PARENT STUDY STATISTICAL ANALYSIS PLAN

Study Code	D7000C00001
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A Phase I/III Randomized, Double-blind Study to Evaluate the Safety, Efficacy, and Neutralizing Activity of AZD5156/AZD3152 for Pre-exposure Prophylaxis of COVID-19 in Participants with Conditions Causing Immune Impairment

Brief Title: Study Understanding Pre-Exposure pRophylaxis of NOVel Antibodies (SUPERNOVA)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Class
AUC_{inf}	Area under the concentration-time curve extrapolated to infinity
AUC_{last}	Area under the concentration-time curve at the last measured time point
CI	Confidence interval
CL	Confidence limit
C_{max}	Maximum concentration
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease 2019
CPS	Clinical pharmacology scientist
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cutoff
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
ESDR	Early safety data review
FAS	Full Analysis Set
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
GSD	Geometric standard deviation
H_0	Null hypothesis
H_A	Alternative hypothesis
HR	Hazard ratio
GCV	Geometric coefficient of variation
IM	Intramuscular
IP	Investigational product

Abbreviation	Definition
IPD	Important protocol deviation
MAAE	Medically attended adverse event
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Minimum required dilution
nAb	Neutralizing antibody
NC	Not calculable
NLF	Nasal lining fluid
NP	Nasopharyngeal
NQ	Not quantifiable
NR	Not reportable
NS	No sample
PbO	Placebo
PDMP	Protocol deviation management plan
PK	Pharmacokinetic(s)
PT	Preferred term
Q1	First quartile
Q3	Third quartile
RR	Relative risk
RRR	Relative risk reduction
Rsq	Coefficient of determination
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SIP	Study integrity plan
SoA	Schedule of activities
SOC	System Organ Class
$t_{½}$	Terminal half-life
TBL	Total bilirubin
t_{max}	Time to maximum concentration
ULN	Upper limit of normal
WHO	World Health Organization

AMENDMENT HISTORY

Change Refers to:	Date	Description of Change	Clinical Study Protocol (CSP)	Rationale
Not applicable	29-Nov-2022 (Ed. 0.2)	Initial approved statistical analysis plan (SAP)	In line with CSP v2	Not applicable
All sections	9-Jun-2023 (Ed. 2.0)	Updated per CSP v6 before the first clinical database lock	In line with CSP v6	The most recently approved version of the SAP was on 29-Nov-2022, before this study's first subject-in. This version of the SAP is aligned with CSP v6 and approved before the database lock of the first Sentinel Safety analysis (Day 29).
All sections	11-Aug-2023 (Ed. 3.0)	Updated per CSP v7 before the clinical database lock of the primary analysis	In line with CSP v7	• This version of the SAP is aligned with CSP v7 and approved before the database lock of the primary analysis. • An interim analysis for futility has been added.
All sections	23-Oct-2023 (Ed. 4.0)	• Anti-drug antibody (ADA) endpoints will be summarized for the Placebo group within the Sentinel Safety Cohort in addition to AZD5156. • Refined the description for ADA-related data summaries concerning adverse events (AEs) and pharmacokinetics (PK) in the Sentinel Safety Cohort and Main Cohort, emphasizing the ADA status specific to AZD5156, AZD3152, and AZD7442. • The process for identification of AEs of special interest (AESIs) was amended, where AstraZeneca's review for final categorization will be performed.	In line with CSP v7	• The interim analysis for futility has been removed. • ADA endpoints will be summarized for all participants with ADA data, hence, both AZD5156 and Placebo participants. • Clarity and specificity in the presentation of ADA-related data summaries were added. • The AESI identification process was modified to utilize a Medical Dictionary for Regulatory Activities (MedDRA) preferred terms list (as originally planned) for initial flagging, followed by a thorough review to validate AESI status.

