STATISTICAL ANALYSIS PLAN

D8850C00003

A PHASE III RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTI-CENTER STUDY IN ADULTS TO DETERMINE THE SAFETY AND EFFICACY OF AZD7442, A COMBINATION PRODUCT OF TWO MONOCLONAL ANTIBODIES (AZD8895 AND AZD1061), FOR POST-EXPOSURE PROPHYLAXIS OF COVID-19

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Version
1.0	29Dec2020	PPD	Not Applicable – First Version
2.0	26Mar2021	PPD	Given that the probability of a participant being exposed to COVID-19 will diminish with increased vaccination roll-out, the primary analysis will be conducted 30 days after the 25th event has been confirmed. To reflect this change in the timing of the primary analysis the interim analysis and related activities have been removed. Enrollment will be stopped after the 25th primary endpoint event has been confirmed, or after 1125 participants have been randomized, whichever comes first. To provide safety and PK assessments after 5 half-lives, the study has been extended to 15 months from last visit on Day 366 to last visit on Day 457. An optional serum sample for PK, ADA and nAb to be added at Day 457. Endpoints for safety and nAb have been adjusted to reflect this additional time point. Caps for Cohorts 1 and 2, not to exceed 80% of the total participants randomized, have been removed. During screening the eCRF is already capturing participant ECOG grade and therefore, for consistency, Performance Status has been added to Medical History.
3.0	06Apr2021	PPD	The planned primary analyses and authoring of the SAP will no longer be conducted by the analysis team at IQVIA. Sections in 4.3 and 4.4 have been revised to indicate AstraZeneca has assumed responsibility as the study sponsor for the primary analysis. To clearly maintain the relationship between the RT-PCR sample and symptoms for the primary

			endpoint durations were set around the assessment of qualifying symptoms. The durations have been adjusted from the previous version to have the Rt-PCR samples collected within 5 days prior or 10 days following the assessment of qualifying symptoms. See section 16.1. To clarify the definition of "High risk for severe Covid-19" Appendix 6 was added specifying data sources to be used when programming each condition.
3.1	06Apr2021	PPD	Added text to allow Anterior Nasal Swabs to be included in the RT-PCR tests used in the primary endpoint.

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1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for protocol D8850C00003. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This SAP is based on protocol version 6.0, dated 12Mar2021.

The term IMP (investigational medicinal product) is used throughout this SAP to include both treatment groups (AZD7442 and placebo). AZD7442 is specified when referring only to those who received active intervention.

2. STUDY OBJECTIVES AND ESTIMANDS

2.1. PRIMARY OBJECTIVES

The primary objectives are:

- To estimate the efficacy of a single intramuscular (IM) dose of AZD7442 compared to placebo for the prevention of coronavirus disease 2019 (COVID-19);
- To assess the safety and tolerability of a single IM dose of AZD7442 compared to placebo.

2.2. SECONDARY OBJECTIVES

The key secondary objective is:

- To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of severe or critical symptomatic COVID-19.

The other secondary objectives are:

- To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection;
- To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19-related death;
- To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of all-cause mortality;
- To assess the pharmacokinetics (PK) of AZD7442 administered as a single dose of 300 mg IM;
- To evaluate anti-drug antibody (ADA) responses to AZD7442 in serum.

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives are:

- To evaluate the single dose PK concentrations of AZD7442 in nasal fluid;
- To determine anti-SARS-CoV-2 neutralizing antibody (nAb) levels in serum following a single IM dose of AZD7442 or placebo;
- To quantify SARS-CoV-2 viral loads in infected participants treated with a single IM dose of AZD7442 or placebo (Illness Visits);
- To quantify duration of viral shedding in participants with symptomatic COVID-19 treated with a single IM dose of AZD7442 or placebo (Illness Visits);
- To characterize resistance to AZD7442 (Illness Visits) – not covered by this SAP;
- To assess symptoms associated with COVID-19 using an e-Diary in participants treated with a single IM dose of AZD7442 or placebo (Illness Visits only);
- To assess additional immune responses following a single IM dose of AZD7442 or placebo – not covered by this SAP.

2.4. ESTIMANDS

Table A: List of Estimands - Primary

	Attributes				
Label	**Definition Population**	**Treatment Condition of Interest**	**Variable/Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
The efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19	Full analysis set, defined as all participants who were randomized and received at least one of the planned injections of IMP. Targeted participants will have the following characteristics: Adults ≥ 18 years of age with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection, symptomatic or asymptomatic, who are therefore at appreciable risk of imminently developing COVID-19, based on available risk assessment at time of enrollment	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component) or placebo	A binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs post dose of IMP and prior to day 183.	For participants who become unblinded to properly consider vaccination for COVID-19, take COVID-19 vaccine or other COVID-19 preventive product prior to having met the criteria for the primary efficacy endpoint, the data will be collected and analyzed regardless (i.e., intercurrent events will be handled using treatment policy strategy).	Prophylactic efficacy, calculated as 1-relative risk. (Relative risk is the incidence of infection in the AZD7442 group relative to the incidence of infection in the control group.)
The safety and tolerability of a single IM dose of	Safety analysis set, defined as all participants who received at least one of the planned injections of IMP. Targeted participants will have the following	Single dose of AZD7442 (× 2 IM injections,	Incidence of adverse events, serious adverse events, medically attended adverse events, and adverse events of	Not Applicable	Descriptive statistics, including number and percentages of participants who

	Attributes				
Label	**Definition Population**	**Treatment Condition of Interest**	**Variable/Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
AZD7442 compared to placebo	characteristics: Adults ≥ 18 years of age with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection, symptomatic or asymptomatic, who are therefore at appreciable risk of imminently developing COVID-19, based on available risk assessment at time of enrollment	1 for each mAb component) or placebo	special interest post dose of IMP.		have the incidence, and number of events.

Table B: List of Estimands – Key Secondary

	Attributes				
Label	**Definition Population**	**Treatment Condition of Interest**	**Variable/Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
The efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of severe or critical symptomatic COVID-19	Full analysis set (see definition in primary estimands). Targeted participants will have the following characteristics: Adults ≥ 18 years of age with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection, symptomatic or asymptomatic, who are therefore at appreciable risk of imminently developing COVID-19, based on available risk assessment at time of enrollment	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component) or placebo	The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring after dosing with IMP.	For participants who become unblinded to properly consider vaccination for COVID-19, take COVID-19 vaccine or other COVID-19 preventive product prior to having met the criteria for this endpoint, data will be collected and analyzed regardless (i.e., intercurrent events will be handled using treatment policy strategy)	Prophylactic efficacy, calculated as 1-relative risk. (Relative risk is the incidence of severe or critical symptomatic illness in the AZD7442 group relative to the incidence of severe or critical symptomatic illness in the control group.)

Table C: List of Estimands –Secondary

	Attributes				
Label	**Definition Population**	**Treatment Condition of Interest**	**Variable/Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
The efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of SARS-CoV-2 infection	Full analysis set (see definition in primary estimands). Targeted participants will have the following characteristics: Adults ≥ 18 years of age with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection, symptomatic or asymptomatic, who are therefore at appreciable risk of imminently developing COVID-19, based on available risk assessment at time of enrollment	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component) or placebo	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.	For participants who become unblinded to properly consider vaccination for COVID-19, take COVID-19 vaccine or other COVID-19 preventive product prior to having met the criteria for this secondary efficacy endpoint, the data will be collected and analyzed regardless (i.e., intercurrent events will be handled using treatment policy strategy).	Prophylactic efficacy, calculated as 1-relative risk. (Relative risk is the incidence of infection in the AZD7442 group relative to the incidence of infection in the control group.)

	Attributes				
Label	**Definition Population**	**Treatment Condition of Interest**	**Variable/Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19-related death	Full analysis set (see definition in primary objectives). Targeted participants will have the following characteristics: Adults ≥ 18 years of age with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection, symptomatic or asymptomatic, who are therefore at appreciable risk of imminently developing COVID-19, based on available risk assessment at time of enrollment	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component) or placebo	The incidence of COVID-19-related death occurring after dosing with IMP	For participants who become unblinded to properly consider vaccination for COVID-19, take COVID-19 vaccine or other COVID-19 preventive product prior to having met the criteria for this secondary efficacy endpoint, the data will be collected and analyzed regardless (i.e., intercurrent events will be handled using treatment policy strategy).	Prophylactic efficacy, calculated as 1-relative risk. (Relative risk is the incidence of COVID-19 related death in the AZD7442 group relative to the incidence of COVID-19 related death in the control group.)

	Attributes				
Label	**Definition Population**	**Treatment Condition of Interest**	**Variable/Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
To estimate the efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of all-cause mortality	Full analysis set (see definition in primary estimands). Targeted participants will have the following characteristics: Adults ≥ 18 years of age with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection, symptomatic or asymptomatic, who are therefore at appreciable risk of imminently developing COVID-19, based on available risk assessment at time of enrollment	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component) or placebo	The incidence of all-cause mortality occurring after dosing with IMP.	For participants who become unblinded to properly consider vaccination for COVID-19, take COVID-19 vaccine or other COVID-19 preventive product prior to having met the criteria for this secondary efficacy endpoint, the data will be collected and analyzed regardless (i.e., intercurrent events will be handled using treatment policy strategy).	Prophylactic efficacy, calculated as 1-relative risk. (Relative risk is the incidence of death (all-cause) in the AZD7442 group relative to the incidence of death (all-cause) in the control group.)

	Attributes				
Label	**Definition Population**	**Treatment Condition of Interest**	**Variable/Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
The pharmacokinetics of AZD7442 administered as a single dose of 300 mg IM	Pharmacokinetic analysis set, defined as all participants who receive at least one of the planned injections of 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. Targeted participants will have the following characteristics: Adults ≥ 18 years of age with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection, symptomatic or asymptomatic, who are therefore at appreciable risk of imminently developing COVID-19, based on available risk assessment at time of enrollment	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component) or placebo	Serum AZD7442 concentrations. PK parameters if data permit.	Not Applicable	Individual AZD7442 (AZD8895 and AZD1061) serum concentration data descriptive statistics; Pharmacokinetic exposure (i.e., AUCs) and other PK parameters may be estimated using non compartmental analysis, if data permit.

