concomitant.
	Missing, not ongoing	Assign as concomitant.

Appendix 2. CTCAE Toxicity Grade, Version 5.0

CTCAE Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anemia	Hemoglobin (g/L)	≥ LLN	≥ 100 g/L - < LLN	≥ 80 - < 100 g/L	< 80 g/L	n/a	n/a
Hemoglobin increased	Hemoglobin (g/L)	No increase from baseline	Increase from baseline > 0 - ≤ 20 g/L	Increase from baseline > 20 - ≤ 40 g/L	Increase from baseline > 40 g/L	n/a	n/a
Platelet count decreased	Platelet count (x10E9/L)	≥ LLN	≥ 75 x 10E9/L – < LLN	≥ 50 - < 75 x 10E9/L	≥ 25 - < 50 x 10E9/L	< 25 x 10E9/L	n/a
White blood cell (WBC) decreased	WBC (x 10E9/L)	≥ LLN	≥ 3.0 x 10E9/L – < LLN	≥ 2.0 - < 3.0 x 10E9/L	≥ 1.0 - < 2.0 x 10E9/L	< 1.0 x 10E9/L	n/a
Leukocytosis	WBC (x 10E9/L)	≤ 100 x 10E9/L	n/a	n/a	> 100 x 10E9/L	n/a	n/a
Absolute neutrophils count decreased	Absolute neutrophils count (x 10E9/L)	≥ LLN	≥ 1.5 x 10E9/L – < LLN	≥ 1.0 - < 1.5 x 10E9/L	≥ 0.5 - < 1.0 x 10E9/L	< 0.5 x 10E9/L	n/a
Absolute lymphocytes count decreased	Absolute lymphocytes count (x 10E9/L)	≥ LLN	≥ 0.8 x 10E9/L – < LLN	≥ 0.5 - < 0.8 x 10E9/L	≥ 0.2 - < 0.5 x 10E9/L	< 0.2 x 10E9/L	n/a
Absolute lymphocytes count increased	Absolute lymphocytes count (x 10E9/L)	≤ 4 x 10E9/L	n/a	> 4 – ≤ 20 x 10E9/L	> 20 x 10E9/L	n/a	n/a

CTCAE Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Eosinophilia	Absolute eosinophils	≤ ULN or ≤ Baseline	> ULN and > Baseline	n/a	n/a	n/a	n/a
Hypernatremia	Sodium (mmol/L)	≤ ULN	> ULN – ≤ 150 mmol/L	> 150 – ≤ 155 mmol/L	> 155 – ≤ 160 mmol/L	> 160 mmol/L	n/a
Hyponatremia	Sodium (mmol/L)	≥ LLN	≥ 130 mmol/L – < LLN	≥ 125 - < 130 mmol/L	≥ 120 - < 125 mmol/L	< 120 mmol/L	n/a
Hyperkalemia	Potassium (mmol/L)	≤ ULN	> ULN – ≤ 5.5 mmol/L	> 5.5 – ≤ 6.0 mmol/L	> 6.0 – ≤ 7.0 mmol/L	> 7.0 mmol/L	n/a
Hypokalemia	Potassium (mmol/L)	≥ LLN	≥ 3.0 mmol/L – < LLN	n/a	≥ 2.5 - < 3.0 mmol/L	< 2.5 mmol/L	n/a
Hypercalcemia	Ionized calcium (mmol/L)	≤ ULN	> ULN – ≤ 1.5 mmol/L	> 1.5 – ≤ 1.6 mmol/L	> 1.6 – ≤ 1.8 mmol/L	> 1.8 mmol/L	n/a
Hypocalcemia	Ionized calcium (mmol/L)	≥ LLN	≥ 1.0 mmol/L – < LLN	≥ 0.9 - < 1.0 mmol/L	≥ 0.8 - < 0.9 mmol/L	< 0.8 mmol/L	n/a
Hypermagnesemia	Magnesium (mmol/L)	≤ ULN	> ULN – ≤ 1.23 mmol/L	n/a	> 1.23 – ≤ 3.30 mmol/L	> 3.30 mmol/L	n/a
Hypomagnesemia	Magnesium (mmol/L)	≥ LLN	≥ 0.5 mmol/L – < LLN	≥ 0.4 - < 0.5 mmol/L	≥ 0.3 - < 0.4 mmol/L	< 0.3 mmol/L	n/a
Hypoglycemia	Glucose (mmol/L)	≥ LLN	≥ 3.0 mmol/L – < LLN	≥ 2.2 - < 3.0 mmol/L	≥ 1.7 - < 2.2 mmol/L	< 1.7 mmol/L	n/a