Change Refers to:	Date	Description of Change	Clinical Study Protocol (CSP)	Rationale
All sections	15-Apr-2024 (Ed. 5.0)	• Updated per CSP v8 for changes to the primary analysis, including adding the dual endpoint for overall and matched variant endpoints. • The process for identification of AESIs was amended to use only a prespecified MedDRA PT search and cardiovascular adjudication. • The analysis visit windows have been updated.	In line with CSP v8	• Inclusion of dual primary endpoints as outlined in CSP v8. • Added clarity on the AESI process • For the Sentinel Safety Cohort, analysis visit windows have been expanded for visits closer to Day 181 to align with the scheduled visit windows in the CSP. In the Main Cohort, the analysis windows have been adjusted overall and standardized to be relative to Day 1, regardless of any delays in the Day 181 dose.
All sections	15-Apr-2024 (Ed. 6.0)	• The analysis strategy and summary measure for the primary efficacy objective and related sensitivity and/or subgroup analysis changed to estimate Relative Risk with a Poisson Regression. • Treatment groups for "AZD7442/AZD7442" have been removed. • Minor edits have been made to other sections.	CSP v8	• The FDA and PMDA health authorities recommended an estimate of relative risk from the Poisson regression model. All subjects are expected to receive Placebo or AZD3152 at the second dosing event on Day 181.

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to give details for the statistical analysis of the parent study of D7000C00001 supporting the clinical study report (CSR). The SAP of the sub-study is separate from that of the parent study. The reader is referred to Version 8 of the clinical study protocol (CSP) and Version 6 of the electronic case report form (eCRF) for details of the study conduct and the data collection.

The term "investigational product" (IP) is used throughout this document to include all treatments of the parent study, namely AZD3152 300 mg, AZD5156 600 mg, AZD7442 (EVUSHELD) 600 mg, and Placebo. AZD5156 is a combination product of two monoclonal antibodies (mAbs), AZD1061 (cilgavimab) and AZD3152. Similarly, AZD7442 is a combination product of two mAbs, AZD1061 (cilgavimab) and AZD8895 (tixagevimab).

1.1 Study Objectives

This study's primary, secondary, and key exploratory objectives, including the neutralizing activity and efficacy estimands/endpoints, are listed in Table 1.

Table 1 Primary, Secondary, and Key Exploratory Objectives and Endpoints

Objective	Estimand Description/Endpoint
Primary – Sentinel Safety Cohort	
To evaluate the safety of AZD5156	Occurrence of AEs collected through approximately 90 days after IP administration and SAEs, MAAEs, and AESIs collected throughout the study
Secondary – Sentinel Safety Cohort	
To characterize the PK of AZD5156 and AZD3152 in serum	AZD5156, AZD1061 (cilgavimab), and AZD3152 concentrations over time and PK parameters (e.g., C_{max}, t_{max}, $t_{½}$, AUC_{last}, and AUC_{inf})
To evaluate the ADA responses to AZD5156, AZD3152, and AZD1061 in serum	Incidence of ADA to AZD5156, AZD3152, and AZD1061; ADA titers
Primary – Main Cohort	
To evaluate the safety of AZD3152, EVUSHELD, and/or Placebo	Occurrence of AEs collected through approximately 90 days after each IP administration and SAEs, MAAEs, and AESIs collected throughout the study

Table 1 Primary, Secondary, and Key Exploratory Objectives and Endpoints

Objective	Estimand Description/Endpoint
To compare the efficacy of AZD3152 to EVUSHELD and/or Placebo in the prevention of symptomatic COVID-19 caused by any SARS-CoV-2 variant	**Population:** SARS-CoV-2-Negative Set **Endpoint**: Confirmed symptomatic COVID-19 case, classified as a binary outcome incorporating the time from the first dose of IP until a participant develops their first symptoms for COVID-19, which is defined as follows: • Positive post-baseline RT-PCR at any time up to 181 days after the last dose (i.e., Visit 9 [Day 361] for participants who receive both planned treatment administrations) AND • Satisfying the modified WHO definition of symptomatic COVID-19 **Intercurrent events**: The set of intercurrent events for the estimand consists of participants who become unblinded to study intervention assignment and/or take other non-investigational products for COVID-19 prevention prior to having met the criteria for the COVID-19 endpoint. Such participants will be censored at the earliest of the following: • The date of unblinding • Receipt of the first dose of any COVID-19 preventive product **Analysis strategy**: While-on-treatment strategy – participants will be analyzed according to randomized treatment and censored at the time of the earliest intercurrent event prior to meeting the endpoint criteria. **Summary measure**: Prophylactic efficacy as a percentage, calculated as 100 – Relative Risk (AZD3152 vs. EVUSHELD and/or Placebo), quantified by a Poisson regression model