	Attributes				
Label	**Definition Population**	**Treatment Condition of Interest**	**Variable/Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
ADA responses to AZD7442 in serum	ADA evaluable analysis set, defined as all participants who received at least one of the planned injections of IMP and who have a non-missing baseline AZD7442 ADA result and at least one non-missing post-baseline AZD7442 ADA result. Targeted participants will have the following characteristics: Adults ≥ 18 years of age with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection, symptomatic or asymptomatic, who are therefore at appreciable risk of imminently developing COVID-19, based on available risk assessment at time of enrollment	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component) or placebo	Incidence of ADA to AZD7442 in serum.	Not Applicable	Descriptive statistics including the number and percentage of participants who have developed ADAs to AZD7442.

Table D: List of Estimands – Exploratory

Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
The single dose pharmacokinetic concentrations of AZD7442 in nasal fluid	A subset of the pharmacokinetic analysis set, per available data, defined as all participants who receive at least one of the planned injections of AZD7442, from whom PK nasal fluid samples are assumed not to be affected by factors such as protocol violations, and who had at least one quantifiable nasal fluid PK observation post dose. Targeted participants will have the following characteristics: Adults ≥ 18 years of age with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection, symptomatic or asymptomatic, who are therefore at appreciable risk of imminently developing COVID-19, based on available risk assessment at time of enrollment	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component)	AZD7442 nasal concentrations.	Not Applicable	Individual concentration data with descriptive statistics
Anti-SARS-CoV-2 nAb levels in serum	The nAb evaluable analysis set, defined as all participants who received at least one of the planned injections of IMP, from whom	Single dose of AZD7442 (× 2 IM injections, 1 for each	Post-treatment GMTs and GMFRs from	Not Applicable	GMT and GMFR with descriptive statistics

Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
following a single IM dose of AZD7442 or placebo	blood samples are assumed not to be affected by factors such as protocol violations, and who had at least one quantifiable serum titer observation post dose. Targeted participants will have the following characteristics: Adults ≥ 18 years of age with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection, symptomatic or asymptomatic, who are therefore at appreciable risk of imminently developing COVID-19, based on available risk assessment at time of enrollment	mAb component) or placebo	baseline value through Day 457 after single IM dose in SARS-CoV-2 neutralizing antibodies (wild-type assay or pseudo neutralization assay).		
SARS-CoV-2 viral loads in infected participants treated with a single IM dose of AZD7442 or placebo (Illness Visits)	Symptomatic COVID-19 analysis set, defined as all participants who were randomized, received at least one of the planned injections of IMP, did not have a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection, and who met the criteria for symptomatic COVID-19 and began Illness Visits following confirmed SARS-CoV-2 infection. Targeted participants will have the following	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component) or placebo	Viral genome copies in NP swabs collected at Illness Visits as determined by qRT-PCR.	Not Applicable	Observed and change from baseline descriptive statistics

Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
	characteristics: Adults ≥ 18 years of age with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection, symptomatic or asymptomatic, who are therefore at appreciable risk of imminently developing COVID-19, based on available risk assessment at time of enrollment.				
Symptoms associated with COVID-19 using an e-Diary in participants treated with a single IM dose of AZD7442 or placebo (Illness Visits only)	Symptomatic COVID-19 analysis set (see definition above). Targeted participants will have the following characteristics: Adults ≥ 18 years of age with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection, symptomatic or asymptomatic, who are therefore at appreciable risk of imminently developing COVID-19, based on available risk assessment at time of enrollment.	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component) or placebo	Symptoms recorded by participants in an Illness e-Diary from Illness Visits Day 2 through Day 28.	Not Applicable	Descriptive statistics, including number and percentage of participants with symptoms.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a Phase III, randomized, double-blind, placebo-controlled, multi-center study assessing the safety and efficacy of a single dose of AZD7442 (× 2 IM injections) compared to placebo for the prevention of COVID-19. Approximately 100 sites will participate in this study.

Participants will be adults ≥ 18 years of age with potential exposure, within 8 days to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection, symptomatic or asymptomatic, who are therefore at appreciable risk of imminently developing COVID-19, based on available risk assessment at time of enrollment (see Protocol Section 5.1). Participants will be enrolled into one of 2 cohorts:

- Cohort 1: Adults ≥ 60 years of age, living in long term care facilities. In this context, long-term care facilities include skilled nursing facilities, assisted living facilities, and independent living facilities for senior adults. In this cohort, “potential exposure to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection" is defined to mean the occurrence of SARS-CoV-2 infection, symptomatic or asymptomatic, in another resident of the facility or in a staff member of the facility.
- Cohort 2: Other adults ≥ 18 years of age with potential exposure to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection. Such individuals may include, but are not limited to those living in institutional residences (military lodging, dormitories, etc.), household contacts, health care workers, long term care facility workers, and workers in occupational or industrial settings in which close contact is common.

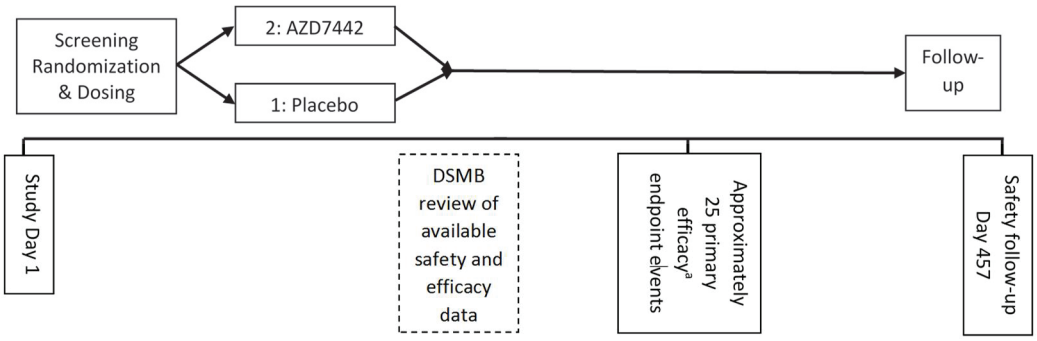
The first 15 participants (Sentinel Cohort), will undergo safety monitoring for 4 hours post IMP administration before dosing further participants. The next 85 participants will undergo safety monitoring for 2 hours pose IMP administration, and, if no hypersensitivity reactions are observed, the remaining participants will undergo safety monitoring for 1 hour post IMP administration. Should hypersensitivity reactions be observed, in the first 100 participants, all participants will be monitored for safety for at least 2 hours post IMP administration.

Up to 1125 participants will be randomized in a 2:1 ratio to receive a single dose (× 2 IM injections) of either 300 mg of AZD7442 (n = approximately 750) or saline placebo (n = approximately 375) on Day 1. Enrollment will continue until the 25th primary endpoint event has been confirmed, or until 1125 subjects have been enrolled, whichever comes first. Formal efficacy assessment is intended at the primary analysis, 30 days after the 25th primary endpoint has occurred.

Following a screening evaluation, on the same day participants will receive a single dose (× 2 IM injections) of IMP. After administration of the dose of IMP on Day 1, participants will undergo follow-up as stated in the schedule of activities. All participants in the study will be assessed for efficacy with all data available through their last

assessment up to visit Day 366 and PK, ADA, nAbs and safety will be assessed up to 15 months following the dose of IMP.

Figure A: Study Design



[a] Primary analysis to be conducted 30 days after the 25th event is observed.

Note: An independent Data Safety Monitoring Board (DSMB) will review available safety and efficacy data after the first 100 participants have been dosed, or after 4 weeks from first participant dosed, whichever comes first. Enrollment will not be paused pending the DSMB's review.

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section 1.3 of the protocol.

3.3. CHANGES TO ANALYSES FROM PROTOCOL

There are no changes to the analyses planned in the protocol.

4. PLANNED ANALYSES

4.1. DATA AND SAFETY MONITORING BOARD

An independent DSMB will provide oversight, to ensure safe and ethical conduct of the study.

The DSMB will meet monthly and make any necessary recommendations to the Sponsor based on their evaluations of emerging data.

In particular, the evaluation of cumulative safety data from the first 100 participants enrolled will be performed by the DSMB, who will advise the Sponsor on whether it is appropriate to proceed. This evaluation will take place as

soon as practical after randomization of the study's 100th participant or after 4 weeks from first participant dosed, whichever comes first. Study enrollment will not be paused pending or during this evaluation by the DSMB.

Further details, composition, and operation of the independent DSMB will be described in a DSMB Charter.

4.2. INTERIM ANALYSIS

No Interim Analysis is planned.

4.3. PRIMARY ANALYSIS

The primary analysis will be conducted 30 days after 25 primary endpoint events have been observed across the active and control groups. The date for the Data Cutoff for this analysis will be calculated as date of onset of primary endpoint event (+30 days).

All planned primary analyses are detailed in this SAP and will be performed by AstraZeneca or its delegates following authorization of this SAP, authorization of the analysis sets, database lock (DBL), and analysis team unblinding. The primary analysis will be carried out by an unblinded analysis team, and the procedure will be detailed in an unblinding plan; participant level unblinding information will be kept strictly confidential, and rationale for any unblinding will be documented.

4.4. FINAL ANALYSIS

The final analysis will be conducted at the end of the study, i.e., after the last participant dosed has completed the Day 457 visit, regardless of the number of events. This analysis will not be controlled for multiplicity and statistical hypotheses will be tested at a nominal 5% significance level (based on a 2-sided test).

All planned final analyses are detailed in this SAP and will be performed by AstraZeneca or its delegates following authorization of this SAP, authorization of the analysis sets, DBL, and general study unblinding.

5. ANALYSIS SETS

5.1. ALL PARTICIPANTS ANALYSIS SET

The all participants analysis set (PAS) will contain all participants who provide informed consent for this study.

5.2. FULL ANALYSIS SET

The Full Analysis Set (FAS) will contain all participants in the PAS who were randomized and received at least one

of the planned injections of IMP, irrespective of their protocol adherence and continued participation in the study. (Note: Per the protocol a dose is two injections, but any participant receiving at least one injection will be included in the FAS based on intent-to-treat (ITT) principle). Participants will be analyzed according to their randomized treatment irrespective of whether or not they have prematurely discontinued, according to the ITT principle. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination.

For analyses and displays based on the FAS, participants will be classified according to randomized treatment regardless of what treatment they actually received.

5.3. SAFETY ANALYSIS SET

The safety analysis set (SAF) will contain all participants in the PAS who received at least one of the planned injections of IMP. (Per the protocol a dose is two injections, but any participant receiving at least one injection will be included in the SAF to account for safety in all participants receiving any injection).

For analyses and displays based on SAF, participants will be classified according to the actual treatment received. Erroneously-treated participants (e.g., 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. A participant who has once or on several occasions received active IMP will be classified as active.