CTCAE Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Creatinine increased	Creatinine (µmol/L)	≤ ULN	> ULN – ≤ 1.5 x ULN	> 1.5 – ≤ 3.0 x ULN **or** > 1.5 – ≤3.0 x baseline	> 3.0 – ≤ 6.0 x ULN **or** > 3.0 x baseline	> 6.0 x ULN	n/a
Alkaline phosphatase (ALP) increased	ALP (U/L)	≤ ULN if baseline normal; ≤ 2.0 x baseline if baseline abnormal	> ULN – ≤ 2.5 x ULN if baseline normal; > 2.0 - ≤ 2.5 x baseline if baseline abnormal	> 2.5 – ≤ 5.0 x ULN if baseline normal; > 2.5 – ≤ 5.0 x baseline if baseline abnormal	> 5.0 – ≤ 20.0 x ULN if baseline normal; > 5.0 – ≤ 20.0 x baseline if baseline abnormal	> 20.0 x ULN if baseline normal; > 20.0 x baseline if baseline abnormal	n/a
Alanine transaminase (ALT) increased	ALT (U/L)	≤ ULN if baseline normal; ≤ 1.5 x baseline if baseline abnormal	> ULN – ≤ 3.0 x ULN if baseline normal; > 1.5 - ≤ 3.0 x baseline if baseline abnormal	> 3.0 – ≤ 5.0 x ULN if baseline normal; > 3.0 – ≤ 5.0 x baseline if baseline abnormal	> 5.0 – ≤ 20.0 x ULN if baseline normal; > 5.0 – ≤ 20.0 x baseline if baseline abnormal	> 20.0 x ULN if baseline normal; > 20.0 x baseline if baseline abnormal	n/a

CTCAE Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Aspartate transaminase (AST) increased	AST (U/L)	≤ ULN if baseline normal; ≤ 1.5 x baseline if baseline abnormal	> ULN – ≤ 3.0 x ULN if baseline normal; > 1.5 - ≤ 3.0 x baseline if baseline abnormal	> 3.0 – ≤ 5.0 x ULN if baseline normal; > 3.0 – ≤ 5.0 x baseline if baseline abnormal	> 5.0 – ≤ 20.0 x ULN if baseline normal; > 5.0 – ≤ 20.0 x baseline if baseline abnormal	> 20.0 x ULN if baseline normal; > 20.0 x baseline if baseline abnormal	n/a
Blood bilirubin increased	Total bilirubin (µmol/L)	≤ ULN if baseline normal; ≤ baseline if baseline abnormal	> ULN – ≤ 1.5 x ULN if baseline normal; > baseline - ≤ 1.5 x baseline if baseline abnormal	> 1.5 – ≤ 3.0 x ULN if baseline normal; > 1.5 - ≤ 3.0 x baseline if baseline abnormal	> 3.0 – ≤ 10.0 x ULN if baseline normal; > 3.0 - ≤ 10.0 x baseline if baseline abnormal	> 10.0 x ULN if baseline normal; > 10.0 x baseline if baseline abnormal	n/a

CTCAE Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Gamma glutamyl transferase (GGT) increased	GGT (U/L)	≤ ULN if baseline normal; ≤ 2.0 x baseline if baseline abnormal	> ULN – ≤ 2.5x ULN if baseline normal; > 2.0 - ≤ 2.5 x baseline if baseline abnormal	> 2.5 – ≤ 5.0 x ULN if baseline normal; > 2.5 - ≤ 5.0 x baseline if baseline abnormal	> 5.0 – ≤ 20.0 x ULN if baseline normal; > 5.0 - ≤ 20.0 x baseline if baseline abnormal	> 20.0 x ULN if baseline normal; > 20.0 x baseline if baseline abnormal	n/a
Hypoalbuminemia	Albumin (g/L)	≥ LLN	≥ 30 g/L - < LLN	≥ 20 - < 30 g/L	< 20 g/L	n/a	n/a
CPK increased	Creatine kinase (U/L)	≤ ULN	> ULN – ≤ 2.5 x ULN	> 2.5 – ≤ 5 x ULN	> 5 – ≤ 10 x ULN	> 10 x ULN	n/a
International normalized ratio (INR) increased	INR	≤ 1.2 if not on anticoagulant; ≤ baseline if on anticoagulant	> 1.2 – ≤1.5 if not on anticoagulant; > baseline - ≤ 1.5 x baseline if on anticoagulant	> 1.5 – ≤2.5 if not on anticoagulant; > 1.5 - ≤ 2.5 x baseline if on anticoagulant	> 2.5 if not on anticoagulant; > 2.5 x baseline if on anticoagulant	n/a	n/a

Appendix 3. Clinical Abnormalities: Vital Signs

Vital Signs	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	ER visit or hospitalization for arrhythmia
Bradycardia (beats/minute) [c]	50-54	45-49	< 45	ER visit or hospitalization for arrhythmia
Hypertension; systolic (mm Hg)	141-150	151-155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension; diastolic (mm Hg)	91-95	96-100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension; systolic (mm Hg)	85-89	80-84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory rate (breaths/minute)	17-20	21-25	> 25	Intubation

ER = emergency room; Hg = mercury.