Table 1 Primary, Secondary, and Key Exploratory Objectives and Endpoints

Objective	Estimand Description/Endpoint
To compare the efficacy of AZD3152 to EVUSHELD and/or Placebo in the prevention of symptomatic COVID-19 attributable to matched variants (variants that do not contain the F456L mutation)	**Population:** SARS-CoV-2-Negative Set **Endpoint**: Confirmed symptomatic COVID-19 case attributable to matched variants, classified as a binary outcome incorporating the time from the first dose of IP until a participant develops their first symptoms for COVID-19, which is defined as follows: • Positive post-baseline RT-PCR at any time up to 181 days after the last dose (i.e., Visit 9 [Day 361] for participants who receive both planned treatment administrations) AND • Satisfying the modified WHO definition of symptomatic COVID-19 AND • Viral sequencing from associated positive RT-PCR is attributable to matched variants **Intercurrent events**: The set of intercurrent events for the estimand consists of participants who become unblinded to the study intervention assignment and/or take other non-investigational products for COVID-19 prevention before meeting the COVID-19 endpoint criteria. Additionally, RT-PCR-confirmed symptomatic COVID-19 infections that are either unrelated to matched variants or undetermined variants will be considered intercurrent events. Such participants will be censored at the earliest of the following: • The date of unblinding • Receipt of the first dose of any COVID-19 preventive product • The date of the first occurrence of an RT-PCR-confirmed symptomatic COVID-19 case not attributable to a matched variant **Analysis strategy**: While-on-treatment strategy – participants will be analyzed according to randomized treatment and censored at the time of the earliest intercurrent event prior to meeting the endpoint criteria. **Summary measure**: Prophylactic efficacy as a percentage, calculated as 100 – Relative Risk (AZD3152 vs. EVUSHELD and/or Placebo), quantified by a Poisson regression model

Table 1 Primary, Secondary, and Key Exploratory Objectives and Endpoints

Objective	Estimand Description/Endpoint
Secondary – Main Cohort	
To compare the nAb responses to the SARS-CoV-2 variants Alpha, Omicron BA.2, Omicron BA.4/5, and/or Omicron XBB.1.5 in serum following AZD3152, EVUSHELD, and/or Placebo administration	GMT and GMFR ratio of SARS-CoV-2 nAbs between the treatment arms at Visit 3 (Day 29) Descriptive statistics for GMTs and GMFRs will include the number of participants, geometric mean, GSD, 95% CI, minimum, and maximum, and summarized per treatment arm and visit.
To describe the incidence of symptomatic COVID-19, severe COVID-19, COVID-19-related hospitalization, and COVID-19-related death in participants receiving study intervention	Incidence of a post-treatment: • Symptomatic COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months) caused by any SARS-CoV-2 variant • Symptomatic COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 and 12 months) caused by any SARS-CoV-2 matched variants • Severe COVID-19 caused by any SARS-CoV-2 variant • Severe COVID-19 caused by any SARS-CoV-2 matched variants • Composite of COVID-19-related hospitalization and/or COVID-19-related death (WHO COVID-19 Clinical Progression Scale score ≥ 4) • COVID-19-related hospitalization (separately) • COVID-19-related death (separately)
To characterize the PK of AZD3152 and AZD7442 in serum	AZD3152, AZD7442, AZD1061, and AZD8895 concentrations over time
To evaluate the ADA responses to AZD3152 and AZD7442 in serum	Incidence of ADA to AZD3152, AZD7442, AZD1061, and AZD8895; ADA titers
Key Exploratory	
To assess the PK of AZD5156, AZD3152, and AZD7442 in NLF	AZD5156, AZD7442, AZD1061, AZD3152, and AZD8895 concentrations over time