5.4. PHARMACOKINETIC ANALYSIS SET

The PK analysis set will contain all participants in the PAS who received at least one injection of AZD7442 components 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. (Per the protocol a dose is two injections, but any participant receiving one injection will be accounted for in the corresponding individual mAb component).

For analyses and displays based on PK analysis set, participants will be included according to the actual treatment received. Participants who received placebo will not be included. Summaries will be displayed by the individual mAb components, AZD8895 and AZD1061.

5.5. ADA EVALUABLE ANALYSIS SET

The ADA evaluable analysis set will contain all participants who received at least one of the planned injections of IMP and who have a non-missing baseline AZD7442 ADA result and at least one non-missing post-baseline AZD7442 ADA result.

5.6. nAb Evaluable Analysis Set

The SARS-CoV-2 nAb evaluable analysis set will contain all participants in the SAF from whom blood samples are assumed not to be affected by factors such as protocol violations, and who had at least one quantifiable serum observation post dose.

5.7. Symptomatic COVID-19 Analysis Set

The symptomatic COVID-19 analysis set will include all participants in the FAS who met the criteria for symptomatic COVID-19 and began Illness Visits following confirmed SARS-CoV-2 infection.

6. General Considerations

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

Study Day will be computed as follows:

- Study Day = (Date of event –Date of dose of IMP) + 1 if the date of the event is on or after the date of the dose of IMP;
- Study Day = (Date of event – Date of dose of IMP) if the date of the event is prior to the date of dose of IMP.

In the situation where the 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 event –Date of illness visit Day 1) + 1.

6.2. Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to the dose of IMP. In the case where the last non-missing measurement and the date and time of the dose of IMP coincide or where time is missing, that measurement will be considered baseline, but adverse events (AEs) and medications

commencing on the date and time of the dose of IMP will be considered post-baseline.

Illness Visit baseline is defined as the first non-missing measurement taken on Illness Visit Day 1, for the first illness episode with laboratory confirmed positive reverse transcriptase polymerase chain reaction (RT-PCR) test result. 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.

6.3. UNSCHEDULED VISITS, RETESTS, AND EARLY TERMINATION DATA

For by-visit summaries, data recorded at the nominal visit will be presented. That is, unscheduled, retest (same visit number assigned), and early termination measurements will not be included in by-visit summaries but might contribute to the baseline timepoint and/or maximum value, where required (e.g. shift table). Visits for human biological samples data will follow a windowing convention as described in Section 6.4.

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

6.4. WINDOWING CONVENTIONS

A windowing convention will be used to determine the analysis value for a given study visit for human biological samples data analyses. The window definitions as following will be used for the following assessments:

- Main study: serum sample for SARS-CoV-2 serology (anti-nucleocapsid testing)
- Main study: serum sample for AZD7442 PK assessment;
- Main study: serum sample for AZD7442 ADA assessment;
- Main study: serum sample for SARS-CoV-2 nAbs assessment (pharmacodynamic [PD]);
- Main study: serum sample exploratory biomarkers;
- Main study: nasal adsorption for exploratory assessments (PK);
- Illness visits schedule: self-collected anterior nasal sample for viral shedding;
- Illness visits schedule: serum sample for AZD7442 PK assessment (PK);
- Illness visits schedule: serum sample for SARS-CoV-2 nAbs assessment (PD);
- Illness visits schedule: nasal adsorption for SARS-CoV-2 mucosal responses and exploratory assessments (PK);

- Illness visits schedule: 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 even number of days exists between two consecutive visits, then the upper limit will be taken as the midpoint value minus 1 day

Table E: Analysis windows for serum sample for SARS-CoV-2 serology testing, serum sample for AZD7442 PK assessment, serum sample for SARS-CoV-2 nAbs assessment (PD) and serum sample exploratory biomarkers by Visit

Visit	Day Relative to Dose	Visit Window (Study Day)
Day 1	≤ 1	≤ 1
Day 8	8	2 - 18
Day 29	29	19 - 43
Day 58	58	44 – 74
Day 92	92	75 - 137
Day 183	183	138 - 274
Day 366	366	275 - 411
Day 457	457	≥ 412

Table F: Analysis windows for serum sample for AZD7442 ADA assessment by Visit

Visit	Day Relative to Dose	Visit Window (Study Day)
Day 1	≤ 1	≤ 1
Day 29	29	2 - 60
Day 92	92	61 - 137
Day 183	183	138 - 274
Day 366	366	275 - 411
Day 457	457	≥ 412

Table G: Analysis windows for serum sample for AZD7442 PK assessment, serum sample for nasal adsorption, serum sample for SARS-CoV-2 nAbs assessment (PD) and serum sample exploratory biomarkers by Visit (Illness Visit Schedule)

Visit	Scheduled Illness Day	Visit Window (Illness Study Day)
Illness Day 1	≤ 1	≤ 1
Illness Day 14	14	8 – 21
Illness Day 28	28	22 - 35

Table H: Analysis windows for Viral Shedding by Visit (Illness Visit Schedule)

Visit	Scheduled Illness Day	Visit Window (Illness Study Day)
Illness Day 1	≤ 1	≤ 1
Illness Day 3	3	2 - 3

Illness Day 5	5	4 - 6
Illness Day 8	8	7 - 11
Illness Day 14	14	12 - 17
Illness Day 21	21	18 - 24
Illness Day 28	28	25 - 35

Windows are applied only to the first illness episode 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.

6.5. COMMON CALCULATIONS

Change from baseline will be calculated as:

- Change from baseline = Test value at post-baseline visit – Baseline value;

Percent change from baseline will be calculated as:

- Percent change from baseline (%) = (Change from baseline at post-baseline visit / Baseline value) * 100%;

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 Visit post Illness Visit Day 1– Illness Visit baseline value;

Percent change from baseline at Illness Visits will be calculated as:

- Percent change from baseline Illness Visit Day 1 (%) = (Change from baseline at Illness Visit Day 1/ Baseline value) * 100%;
- Percent change from baseline at Illness Visits after Illness Visit Day 1 (%) = (Change from baseline at Visit post Illness Visit baseline / Illness Visit Baseline value) * 100%.

If baseline is not available, the change from baseline and percent change from baseline will not be calculated and will remain missing.

7. STATISTICAL CONSIDERATIONS

For continuous data, descriptive statistics (i.e., n [number of participants with available data], mean, standard deviation [SD], median, minimum, maximum, and quartile values) will be presented by treatment group 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.

For categorical data, the number and percentages of participants in each category will be presented by treatment group and visit, when applicable. The denominator for percentage calculations is the underlying analysis set population N values unless otherwise stated.

7.1. SAMPLE SIZE CALCULATION

Approximately 1125 participants will be randomized in a 2:1 ratio to receive a single IM dose of AZD7442 (divided in 2 sequential injections, one for each mAb component) (the active group, n = approximately 750) or saline placebo (the control group, n = approximately 375) on Day 1.

The sample size calculations are based on the primary efficacy endpoint and were derived following a modified Poisson regression approach (Zou 2004). All participants will be followed for the entire duration of the study. The primary analysis will be conducted 30 days after the 25th primary endpoint event has occurred. The study will have approximately 90% power to demonstrate that the lower bound of the 2-sided 95% CI for efficacy is greater than zero, assuming an attack rate of 4.5% in the placebo group and true efficacy of 75% (equating to an attack rate of 1.1% in the AZD7224 group).

To mitigate the uncertainty around these assumptions, a blinded sample size re-estimation (BSSR) may be conducted prior to the primary analysis. The overall event rate, as well as the data from external sources (e.g., prophylactic efficacy of other COVID-19 preventive mAbs), will be used in the sample size re-estimation and strictly no treatment information from this study will be used in the review. The summaries will not contain any information that would potentially reveal treatment assignments. The review may result in an adjustment of sample size when the observed attack rate is greatly different than expected. Since this review will be performed in a blinded fashion, no adjustment for the Type I error is needed. Full details will be in a BSSR plan.

A final analysis will be conducted at the end of the study, i.e., when the last participant dosed has completed the Day 457 visit.

7.2. MISSING DATA

Missing efficacy data will be handled as described in Sections 16.1.2, 16.2.4, and 16.3.2 of this analysis plan.

Partial or completely missing medication dates will be handled as described in APPENDIX 1.

7.3. STATISTICAL TESTS

Unless stated otherwise, statistical tests will be conducted at the two-sided 5% significance level. Confidence Intervals (CIs) will be two-sided with 95% coverage.

The null hypothesis is: There is no difference in efficacy between AZD7442 and placebo in preventing COVID-19 (i.e. efficacy is equal to 0). Whereas, the alternative hypothesis is: There is a difference in efficacy between AZD7442 and placebo in preventing COVID-19 (i.e. efficacy is not equal to 0). That is:

- Null hypothesis: No difference (i.e. Efficacy = 0)
- Alternative hypothesis: There is a difference (i.e. Efficacy $\neq$ 0)

The primary efficacy endpoint will be formally assessed at the primary analysis. The primary analysis will be conducted 30 days after the 25th primary endpoint event has occurred. Additional events may occur after the primary analysis. These will be evaluated and reported as exploratory endpoints at the end of study analysis. All participants will be followed for the entire duration of the study. Efficacy will be presented with a 2-sided 95% CI, and statistical significance will be achieved if the 95% CI lower bound is > 0.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

If the primary endpoint achieves statistical significance a hierarchical approach will be used to control for multiplicity of the primary and key secondary efficacy endpoints.

With that, the overall Type I error is controlled at 0.05. Therefore, no further multiplicity adjustment is necessary.

7.5. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers internationally. Data from all centers will be pooled together in the analyses and there are no plans to perform an analysis of homogeneity of the results across centers.

7.6. EXAMINATION OF SUBGROUPS

Subgroup analyses will be conducted as stated in Sections 16.1.7. It should be noted that the study was not designed to detect treatment differences with high statistical power within subgroups.

The subgroups are:

- Categorical age (years) at informed consent (3 groupings 1: ≥ 60 years and < 60 years, 2: ≥ 65 years and < 65 years, 3: ≥ 75 years and < 75 years);
- Sex (male and female);
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islanders, White);
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino);
- COVID-19 co-morbidities at baseline (at least one co-morbidity, no co-morbidity) (use the medical history electronic case report form (eCRF) page);
- SARS-CoV-2 RT-PCR status at baseline (positive or negative).
- High Risk for severe COVID-19 at baseline (History of Obesity, Obese (BL BMI≥30), Morbid Obesity (BL BMI ≥40), Chronic kidney disease (CKD), Diabetes, Immunosuppressive disease, Immunosuppressive treatment, Cardiovascular disease (CV disease), Chronic obstructive pulmonary disease (COPD), Chronic liver disease, Hypertension, Asthma, Cancer, Smoking, Sickle cell disease) (yes/no; Refer to Appendix 6 for description of each condition);

If models of subgroup analysis do not converge due to sparse data, only descriptive counts and percentages will be presented.

7.7. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher.

8. OUTPUT PRESENTATIONS

APPENDIX 2 shows conventions for presentation of data in outputs.

9. DISPOSITION AND WITHDRAWALS

All participants who provide informed consent will be accounted for in this study.

9.1. DISPOSITION

Number of participants screened will be presented overall for the PAS. Number and percentage of participants who with screen failure and reason for screen failure will also be presented overall based on the PAS. Number and percentage of participants randomized will be presented overall and by treatment group for the PAS.

Number and percentages of participants ongoing in study (for primary analysis only) and who discontinued early from the study (including reason for withdrawal) will be provided overall and by planned treatment group based on the FAS.

The number of participants included and excluded from each analysis set (including reason for exclusion) will be summarized overall and by planned treatment group based on the FAS. A listing showing inclusion and exclusion of each participant from each analysis set, including reason for exclusion, will be provided.

9.2. PROTOCOL DEVIATIONS

Number and percentage of participants with important protocol deviations, as identified by the study team in a blinded fashion before the DBL, will be provided overall and by planned treatment group based on the FAS for each category of protocol deviations specified in the Protocol Deviations Management Plan.

A listing of protocol deviations identified by the study team (important or not) will be provided.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) – collected at informed consent;
- Cohort (Cohort 1: Adults >= 60 residing in a long-term care facility Cohort 2: Other adults >= 18)
- Age groups (>= 18 to < 60 years, >= 60 to < 70 years, >= 70 to <80 years and >= 80 years, >= 60 years, >= 65 years and >= 75 years);
- Sex (refer to Section 7.6);
- Race (refer to Section 7.6);
- Ethnicity (refer to Section 7.6);
- Weight (kg);
- Height (cm);
- Body Mass Index (BMI) (kg/m^2);
- BMI group (kg/m^2) (< 18.5, ≥ 18.5 - < 25, ≥ 25 - < 30 , ≥ 30 - < 40 and ≥40)
- Smoking status (current, former, never);
- ECOG performance status (0,1 and >1);

- Home or other confinement status (yes/no);
- High Risk for severe COVID-19 at baseline (History of Obesity, Obese (BL BMI≥30), Morbid Obesity (BL BMI ≥40), CKD, Diabetes, Immunosuppressive disease, Immunosuppressive treatment, CV disease, COPD, Chronic liver disease, Hypertension, Asthma, Cancer, Smoking, Sickle cell disease) (yes/no);
- Subgroups specified in Section 7.6 and not previously listed above.

Continuous demographic and other baseline characteristics will be summarized using descriptive statistics overall and by planned treatment group based on the FAS. For categorical demographic and other baseline characteristics, number and percentage of participants in each category will be provided overall and by planned treatment group based on the FAS. If there are major differences between the FAS and the SAF, the summaries will be repeated and presented by actual treatment arm for the SAF. No statistical testing will be carried out for demographic or other baseline characteristics.

10.1. DERIVATIONS

BMI, in kg/m^2, will be calculated as follows:

- BMI (kg/ m^2) = weight (kg)/ [height $(m)^2$].

11. MEDICAL HISTORY

Medical history is defined as any medical conditions/diseases that started and stopped before the first dose of IMP.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 23.1 or higher, and will be summarized by System Organ Class (SOC) and Preferred Term (PT) overall and by planned treatment group based on the FAS. A participant having more than one medical condition/disease within the same SOC/PT will be counted only once for that SOC or PT.

COVID co-morbidities are collected on the Medical history page of the eCRF. The number and percentage of patients with each co-morbidities and also with any co-morbidities will be summarized overall and by planned treatment group based on the FAS.

All medical history will be listed.

12. CONCOMITANT ILLNESSES

Concomitant conditions/illnesses are defined as any medical conditions/illnesses 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.

Concomitant conditions/illnesses will be coded using the MedDRA, version 23.1 or higher, and will be summarized by SOC and PT overall and by planned treatment group based on the FAS. A participant having more than one medical condition/illness within the same SOC or PT will be counted only once for that SOC or PT.

All concomitant conditions/illnesses will be listed.

13. MEDICATIONS

Prior medications are defined as any medication that started and stopped prior to the dose of IMP.

Concomitant medications are defined as:

- Any medication that started before the dose of IMP AND was ongoing at the time of the dose of IMP or ended on the date of dose of IMP;
- Any medication that started on or after the dose of IMP.

Partially or completely missing medication start and stop dates will be handled as described in APPENDIX 1.

All medications will be coded using the World Health Organization (WHO) Drug Global dictionary, version B3 March 2020, or a more recent version.

Prior and concomitant medications will be summarized by Anatomical Therapeutic Class (ATC) level 2 and preferred drug name overall and by planned treatment group based on the FAS. 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.

All collected prior and concomitant medications will be listed.

14. EXPOSURE TO STUDY INTERVENTION

Due to the simplicity of dosing for this study, exposure is summarized in the participant disposition table. All exposure data will be listed.

15. COMPLIANCE WITH STUDY INTERVENTION

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

16. EFFICACY ENDPOINTS

Unless otherwise indicated, all efficacy summaries and figures will be presented based on the FAS.

16.1. PRIMARY EFFICACY

16.1.1. PRIMARY EFFICACY ENDPOINT

The primary endpoint is the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose of IMP and prior to Day 183. The primary efficacy endpoint is to be to be assessed 30 days after the 25th event has occurred.

Participants will be included as an event in the primary endpoint if they have RT-PCR-confirmed SARS-CoV-2 prior to Day 183 and present with at least one of the qualifying symptoms in Table I:. The onset of symptoms will commonly occur between 2 and 8 days of infection with detectable virus typically up to 15 days. To maintain the relationship between the RT-PCR sample and symptoms the sample should be collected on or close to the symptom assessment but must be collected within 5 days prior or 10 days following the assessment of qualifying symptoms. This duration will allow subjects time to assess and confirm symptoms under medical supervision after the onset of symptoms, which will typically, but not always, occur at Illness Visit Day 1. 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 nasopharyngeal (NP) swabs, or if only a central laboratory result is available. If only a local NP swab laboratory result is available, then the local laboratory result will be used. If neither central nor local NP swab laboratory results are available, an anterior nasal sample will be used to determine the RT-PCR result. If no SARS-CoV-2 RT-PCR sample is available, the participant will be considered as not having met the primary endpoint. 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, the participant will be considered as not having met the primary endpoint.

Table I: COVID-19 Qualifying Symptoms

Duration	Symptom
No minimum duration	Fever
	Shortness of breath
	Difficulty breathing
	New onset confusion (only for participants ≥ 60 years old)
	Appetite loss or decrease food intake (only for participants ≥ 60 years old)
	Increased supplemental oxygen requirement (only for participants ≥ 60 years old on baseline supplemental oxygen)
Must be present for ≥ 2 days	Chills
	Cough
	Fatigue
	Muscle aches
	Body aches
	Headache
	New loss of taste
	New loss of smell
	Sore throat
	Congestion
	Runny nose
	Nausea
	Vomiting
	Diarrhea

Adapted from (CDC, 2020)
CDC, Centers for Disease Control and Prevention

16.1.2. Missing Data Imputation Method for Primary Efficacy Endpoint

No missing data imputation method will be used for primary efficacy analysis. For participants who withdraw from the study prior to having met the criteria for the primary efficacy endpoint, absence of data following these participants' withdrawal (or lost to follow-up, death not caused by SARS-CoV-2) will be treated as missing. Participants will be considered as not having the event through the time of their last observation.

Sensitivity analyses will be explored to assess the robustness of treatment effects for the primary efficacy endpoint, where different missing data mechanisms will be explored using multiple imputation approaches. Full details of the sensitivity analyses are specified in Section 16.1.5.

16.1.3. Primary Estimand

The treatment condition of interest is single dose of AZD7442 (two IM injections, one for each mAb component, AZD8895 and AZD1061). The alternative treatment condition to which comparison will be made is a placebo.

The population of participants targeted in the primary estimand includes adults at least 18 years of age with potential

exposure, within 8 days, to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection, symptomatic or asymptomatic, who are therefore at appreciable risk of imminently developing COVID-19, based on available risk assessment at time of enrollment.

The primary endpoint (variable) to be obtained is a binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs post dose of IMP and prior to Day 183.

The primary estimand uses a treatment policy strategy. Data for participants who become unblinded to properly consider vaccination for COVID-19, take COVID-19 vaccine or other COVID-19 preventive product, prior to having met the criteria for the primary efficacy endpoint, are collected and analyzed regardless of the intercurrent event.

The population-level summary measure is prophylactic efficacy, calculated as 1 - relative risk (RR). (RR is the incidence of infection in the AZD7442 group relative to the incidence of infection in the control group.)

16.1.4. PRIMARY ANALYSIS OF PRIMARY EFFICACY ENDPOINT

The primary efficacy analysis of the primary endpoint will be performed on the FAS. The primary analysis occurs 30 days after the 25th event has occurred. For participants who withdraw from the study prior to having met the criteria for the primary efficacy endpoint, absence of data following these participants' withdrawal (or lost to follow-up, death not caused by SARS-CoV-2) will be treated as missing and participants will be considered as not having the event through the time of last observation. Participants with deaths that are caused by SARS-CoV-2 (death related to COVID marked on the death eCRF page) or hospitalizations that are characterized to be severe COVID-19 (defined in Section 16.2.1) will also be considered as having the event.

A Poisson regression model with robust variance (Zou, 2004) adjusting for follow-up time, will be used as the primary efficacy analysis model to estimate the RR on the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose of IMP between the AZD7442 and the placebo groups. The model contains the planned treatment group and the log of the follow-up time as an offset. Calculation of follow-up time is detailed as following:

- For participants who meet the primary endpoint before Day 183, the follow up time will be calculated as (Date of Onset of Primary Endpoint) – (Date of Dosing) + 1. The Date of Onset of Primary Endpoint is defined as the assessment date of qualifying COVID symptoms, if associated with a positive SARS-COV-2 RT-PCR lab test from a sample collected within 5 days prior or 10 days after symptom assessment. In the case of death due to COVID-19 or hospitalization due to severe COVID-19, the Date of Onset of Primary Endpoint is the earliest date of death/date of hospital admission when a qualifying symptom assessment is not observed.
- For participants who do not experience a primary endpoint event before Day 183, the efficacy follow-up time will be considered censored and determined based on the following:

- If an end of study date occurs before Day 183, the efficacy follow-up time will be calculated as (Date of End of Study or Date of Last Assessment, whichever is later) – (Date of Dosing) + 1.
- If an end of study date occurs after Day 183, the efficacy follow-up will be censored at Day 183.