Table 1 Primary, Secondary, and Key Exploratory Objectives and Endpoints

Objective	Estimand Description/Endpoint
To characterize viral resistance to AZD3152 in participants with confirmed COVID-19	Genotypic and susceptibility analyses of SARS-CoV-2 variants to AZD3152

ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; AUC_{inf} = area under the concentration-time curve from time zero extrapolated to infinity; AUC_{last} = area under the concentration-time curve at the last measured time point; CI = confidence interval; C_{max} = maximum concentration; COVID-19 = Coronavirus disease 2019; GMFR = geometric mean fold rise; GMT = geometric mean titer; GSD = geometric standard deviation; IP = investigational product; MAAE = medically attended adverse event; nAb = neutralizing antibody; NLF = nasal lining fluid; PK = pharmacokinetic(s); RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; $t_{½}$ = terminal half-life; t_{max} = time to maximum concentration; WHO = World Health Organization

The analyses for the non-key exploratory endpoints listed in the CSP will be detailed in the exploratory SAP.

1.2 Study Design

D7000C00001 is a Phase I/III study (parent study) being conducted in conjunction with a Phase II sub-study that will be conducted with approximately 3706 participants (approximately 3256 in the parent study and 450 in the sub-study) to evaluate the safety, efficacy, pharmacokinetics (PK), and neutralizing activity of AZD3152 compared with AZD7442 or Placebo for pre-exposure prophylaxis of Coronavirus disease 2019 (COVID-19) and separately evaluate the safety and PK of AZD5156, a combination of AZD3152 and AZD1061 (cilgavimab). The study will be conducted globally.

The parent study will have two cohorts: the Sentinel Safety Cohort and the Main Cohort. The Sentinel Safety Cohort will compare AZD5156 with Placebo, while the Main Cohort will compare AZD3152 with AZD7442 and/or Placebo. The CSP's schedule of activities (SoA) summarizes the study procedures and timing.

The Sentinel Safety Cohort (Phase I) will enroll approximately 56 participants, who will be randomized to receive AZD5156 (40 participants) or Placebo (16 participants). Participants will receive study intervention intramuscularly either in the gluteal or anterolateral thigh. Dosing within the Sentinel Safety Cohort will be staggered, with participants allocated sequentially to four subcohorts (1a, 1b, 2a, and 2b). Within each subcohort, participants will be randomized to receive AZD5156 or Placebo in a 5:2 ratio. An early safety data review (ESDR) will be conducted after Visit 4 (Day 8) and Visit 5 (Day 15) of each subcohort, and enrollment of the Main Cohort will be initiated if the safety review of all the Sentinel Safety Cohort data up to Day 15 concludes that the safety profile is acceptable. Sentinel Safety Cohort randomization will be stratified by injection site (1:1 gluteal or anterolateral thigh). The duration of a Sentinel Safety Cohort participant's involvement in the study will be approximately 12 months from when the study intervention is administered. A description of the Sentinel Safety Cohort's treatment assignment is presented in Table 2.

Table 2 Description of Sentinel Safety Cohort

Subcohort	Active Treatment (n)	Comparator Treatment (n)	IM Injection Site
1a	AZD5156 600 mg (5)	Placebo (2)	Gluteal
1b	AZD5156 600 mg (5)	Placebo (2)	Anterolateral thigh
2a	AZD5156 600 mg (15)	Placebo (6)	Gluteal
2b	AZD5156 600 mg (15)	Placebo (6)	Anterolateral thigh

IM = intramuscular; n = number of participants

The Main Cohort (Phase III) will enroll approximately 3200 participants.