For participants who continue to participate in the study at the time of the primary analysis, the Data Cutoff date will be used as their last assessment date. For patients with no post-baseline visit data available, the date of IMP administration will be used i.e. follow-up will be 1 day.

Efficacy is the incidence of infection in the AZD7442 group relative to the incidence of infection in the placebo group, expressed as a percentage. Efficacy will be calculated as relative risk reduction (RRR) = 100% x (1 - relative risk).

For the primary analysis, RRR and its corresponding 2-sided 95% CI will be estimated from the Poisson regression model with robust variance. In addition, the 2-sided p-value testing null hypothesis that there is no difference in efficacy between AZD7442 and placebo (i.e. efficacy is equal to 0) will be obtained from the model. Statistical significance will be achieved if the lower bound of the 95% CI for efficacy is > 0, which corresponds to an observed two-sided p-value < 0.05. For the final analysis nominal 95% CI's will be presented.

The Poisson regression with robust variance analysis will be implemented by using the SAS PROC GENMOD procedure with the REPEATED statement for participant ID and logarithm link as well as OFFSET option. The estimated parameter $\hat{\beta}$ [i.e., log((RR)^)], 2-sided 95% CI for $\hat{\beta}$, and the 2-sided p- value will be obtained from the SAS outputs. The estimated RR and corresponding CI for the RR is given by exponentiating $\hat{\beta}$ and its confidence limits. Therefore, the percent of RRR is given by [(1 – exp($\hat{\beta}$)) * 100%]. The CI for the percent of RRR is given by ([1 – exp(upper confidence limit for $\hat{\beta}$) * 100%], [1 – exp(lower confidence limit for $\hat{\beta}$) * 100%]).

If convergence cannot be achieved with the Poisson regression with robust variance analysis model, an Exact Poisson Regression model will be used as the primary analysis model to test the treatment effect on SARS-CoV-2 RT-PCR-positive symptomatic illness between AZD7442 and placebo groups. SAS procedure of PROC GENMOD with EXACT statement will be used to perform the analysis. The RR of AZD7442 over placebo for the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose and the 95% CI will be obtained from the SAS procedure. The percent of RRR and the 95% CI will be reported following the relationship of RRR (%) = (1-RR) * 100%.

16.1.5. SENSITIVITY ANALYSES FOR PRIMARY EFFICACY ENDPOINT

As a sensitivity analysis to the handling of missing data in the analysis of the primary efficacy endpoint, the primary analysis of the primary efficacy endpoint (refer to Section 16.1.4) will be repeated, without using log follow-up time as offset. For participants who do not have a SARS-CoV-2 RT-PCR-positive symptomatic illness status occurring post dose of IMP and withdraw from the study prior to the time of analysis, their event status will be imputed assuming the observed placebo attack rate using multiple imputation techniques as described in the following paragraphs.

The primary analysis using Poisson regression with robust variance requires a participant-level dataset. A repeated imputation approach is introduced to impute the status of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose of IMP for missing observations at the participant level for the model fitting. By incorporating the between-imputation variance, a reliable statistical inference in both hypothesis testing and CI estimation of the treatment effect is expected through the repeated imputation (Little and Rubin, 2002). In the primary analysis the missing outcome for participants who drop out (e.g., withdrawal, lost to follow-up, death not caused by SARS-CoV-2, etc.) prior to reaching cut-off time for analysis without a SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose of IMP will be imputed using placebo event rate. The imputation and subsequent analysis will be carried out using SAS PROC MI (Monotone Logistic Regression Method) and SAS PROC MIANALYZE. The detailed imputation steps are described as follows.

- Step 1: For the participants in the AZD7442 arm who do not have a SARS-CoV-2 RT-PCR-positive symptomatic illness and are not followed through cut-off time of analysis, their treatment code of "AZD7442" will be substituted with "placebo" to ensure the placebo SARS-CoV-2 RT-PCR-positive symptomatic illness rate is applied in the imputation for the AZD7442 dropouts. Missing events in both arms will then be imputed with the placebo rate. The imputation will be executed using SAS Proc MI (e.g., logistic regression with the recoded treatment term). The random seed is 12345;
- Step 2: The original treatment code will be restored after the SARS-CoV-2 RT-PCR-positive symptomatic illness statuses have been imputed. A complete dataset comprises the imputed SARS-CoV-2 RT-PCR-positive symptomatic illness status and observed SARS-CoV-2 RT-PCR-positive symptomatic illness status;
- Step 3: Analyze the complete dataset using a Poisson regression model with robust variance to estimate the RR on the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness between AZD7442 and placebo, with the term of planned treatment group. The point estimate of log-transformed RR and its variance will be extracted from the model;
- Steps 2-3 will be repeated 20 times. SAS procedure PROC MIANALYZE will be used to combine inferences from the 20 completed datasets, that will result in a combined point estimate of log-transformed RR and the variance.

Additional sensitivity analysis will be carried out as given below

- Multiple imputation as described above using the observed event rate per treatment group for their event status. That is, the replacement of the treatment code in Step 1 and the restoration in Step 2 will be skipped.
- At the final analysis, the efficacy will also be estimated from a Poisson Regression model with robust variance and offset including the log of the follow-up time, which includes all SARS-CoV-2 RT-PCR positive symptomatic illness events, i.e. including those that occurred on or after Day 183.

16.1.6. SUPPLEMENTARY ANALYSES FOR PRIMARY EFFICACY ENDPOINT

To support the primary analysis, time to event (i.e., the duration in days from dose to first event or censoring) analyses will be performed as follows. A Cox proportional hazard (PH) model, with treatment group as the only covariate, will be fitted to the data, and the Efron method will be used to control for ties. Kaplan-Meier curves with log-rank test p-values and estimates (hazard ratio, as well as the corresponding 95% CI) from the Cox PH model will be presented for the AZD7442 and placebo groups based on observed events, showing the cumulative incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose of IMP and prior to Day 183.

In addition, the absolute risk reduction of AZD7442 over placebo in preventing the incidence of the SARS-CoV-2 RT-PCR positive symptomatic illness up to Day 183 will be presented, along with the 2-sided 95% CI using the Miettinen and Nurminen's score method (Miettinen and Nurminen, 1985). The absolute risk reduction will be implemented using the SAS PROC FREQ procedure.

16.1.7. SUBGROUP ANALYSES FOR PRIMARY EFFICACY ENDPOINT

Subgroup analysis will be performed for the primary efficacy endpoint, SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose of IMP and prior to Day 183. For subgroup analysis, FAS will be used. Treatment-by-subgroup interaction will be tested using the Poisson regression with robust variance model adjusting for follow-up time with the terms of planned treatment group, subgroup, and treatment-by-subgroup interaction, which will be implemented using PROC GENMOD procedure. If this full model does not achieve convergence, a reduced model of planned treatment group, subgroup, and treatment-by-subgroup interaction will be considered. Within each level of a subgroup, the RRR and its corresponding 95% CI will be estimated using a Poisson regression model with robust variance with the term of treatment. A forest plot of the RRR and the 95% CI will be presented. In the event that the Poisson regression model does not converge, an exact Poisson model will be used to generate the RRR and the corresponding 95% CI.

The subgroup analysis will be conducted for the subgroups in Section 7.6 on the FAS population.

If a subgroup corresponding to one of the factor levels included in the analysis model, the corresponding factor will not be included in the model.

16.1.8. ADDITIONAL ESTIMANDS FOR PRIMARY EFFICACY ENDPOINT

Additional estimands will also be used for the primary efficacy as shown in Table J:

Table J: List of Additional Estimands for Primary Efficacy

	Attributes				
Label	**Definition Population**	**Treatment Condition of Interest**	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
The efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19 – While on Treatment Estimand	Full analysis set, defined as all participants who were randomized and received at least one of the planned injections of IMP. Targeted participants will have the following characteristics: Adults ≥ 18 years of age with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection, symptomatic or asymptomatic, who are therefore at appreciable risk of imminently developing COVID-19, based on available risk assessment at time of enrollment	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component) or placebo	A binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs post dose of IMP and prior to Day 183.	For participants who become unblinded to properly consider vaccination for COVID-19, take COVID-19 vaccine or other COVID-19 preventive product prior to having met the criteria for the primary efficacy endpoint, only data prior to the intercurrent events (i.e., up to the time of unblinding, or the vaccine or other preventative product is received, whichever comes first) will be considered (i.e., intercurrent events will be handled using while on treatment strategy).	Prophylactic efficacy, calculated as 1-relative risk. (Relative risk is the incidence of infection in the AZD7442 group relative to the incidence of infection in the control group.)
The efficacy	A subset of the full analysis set, defined as	Single dose	A binary response,	For participants who	Prophylactic

Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19– Per Protocol Estimand	all participants who were randomized, received at least one of the planned injections of IMP, and who have no significant deviations from the protocol prior to Day 183 or meeting the primary endpoint (whichever occurs first). Targeted participants will have the following characteristics: Adults ≥ 18 years of age with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection, symptomatic or asymptomatic, who are therefore at appreciable risk of imminently developing COVID-19, based on available risk assessment at time of enrollment	of AZD7442 (× 2 IM injections, 1 for each mAb component) or placebo	whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs post dose of IMP and prior to Day 183.	become unblinded to properly consider vaccination for COVID-19, take COVID-19 vaccine or other COVID-19 preventive product prior to having met the criteria for the primary efficacy endpoint, the data will be collected and analyzed regardless (i.e., intercurrent events will be handled using treatment policy strategy).	efficacy, calculated as 1-relative risk. (Relative risk is the incidence of infection in the AZD7442 group relative to the incidence of infection in the control group.)

16.2. SECONDARY EFFICACY

The key secondary efficacy endpoint is:

- The incidence of the first case of SARS-CoV-2 RT PCR-positive and severe or critical symptomatic illness that occurs prior to Day 183.

The other secondary efficacy endpoints are:

- 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;
- The incidence of COVID-19-related death occurring after dosing with IMP;
- The incidence of all-cause mortality occurring after dosing with IMP;
- Please refer to Section 17 for other secondary endpoints related to PK and ADA data.

The analysis of the secondary efficacy endpoints will be performed on the FAS.

16.2.1. KEY SECONDARY EFFICACY ENDPOINT

The key secondary endpoint is the incidence of the first case of SARS CoV-2 RT PCR-positive and severe or critical symptomatic illness that occurs prior to Day 183. The severity of COVID-19 will be evaluated in participants who test positive for SARS-CoV-2 by RT-PCR. A diagnosis of severe or critical COVID-19 will include laboratory-confirmed COVID-19 (SARS-CoV-2 RT-PCR-positive symptomatic illness) plus meeting the severity criteria. Participants with severe disease can be identified using the 'COVID 19 Severity form' eCRF page, and selecting those participants with either 'Has the Subject Symptoms of Pneumonia' or 'Has the Subject Symptoms of Hypoxemia' marked as 'Yes' and with a 'WHO clinical progression scale' score of 5 or higher. The date symptoms became severe will use the data populated in the 'COVID 19 Severity form' eCRF field 'Date of Severity Assessment'. Any participants who experience death due to COVID-19 in the absence of a diagnosis of severe or critical COVID-19 will be included in this endpoint. Participants with hospitalizations that are characterized to be severe COVID-19 (as described above) will also be considered as having the event. The calculation of the follow up time (included as offset in model) will be calculated by using date symptoms become severe as the date of onset of endpoint, or date of death (as applicable), described in Section 16.1.4. Similar descriptive statistics as for the primary endpoint will be provided.

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.

The primary and the key secondary efficacy hypotheses will be assessed in a hierarchical order, 95% CI's will be

presented as detailed for the primary endpoint. More details on multiplicity are provided in Section 7.4.

16.2.2. ESTIMANDS FOR KEY SECONDARY EFFICACY

The treatment condition of interest is single dose of AZD7442 (two IM injections, one for each mAb component, AZD8895 and AZD1061). The alternative treatment condition to which comparison will be made is a placebo.

The population of participants targeted in the key secondary estimand includes adults at 18 years of age with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection, symptomatic or asymptomatic, who are therefore at appreciable risk of imminently developing COVID-19, based on available risk assessment at time of enrollment.

The key secondary endpoint (variable) to be obtained is a binary response, whereby a participant is defined as a COVID-19 severe or critical case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness that meets the severity criteria occurs post dose of IMP that occurs prior to Day 183.

The estimand for the key secondary efficacy endpoint uses a treatment policy strategy. Data for participants who become unblinded to properly consider vaccination for COVID-19, take COVID-19 vaccine or other COVID-19 preventive product, prior to having met the criteria for the key-secondary efficacy endpoint, are collected and analyzed regardless of the intercurrent event.

The population-level summary measure is prophylactic efficacy, calculated as 1 - relative risk. (Relative risk is the incidence of infection in the AZD7442 group relative to the incidence of infection in the control group.)

Additional estimands will also be used for the key secondary efficacy as shown in Table K:.

Table K: List of Additional Estimands for Key Secondary Efficacy

	Attributes				
Label	**Definition Population**	**Treatment Condition of Interest**	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
The efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of severe or critical symptomatic COVID-19 – While on treatment Estimand	Full analysis set, defined as all participants who were randomized and received at least one of the planned injections of IMP. Targeted participants will have the following characteristics: Adults ≥ 18 years of age with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection, symptomatic or asymptomatic, who are therefore at appreciable risk of imminently developing COVID-19, based on available risk assessment at time of enrollment	Single dose of AZD7442 (× 2 IM injections, 1 for each mAb component) or placebo	The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring after dosing with IMP.	For participants who become unblinded to properly consider vaccination for COVID-19, take COVID-19 vaccine or other COVID-19 preventive product prior to having met the criteria for the primary efficacy endpoint, only data prior to the intercurrent events (i.e., up to the time of unblinding, or the vaccine or other preventative product is received, whichever comes first) will be considered (i.e., intercurrent events will be handled using while on treatment strategy).	Prophylactic efficacy, calculated as 1-relative risk. (Relative risk is the incidence of infection in the AZD7442 group relative to the incidence of infection in the control group.)
The efficacy	A subset of the full analysis set, defined	Single dose	The incidence of SARS-	For participants who	Prophylactic

Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/ Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
of a single IM dose of AZD7442 compared to placebo for the prevention of severe or critical symptomatic COVID-19 – Per Protocol Estimand	as all participants who were randomized, received at least one of the planned injections of IMP, and who have no significant deviations from the protocol prior to Day 183 or meeting the key secondary endpoint (whichever occurs first). Targeted participants will have the following characteristics: Adults ≥ 18 years of age with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection, symptomatic or asymptomatic, who are therefore at appreciable risk of imminently developing COVID-19, based on available risk assessment at time of enrollment	of AZD7442 (× 2 IM injections, 1 for each mAb component) or placebo	CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring after dosing with IMP.	become unblinded to properly consider vaccination for COVID-19, take COVID-19 vaccine or other COVID-19 preventive product prior to having met the criteria for the primary efficacy endpoint, the data will be collected and analyzed regardless (i.e., intercurrent events will be handled using treatment policy strategy).	efficacy, calculated as 1-relative risk. (Relative risk is the incidence of infection in the AZD7442 group relative to the incidence of infection in the control group.)

16.2.3. OTHER SECONDARY EFFICACY ENDPOINTS

The following endpoints will be presented along with 95% CIs and p-values, these will be nominal, as they are not controlled for multiplicity.

16.2.3.1. 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

A secondary endpoint is the incidence of participants who have a post-treatment response for SARS-CoV-2 nucleocapsid antibodies.

Serum samples will be collected as per the schedule of events (refer to protocol Section 1.3) for SARS-CoV-2 serology testing to monitor participants for infection. To be considered post-baseline positive in the endpoint analysis, the participant should have a positive result from the validated assay performed at the central laboratory. The calculation of the follow up time (included as offset in model) will be calculated by using date of first positive response.

In addition, the proportion of participants who have a post-treatment response (negative at baseline to positive post treatment with study intervention) for SARS-CoV-2 nucleocapsid antibodies will be summarized by treatment group, visit and overall.

16.2.3.2. The incidence of COVID-19 related death occurring after dosing with IMP

A secondary endpoint is the incidence of participants who have a COVID-19 related death after dosing with IMP.

The number and percentage of participants who died due to COVID-19 as primary cause of death will be summarized by nominal visit and actual treatment group based on the FAS. The incidence of COVID-19 related deaths will be analyzed in the same way as the primary endpoint. The calculation of the follow up time (included as offset in model) will be calculated by using date of death as the date of onset of endpoint, described in Section 16.1.4.

16.2.3.3. The incidence of all-cause mortality occurring after dosing with IMP

Incidence of all-cause mortality is collected on the Death eCRF form. The number and percentage of participants who died due to any cause will be summarized by nominal visit and actual treatment group based on the FAS. The incidence of COVID-19 related deaths will be analyzed in the same way as the primary endpoint. The calculation of the follow up time (included as offset in model) will be calculated by using date of death as the date of onset of endpoint, described in Section 16.1.4.

16.2.4. Missing Data Imputation Method for Secondary Efficacy Endpoints

No imputation method will be used for the analysis of the key or other secondary efficacy endpoints.

Imputations will be made for sensitivity analyses of the key secondary efficacy endpoint, described in Section 16.2.6.

16.2.5. Analysis of Secondary Efficacy Endpoints

The key secondary efficacy endpoint will be analyzed as described in Section 16.2.1.

All other secondary efficacy endpoints described in the Section 16.2.3 will be analyzed in the same manner as the primary analysis of the primary efficacy endpoint (refer to Section 16.1.4).

The key secondary efficacy endpoint will be assessed by a hierarchical order. More details on multiplicity control are described in Section 7.4. For the other secondary efficacy endpoints, the 95% CIs and p-values will be nominal as they are not controlled for multiplicity.

16.2.6. Sensitivity Analyses for Secondary Efficacy Endpoints

For the key secondary efficacy endpoint, the same sensitivity analyses as for the primary efficacy endpoint will be performed (refer to Section 16.1.5).

No sensitivity analysis will be performed for the other secondary efficacy endpoints.

16.2.7. Supplementary Analyses for Secondary Efficacy Endpoints

For the key secondary efficacy endpoint, the same supplementary analyses as for the primary efficacy endpoint will be performed (refer to Section 16.1.6). However, these supplementary analyses will be limited by the number of key secondary efficacy events. If the number of events is too low, these analyses may not be performed.

16.2.8. Subgroup Analyses for Secondary Efficacy Endpoints

Subgroup analyses for secondary endpoints will be conducted if their sample is sufficient. The same methodology for the primary endpoint will be employed. If the model will not converge because the sample is too small, then only descriptive statistics such as counts and percentages and where applicable continuous summary statistics will be presented.

16.3. Exploratory Efficacy

The exploratory efficacy endpoints are:

- Viral genome copies in nasopharyngeal (NP) swabs collected at Illness Visits as determined by qRT-PCR (Illness Visits only);
- Duration of SARS-CoV-2 shedding in over time (Illness Visits only);
- Genotypic analysis and biochemical and/or susceptibility analysis of SARS-CoV-2 variants to AZD7442 (Illness Visits only);
- Symptoms recorded by participants in an Illness e-Diary from Illness Visits Day 2 through Day 28;
- Assessment of additional immune responses following a single IM dose of AZD7442 or placebo.

Only nominal p-values will be provided for exploratory efficacy endpoints (see Section 7.4). See Section 17 for details on exploratory endpoints for PK, PD and ADA data.

16.3.1. EXPLORATORY EFFICACY ENDPOINTS

16.3.1.1. Viral Genome Copies in NP Swabs Collected at Illness Visits as Determined by qRT-PCR

An exploratory efficacy endpoint is the viral genome copies in NP swabs which will be collected via SARS-CoV-2 RT-PCR test at central laboratory at Illness visits as described in protocol section 1.3. The analysis will be performed on a subset of the pharmacokinetic analysis set, defined as all participants who receive at least one of the planned injections of AZD7442, 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. Observed and change from baseline for Illness Visits (as defined in Section 6.5) in viral load will be summarized by planned treatment group and time points for the Illness Visits. Illness visits with corresponding positive RT-PCR test will be used for the summary.

A listing will be provided for all viral genome 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.

16.3.1.2. 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. This analysis will not be covered in this SAP.