Prior to CSP Version 7.0, the comparator for the Main Cohort was AZD7442, as the immunobridging portion of the study was incorporated into the parent study. In response to the request of regulatory authorities, a sub-study specifically for immunobridging was initiated and outlined in CSP Version 6.0, conducted in the US only. The parent study has become an efficacy and safety study, and the comparator has been changed to include Placebo, which was implemented in CSP Version 7. Since the comparator is administered on two occasions, a participant randomized to the comparator arm may receive:

a) two doses of AZD7442; two administrations of AZD7442 is not expected; All sites are anticipated to administer the second dose as Placebo under CSP Version 7
b) a dose of AZD7442 and a dose of Placebo, or
c) two doses of Placebo.

The participants in the Main Cohort will be randomized 1:1 to receive AZD3152 300 mg, or the comparator will be administered intramuscularly in the anterolateral thigh on Day 1. Participants will receive a second dose of their original randomized study intervention (i.e., the active treatment or the comparator) six months after Visit 1 (Day 1). The Main Cohort randomization will be stratified by the following variables:

- COVID-19 vaccination status within six months prior to randomization (Yes, No)
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection within six months prior to randomization (Yes, No)
- AZD7442 use within 12 months prior to randomization (Yes, No)

The duration of a Main Cohort participant's involvement in the study will be approximately 15 months from when the first dose of the study intervention is administered. A description of the Main Cohort's treatment assignment is presented in Table 3.

Table 3 Description of Main Cohort

Active Treatment (n)	Comparator Treatment (n)	IM Injection Site
AZD3152 300 mg (1600)	Comparator* (1600)	Anterolateral thigh

IM = intramuscular; n = number of participants
*The Main Cohort Placebo arm also contains participants who were dosed with AZD7442 prior to the implementation of clinical study protocol Version 7.0.

Randomization errors, which could result in participants receiving a dose or product they were not randomly assigned to, are minimized since the IP doses consist of no more than one or two injections.

For the Main Cohort, following study intervention administration, if a participant believes they have contracted COVID-19, they will be required to contact the site as soon as possible. The investigator will assess whether the participant meets the clinical criteria for SARS-CoV-2 infection (as defined by the World Health Organization [WHO]) and will need to conduct Illness Visits within three days after the participant has reported such symptoms. The Illness Visit schedule is to be performed in addition to the Main Cohort visit schedule. If these Illness Visits overlap with a scheduled visit (according to respective visit windows), a single visit may be done with the combined study procedures completed once (thus, duplicate sampling will not be required). Sentinel Safety Cohort participants will not participate in the Illness Visits.

An independent Data Safety Monitoring Board (DSMB) will provide oversight to ensure the safe and ethical conduct of the Main Cohort of the study, as discussed in the CSP.

For the Main Cohort only, an independent cardiovascular event adjudication committee will provide an independent, external, systematic, and unbiased assessment of blinded data to evaluate cardiovascular and thrombotic events systematically.

1.3 Sample Size and Number of Participants

Approximately 3256 adults will be randomized in the parent study. In the Sentinel Safety Cohort, approximately 56 healthy adults 18 to 55 years of age will be randomized (5:2) to receive either AZD3152 (40 participants in total) or Placebo (16 participants in total). In the Main Cohort, approximately 3200 additional participants will be randomized 1:1 to receive AZD3152 or the comparator.

The overall symptomatic COVID-19 blinded event rate and the data from external sources (e.g., prophylactic efficacy of other COVID-19-preventive mAbs) may be used in a 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 lower than expected. Since this review will be performed in a blinded fashion, no adjustment for the Type I error is needed.

The sample size of the Main Cohort was derived prior to the inclusion of the matched variant endpoint (introduced in CSP Version 8.0) and statistical testing of two primary efficacy endpoints. A target sample of approximately 3200 participants was selected to reach the required number of events. Approximately 40 events would have at least 90% power to demonstrate that the upper bound of the two-sided 95% confidence interval (CI) of the hazard ratio (HR) is less than 1, assuming that the annual event rate is approximately 3.2% in the comparator arm, an HR of 0.30 (70% efficacy), a significance level of 5%, and

10% attrition. The assumptions are based on data from prior AZD7442 studies and reported event rate estimates among those with immunocompromising conditions.

The addition of dual primary efficacy endpoints has not changed the study target enrollment. Statistical methodology for the primary endpoint has been changed from methods used to determine the target enrolment and assumed effect size however both methods should give similar results. Assumptions for the dual efficacy endpoints (all confirmed events and events attributable to matched variants) are presented in Table 4 and Table 5 with varying levels of AZD3152 resistance. The efficacy of resistant variants, such as those with the F456L mutation, is assumed to be 0%, and the efficacy for matched variants is 70%. It is projected that if AZD3152-resistant events do not exceed 67% in the study, the efficacy for all confirmed events could be within the range of 30% to 60%, ensuring at least 90% power with the current enrolment target of N = 3200. For the matched variants endpoint, the endpoint with events attributed to matched variants requires at least 43 matched events to maintain 90% power, assuming 70% efficacy. If efficacy for the matched variants endpoint is 50%, 112 events attributed to matched variants will be required to maintain 90% power. A significance level of $\alpha = 2.5\%$ has been used for both calculations.

Table 4 Estimated Primary Events and Assumptions

	Endpoint 1 – All Confirmed Events	**Endpoint 2 – Matched Variant Events**
Target enrolment	Approximately 3200 participants (Main Cohort)	
Type I error control	Holm's step-down procedure to maintain the overall Type I error across primary endpoints at 5% ($\alpha = 5\%$)	
Assumed efficacy	Symptomatic COVID-19 efficacy is assumed to range between 30% to 60%.	Symptomatic COVID-19 attributable to matched variants efficacy is assumed to be 70%.
Target events	A minimum of 68 events are required to provide > 90% power under assumptions outlined in Table 5.	A minimum of 43 matched variant events are required to provide > 90% power (assumed efficacy 70%).

Table 5 Number of Events Required by Maximum Resistant Variant Proportions for Endpoint 1 – All Confirmed Events

Assumed Efficacy (All Confirmed Events)	**Maximum Proportion of AZD3152 Resistance**	**Events Required for 90% Power**
70%	0%	43
60%	20%	68
50%	38%	112
40%	54%	199

Table 5 Number of Events Required by Maximum Resistant Variant Proportions for Endpoint 1 – All Confirmed Events

Assumed Efficacy (All Confirmed Events)	Maximum Proportion of AZD3152 Resistance	Events Required for 90% Power
30%	67%	398

The Main Cohort sample size of 3200 participants provides a safety database of over 1600 participants who will receive AZD3152 compared with 1600 participants receiving the comparator within the study.

In order to maximize the chance of having a balance between the treatment arms within the randomization stratification factors, the Sentinel Safety and Main Cohorts will be stratified as outlined in Section 1.2.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

The analysis strategy and summary measure for primary efficacy objective and related sensitivity and/or subgroup analysis has been modified based on feedback from health authorities. Statistical methodology will estimate relative risk of symptomatic COVID-19 using a Poisson regression model with robust variance adjusting for unequal follow-up time with an offset for the log of time at risk. The robust Poisson model is generally considered to be a conservative and acceptable approach.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Analyses Timing

The Sentinel Safety Cohort will be summarized separately from the Main Cohort. Descriptive summaries by treatment arm will be conducted after all Sentinel Safety Cohort participants have completed Visit 6 (Day 29), Visit 8 (Day 91), Visit 9 (Day 181), and the end-of-study visit or have withdrawn from the study. The Visit 6 (Day 29) analysis will present available safety data and serum PK concentrations on Day 29; the remaining analyses will include all available data when concluded.

The study will maintain a double-blind period until a median follow-up time is greater than 181 days in the SARS-CoV-2-Negative Set and the required number of events are observed for the dual primary endpoints to support the primary efficacy and safety objectives and trigger the primary analysis. If sufficient events are unlikely to be observed for either endpoint or all participants have been followed for more than 361 days or withdrawn from the study, the database will be locked for the primary analysis.