16.3.1.3. Symptoms recorded by participants in an Illness e-Diary from Illness Visits Day 2 through Day 28

A group of exploratory endpoints are symptoms collected by participants in an illness e-Diary. Symptoms from the first SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose will be summarized. Illness visits with

corresponding positive RT-PCR test will be used for the summary. The number and percentage of participants with these symptoms, onset study day of these symptoms, and the duration days will be summarized by treatment group for the symptomatic COVID-19 analysis set. Percentage is based on the number of participants with illness visits corresponding to a positive RT-PCR result. The analysis will be based on participants in FAS.

All symptoms from each illness visit will be listed, 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.

16.3.1.4. Assessment of additional immune responses following a single IM dose of AZD7442 or placebo

An exploratory efficacy endpoint is assessment of additional immune responses following a single IM dose of AZD7442 or placebo. This analysis will not be covered in this SAP.

16.3.2. Missing Data Imputation Method for Exploratory Efficacy Endpoints

No imputation method will be used for exploratory efficacy endpoints.

16.3.3. Sensitivity Analyses for Exploratory Efficacy Endpoints

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

16.3.4. Supplementary Analyses for Exploratory Efficacy Endpoints

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

17. Pharmacokinetic, Pharmacodynamic and ADA Endpoints

The PK and ADA secondary endpoints are:

- Serum AZD7442 concentrations;
- PK parameters, if data permit;
- The incidence of ADA to AZD7442 in serum.

The exploratory PD and ADA endpoints are:

- AZD7442 nasal fluid concentrations;
- Post-treatment geometric mean titers (GMTs) and geometric mean fold rises (GMFRs) for nAbs to SARS-COV-2 from baseline value through Day 457 after single IM dose in SARS-CoV-2

neutralizing antibodies (wild-type assay or pseudo neutralization assay).

Other exploratory assays for humoral, mucosal and cellular immune responses may be performed based upon emerging safety, efficacy and PD data.

17.1. Analysis of PK, PD and ADA Endpoints

17.1.1. 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.

17.1.2. The Incidence of ADA to AZD7442 in Serum

17.1.2.1. 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 result from each sample will be reported as either positive or negative. If the sample is positive, the ADA titer will be reported as well. 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 (TE-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;
- TE-ADA persistently positive, defined as TE-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;
- TE-ADA transiently positive, defined as TE-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).

17.1.2.2. 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 17.1.2.1) in different treatment groups will be presented based on the ADA evaluable analysis set. Descriptive statistics of the maximum titer will also 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 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.

17.1.3. AZD7442 Nasal Fluid Concentrations

Individual AZD7442 (AZD8895 and AZD1061) nasal fluid concentration data will be listed and tabulated by mAb component, along with descriptive statistics appropriate for concentration data, for the subset of participants in the PK analysis set who have at least one quantifiable nasal fluid PK observation post-dose.

17.1.4. Neutralizing Antibody Geometric Mean Titers and Geometric Mean Fold Rise

Geometric mean titers (GMTs) and geometric mean fold rises (GMFRs) for nAbs will be calculated for the active and control groups and will be summarized at each scheduled visit as per protocol section 1.3. GMT and GMFR summaries will be based on the nAb evaluable analysis set.

Descriptive statistics for GMTs and GMFRs will include number of participants, geometric mean, geometric standard deviation (GSD), 95% CI, minimum and maximum.

The GMT will be calculated as the antilogarithm of Σ(log 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 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 (log transformed (post-dose titer/ pre-dose titer)/n). The GSD and 95% CIs for GMFR will be calculated similarly to those for GMT.

17.1.5. Missing Data Imputation Method for PK, PD and ADA Endpoints

The PK descriptive analyses of serum AZD7442 concentrations (Section 17.1.1) and AZD7442 nasal fluid concentrations (Section 17.1.3) 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 plasma 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. Plasma 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 plasma 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 (Section 17.1.2) 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.

The analysis of neutralizing antibody geometric mean titers and geometric mean fold rise (Section 17.1.4) 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.

17.1.6. SENSITIVITY ANALYSES FOR EXPLORATORY EFFICACY ENDPOINTS

No sensitivity analysis will be performed for the PK, PD and ADA endpoints.

17.1.7. SUPPLEMENTARY ANALYSES FOR EXPLORATORY EFFICACY ENDPOINTS

No supportive analysis will be performed for the PK, PD and ADA endpoints.

18. SAFETY ENDPOINTS

The safety of AZD7442 will primarily be assessed by:

- Incidence of AEs post dose of IMP;
- Incidence of SAEs post dose of IMP;
- Incidence of medically attended adverse events (MAAEs, defined in Protocol Section 8.3.5) post dose of IMP;
- Incidence of adverse events of special interest (AESIs, defined in Protocol Section 8.3.4) post dose of IMP.

There are also other safety endpoints, including:

- Deaths;
- Laboratory evaluations;
- Vital signs;
- ECG evaluations;
- Physical examinations.

All safety summaries will be presented by actual treatment group based on the SAF. Additional summaries may be presented by whether participants receive COVID-19 vaccination (Yes/No) during study and unblinding status (Yes/No) during study. Data will be presented using all the available data up to 15 month following the dose of IMP to the last assessment unless stated otherwise. There will be no statistical comparisons between the treatment groups

for safety data.

18.1. ADVERSE EVENTS

All AEs will be coded using the MedDRA dictionary, version 23.1 or higher.

Unless specified, event summary refers to the summary of number of participants with the corresponding adverse event.

Overall summaries of number and percentage of participants with an AE in the following categories will be provided by actual treatment group based on the SAF.

- All AEs;
- All SAEs;
- Related SAEs;
- AEs leading to study discontinuation;
- Related AEs leading to study discontinuation;
- MAAEs;
- Related MAAEs;
- AEs with outcome of death;
- AESIs

Should a participant experience multiple events within a category, the participant will be counted only once for that category.

An overall summary of number and percentage of participants within categories of all SAEs, related SAEs, AEs leading to study discontinuation, related AEs leading to study discontinuation, MAAEs, AEs with outcome of death, and AESIs during the entire period of study will be provided by actual treatment group based on the SAF.

18.1.1. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

AEs will be recorded from the time of 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 of the informed consent form.

AEs and SAEs post the dose of IMP will be summarized by SOC and PT by actual treatment group. Specific AEs will be counted once for each participant for calculating percentages. The most frequent AEs, defined as AEs with

an incidence of at least 5% in either treatment group, will be summarized by PT by actual treatment group.

Summary of AEs and SAEs post the dose of IMP will be broken down further by maximum severity. If the same AE occurs multiple times for a particular participant, the highest/worst severity (i.e. from highest to lowest: fatal, life-threatening, severe, moderate and mild). Separate summaries of related AEs and related SAEs will be provided by SOC and PT by actual treatment group.

Listings of AEs and SAE details will be provided. SAEs that started prior to the dose of IMP, and AEs and SAEs starting after Day 457 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 an SAE prior to the dose of IMP. Otherwise, it will be considered as an SAE post dose of IMP.

18.1.1.1. Severity for AEs

Severity will be classified as mild, moderate, severe, potentially life-threatening or fatal (increasing severity) by using grading for AEs. Severity for AEs will be collected on the 'Adverse Events' form of the eCRF. Should a participant experience multiple events within a SOC or PT, only the participant's worst severity food and drug association grade will be counted for that SOC or PT.

18.1.1.2. Relationship to IMP/Other Medication/Study Procedure

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.

18.1.2. AEs Leading to Discontinuation of IMP

AEs leading to permanent discontinuation of IMP are not expected due to this being a single dose study. Given the single dose is comprised of 2 sequential injections, the AE would need to occur immediately after the 1st injection and lead to discontinuation of the 2nd injection — this scenario is expected to be rare. Therefore, no summary will be prepared.

A listing of all AEs leading to discontinuation of IMP will be provided, if data permit.

18.1.3. AEs Leading to Discontinuation of Study

A summary of AEs during the study leading to permanent discontinuation of study by SOC and PT will be prepared. A summary of related AEs leading to permanent discontinuation of study by SOC and PT will also be prepared.

A listing of all AEs leading to permanent discontinuation of study will be provided.

18.1.4. AEs with Outcome of Death

AEs with outcome of death are those AEs with "Fatal" outcome recorded on the "Adverse Event" form of the eCRF. A summary of AEs with outcome of death by SOC and PT will be prepared.

18.1.5. Medically Attended Adverse Events

MAAEs are AEs leading to medically attended visits that were not routine visits for physical examination or dosing, such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. AEs, including abnormal vital signs, identified on a routine study visit or during the scheduled Illness Visits will not be considered MAAEs. MAAEs will be recorded from Day 1, post dose, through the last participant contact.

A summary of MAAEs by SOC and PT by actual treatment group will be prepared. Should a participant experience multiple events within a SOC or PT, the participant will be counted only once for that SOC or PT. A summary of related MAAEs by SOC and PT will also be prepared.

18.1.6. Adverse Events of Special Interest

AESIs are:

- Anaphylaxis and other serious hypersensitivity reactions, including immune complex disease;
- Injection site reactions.

AESIs are indicated on the eCRF and will be recorded from Day 1, post dose, through the last participant contact. A summary of AESIs by AESI category and PT by actual treatment group will be prepared. Should a participant experience multiple events within an AESI category or PT, the participant will be counted only once for that SOC or PT.

A listing of all AESIs will be provided.

18.2. Deaths

COVID-19 related deaths and the all-cause mortality rate are summarized as secondary efficacy endpoints, see Sections 16.2.3.2 and 16.2.3.3. In addition, 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 SAF. Data will be taken from the "Death Details" page of the eCRF. All death data will be listed.

18.3. Laboratory Evaluations

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. Chemistry, hematology, coagulation and urinalysis will be performed as per the schedule of events (refer to protocol, Section 1.3). A list of laboratory parameters to be included in the outputs is included in APPENDIX 3.

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, will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following summaries will be provided by actual treatment group based on the SAF for each of chemistry, hematology, coagulation, and urinalysis laboratory parameter:

- 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 6.5 (for coagulation parameters) in SI units by Illness Visit (the Illness Visits corresponding to positive RT-PCR test will be used in the summary);
- Number and percentage of participants in each laboratory parameter category by visit (for categorical parameters);
- 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 18.3.1);
- 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 18.3.2);
- Maximum post-baseline alanine aminotransferase/transaminase (ALT)/ aspartate aminotransferase/transaminase (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.

All lab data will be listed.

18.3.1. CTCAE Toxicity Grades

Quantitative laboratory parameters with available CTCAE toxicity grades will be categorized as follows where higher grades representing a more severe toxicity (refer to APPENDIX 1 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.

18.3.2. LABORATORY NORMAL RANGES

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.

18.4. VITAL SIGNS

The following vital sign parameters will be collected for this study as per the schedule of events (refer to protocol, Section 1.3):

- Systolic blood pressure (SBP) (mmHg);
- Diastolic blood pressure (DBP) (mmHg);
- Heart rate (beats per minute [bpm]);
- Body temperature (C);
- Oxygen saturation (%);
- Respiratory rate (breaths/min).

For severity grades of abnormal Vital Signs refer to APPENDIX 5.

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

- Observed and change from baseline by visit;
- Observed and change from baseline (as defined in Section 6.5) by Illness Visit (the first illness episode with positive RT-PCR test result will be used for the summary);

- Number and percentages of participants with at least one abnormal post-baseline observed value (refer to APPENDIX 5).

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.

18.5. ECG EVALUATIONS

The following electrocardiogram (ECG) parameters will be measured for this study as per the schedule of events (refer to protocol, Section 1.3):

- Heart rate (bpm);
- PR interval (msec);
- RR interval (msec);
- QRS interval (msec);
- QT interval (msec);
- QTc interval (msec);
- QTcF interval (msec);
- QTcB interval (msec);
- Overall ECG interpretation (Investigator's judgment):
  - Normal;
  - Abnormal, not clinically significant;
  - Abnormal, clinically significant.

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 worst of the 3 measurements collected on a visit will be used for the shift from baseline summaries for that visit. 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. All individual measurements will be listed.

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 18.5.1);

18.5.1. ECG MARKEDLY ABNORMAL CRITERIA

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 msec;
  - > 480 msec;
  - > 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.

18.6. PHYSICAL EXAMINATION

Physical examinations will be conducted as per the schedule of events (refer to protocol Section 1.3). Clinically significant findings at screening will be recorded on the Medical History form of the eCRF while clinically significant changes from screening will be recorded on the Adverse Events form of the eCRF for the post-screening visits. Hence, clinically significant findings/changes will be summarized though the Medical history summary (refer to Section 11) or AE summaries (refer to Section 18.1), as appropriate. That is, no summaries will be specifically provided for the general physical examination.

19. OTHER DATA COLLECTED

The following data collected on the eCRF will be summarized in listings only:

- Pregnancy test and report;
- Weekly telephone contact for safety monitoring;
- Medication Error.

20. REFERENCES

CDC. (Centers for Disease Control and Prevention). Coronavirus Disease 2019 (COVID-19), Symptoms of Coronavirus. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. Published 2020. Accessed 01 July 2020.

Little, R. J. A. and Rubin, D. B. Statistical Analysis with Missing Data, 2nd Edition, Hoboken, NJ: John Wiley & Sons 2002; 257.

Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med. 1985;4(2):213-26.

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

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. PROGRAMMING CONVENTIONS FOR OUTPUTS

DATES & TIMES

Depending on data available, dates and times will take the form yyyy-mm-dd hh:mm:ss.

SPELLING FORMAT

English US.

PAPER SIZE, ORIENTATION, AND MARGINS

The size of paper will be letter and the page orientation will be landscape. Margins will provide at least 1 inch (2.54 centimeters) of white space all around the page.

FONTS

The font type 'Courier New' will be used, with a font size of 8. The font color will be black with no bolding, underlining, italics or subscripting.

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in the given order:

Treatment Group	Tables and Graphs	Listings
AZD7442	1	1
Placebo	2	2
Total [1]	5	n/a
Randomized, Not Dosed	n/a	3
Screen Failure	n/a	4

[1] Not applicable for efficacy tables, safety tables and graphs.

PRESENTATION OF PK ANALYSES

Groups will be represented as follows and in the given order for participants who receive AZD7442 only:

Treatment Group	Tables and Graphs	Listings
AZD8895	1	1
AZD1061	2	2

PRESENTATION OF NOMINAL VISITS

For outputs, analysis visits will be represented as follows and in that order:

Long Name (default)	**Short Name**
Screening	Scrn
Rescreening	RScrn
Day 1	D1
Day 8	D8
Day 29	D29
Day 58	D58
Day 92	D92
Day 183	D183
Day 366	D366
Day 457	D457

For outputs, analysis visits regarding Illness Visit will be represented as follows and in that order:

Long Name (default)	**Short Name**
Episode 1 Illness Visit Day X, X=1,3,5,8,11,14,21,28	1IL-DXX, X=1,3,5,8,11,14,21,28
Episode 2 Illness Visit Day X, X=1,3,5,8,11,14,21,28	2IL-DXX, X=1,3,5,8,11,14,21,28

Long Name (default)	Short Name
Episode Y Illness Visit Day X, X=1,3,5,8,11,14,21,28 Y = 1, 2, 3, and so on, as applicable	YIL-DXX, X=1,3,5,8,11,14,21,28 Y = 1, 2, 3, …

DESCRIPTIVE STATISTICS

If the original data has N decimal places, then the summary statistics will have the following decimal places:

- Minimum and maximum: N;
- Mean, median, Q1, Q3, lower and upper bounds of two-sided 95% CI: N + 1;
- SD: N + 2

PERCENTAGES

Percentages will be reported to one decimal place. Rounding will be applied, except for percentages < 0.1 but > 0.0 which will be presented as '< 0.1' and percentages < 100.0 but >99.9 which will be presented as '>99.9'.

Where counts are zero, no percentages will appear in the output.

P-VALUES

p-values will be reported to four decimal places. Rounding will be applied, except for the p-values < 0.0001 which will be presented as '< 0.0001' and p-values < 1.0000 but > 0.9999 which will be presented as '> 0.9999'.

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the output template):

- Randomized (planned) treatment group (or actual treatment received if it's a safety output);
- Participant ID;
- Parameter, when applicable;
- Date/Time, when applicable;
- Timepoint, when applicable

APPENDIX 3. LABORATORY ASSESSMENTS

Chemistry (SI unit)

- Alkaline phosphatase (ALP) (U/L)
- Alanine aminotransaminase (ALT) (U/L)
- Aspartate aminotransaminase (AST) (U/L)
- Total bilirubin (µmol/L)
- Conjugated bilirubin (µmol/L)
- Gamma glutamyl transferase (GGT) (U/L)
- C-Reactive protein (CRP) (nmol/L)
- Albumin (g/L)
- Creatinine (µmol/L)
- Glucose (mmol/L)
- Creatine kinase (CK) (U/L)
- Sodium (mmol/L)
- Potassium (mmol/L)
- Calcium (mmol/L)
- Phosphate (mmol/L)
- Urea (mmol/L)

Hematology (SI unit)

- Hemoglobin (g/L)
- Hematocrit
- Mean corpuscular volume (MCV) (fL)
- Red blood cells (RBC) count total (x10E12/L)
- White blood cell (WBC) count total (x10E9/L)
- Mean corpuscular hemoglobin (MCH) (pg)
- Mean corpuscular hemoglobin concentration (MCHC) (g/L)
- Absolute neutrophils count (x10E9/L)
- Absolute lymphocyte count (x10E9/L)
- Absolute monocyte count (x10E9/L)
- Absolute eosinophils count (x10E9/L)
- Absolute basophils count (x10E9/L)
- Absolute reticulocyte count (x10E9/L)
- Platelet count (x10E9/L)

Coagulation (SI unit)

- International normalized ratio (INR)
- Activated partial thrombin time (aPTT) (s)
- Prothrombin time (PT) (s)

Urinalysis (SI unit)

Dip stick

- Blood
- Protein
- Glucose

Microscopy

- White blood cells
- Red blood cells
- Casts

APPENDIX 4. CTCAE TOXICITY GRADE, VERSION 5.0

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (accessed on 22-Apr-2020)

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
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

CTCAE Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
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
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

CTCAE Term	Laboratory Test	No Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
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
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 5. CLINICAL ABNORMALITIES: VITAL SIGNS

Vital Signs [a]	Vital Signs Grade			
	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) [b] (°F) [b]	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

Note: Record vital signs as adverse events only if clinically relevant and changed from baseline.

[a] Participant should be at rest for vital signs measurements.

[a] No recent hot or cold beverages or smoking.

[b] Use clinical judgment when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.

ER = emergency room; Hg = mercury.

APPENDIX 6. HIGH RISK OF SEVERE COVID-19 AT BASELINE

High Risk of Severe COVID- 19 Condition	Description
History of Obesity: (eCRF)	COVID Co-Morbidities eCRF: "Does the subject have a history of Obesity -- those with a BMI greater than 30" Programming example: MHDIAGYN4="Yes"
Morbid Obesity: BMI>=40 (Derived)	Derived from the subjects reported hight and weight at baseline
Obese: BMI>=30 (Derived)	Derived from the subjects reported hight and weight at baseline
CKD	COVID Co-Morbidities eCRF: "Does the subject have a history of Chronic kidney disease?" Programming example: MHDIAGYN1="Yes"
Diabetes	COVID Co-Morbidities eCRF: "Does the subject have a history of Type 1 diabetes?" "Does the subject have a history of Type 2 diabetes?" Programming example: MHDIAGYN15="Yes" or MHDIAGYN7="Yes"
Immunosuppressive disease	From reported Medical History Term Programming example: SOC_NAME=" IMMUNE SYSTEM DISORDERS" and HLGT different than 'ALLERGIC CONDITIONS'
Immunosuppressive treatment	From reported Concomitant medications identified as prior and ongoing with ATC2 is 'L01' or 'L04'.
CV disease	COVID Co-Morbidities eCRF: "Does the subject have a history of Serious heart conditions like heart failure and coronary artery disease" Programming example: MHDIAGYN5="Yes"
COPD	COVID Co-Morbidities eCRF: "Does the subject have a history of Chronic obstructive pulmonary disease (COPD), like emphysema?" Programming example: MHDIAGYN2=" Yes"
Chronic liver disease	COVID Co-Morbidities eCRF: "" Programming example: MHDIAGYN13=" Yes"
Hypertension	COVID Co-Morbidities eCRF: "Does the subject have a history of High blood pressure?" Programming example: MHDIAGYN12=" Yes"
Asthma	COVID Co-Morbidities eCRF: Does the subject have a history of Asthma? Programming example: MHDIAGYN8="Yes"
Cancer	From ongoing Medical History terms where SOC NAME='NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)' and PT name different than 'UTERINE LEIOMYOMA'
Smoking	COVID Co-Morbidities, specific question: What is the subject's smoking history? MHDIAGYN17="1" ("Current")
Sickle cell disease	COVID Co-Morbidities eCRF: Does the subject have a history of Sickle cell disease? Programming example:MHDIAGYN6=" Yes"

Note: Final programming logic may differ to address the specific data elements such as additional fields, different field name or levels.

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