The prevalence of resistant variants is likely to vary considerably throughout the study. A minimum of 199 overall events, including 43 events attributable to matched variants, are required to ensure sufficient statistical power for evaluating both primary endpoints. These minimum targets are based on the assumptions of 40% and 70% efficacy for the overall and matched variant endpoints, respectively. The primary analysis for the Main Cohort will be conducted only after meeting all of the following requirements:

- The median follow-up time exceeds 181 days in the SARS-CoV-2-Negative Set.
- A minimum of 43 primary events of symptomatic COVID-19 attributable to matched variants is observed.
- At least 199 primary events of symptomatic COVID-19 (all RT-PCR-confirmed events) are observed.

The primary analysis for the Main Cohort will include analyzing all available data for the primary and secondary endpoints, including the next-generation sequencing (NGS) data. To maintain the integrity of the study for rigorous evaluation of safety and efficacy through the end of the study, the site personnel and participants will remain blinded to the treatment assignment until the end of the study and the final readout. The procedure to maintain the treatment assignment's "blind" will be detailed in a study integrity plan (SIP).

An additional analysis readout may be conducted to evaluate the efficacy of the first IP dose through Day 181 and the safety and PK of the second IP dose at Visit 7 (Day 210). This analysis will only be conducted if the primary analysis has been previously conducted and all participants have been followed for more than 181 days or withdrawn from the study.

If there is a medical need for AZD3152 to be submitted for urgent health authority review, additional analyses, including efficacy, will be conducted. If conducted before the primary analysis, the SIP will provide details about the analyses and data readouts that may reveal treatment assignments.

3.2 Analysis Populations

The analysis population definitions are presented below:

Table 6 Analysis Sets

Analysis Set	Description	Reporting Cohort	Reporting Purpose
Screened Set	This population will include all participants who provided informed consent for data collection in this study.	Sentinel Safety & Main	Disposition data
FAS / Safety Set 1	These populations will consist of all randomized participants who received part or all of the study intervention. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination. Participants in the FAS will be classified according to the assigned treatment. Safety Set 1 will include participants from the FAS but report participants according to the "actual" treatment received regardless of the assigned treatment.	Sentinel Safety & Main	Study population, safety, and efficacy data
Safety Set 2	This population will include all participants in Safety Set 1 who received both doses of the study intervention scheduled for Day 1 and Day 181. Participants in this population will be classified according to the actual mAb components received regardless of their assigned treatment.	Main	AE data
SARS-CoV-2 nAb Set	This population will include all participants in Safety Set 1 with baseline and at least one post-dose antibody measurement. 1. Participants with protocol deviations outlined in the PDMP that may interfere with serum SARS-CoV-2 nAb titers or interpretation of nAb responses may be excluded or have data collected on or after the protocol deviations be set to missing. 2. Participants with a positive baseline central SARS-CoV-2 RT-PCR test will be excluded from this analysis set. 3. Participants with compromised adherence, infections, or treatments: If a participant's assigned dose of the study intervention is not adhered to, or if the participant becomes infected with SARS-CoV-2 (including a central or local RT-PCR test or asymptomatic cases identified by a change from seronegative to seropositive in SARS-CoV-2 anti-nucleocapsid serology), or receives a COVID-19 treatment or vaccination capable of modifying nAb levels, their subsequent nAb data will be considered missing. Infection with SARS-CoV-2 may be identified through AEs, laboratory data, or other relevant data collected within the study. Participants in this population will be classified according to the actual mAb components received regardless of their assigned treatment.	Sentinel Safety & Main	nAb data

Table 6 Analysis Sets

Analysis Set	Description	Reporting Cohort	Reporting Purpose
SARS-CoV-2-Negative Set	This population will include all participants in the FAS without evidence of a current SARS-CoV-2 infection at baseline. Participants with positive RT-PCR test results at baseline will be excluded from this analysis set. If multiple test results are collected and in conflict, the last baseline central RT-PCR available test result will be used. Unless specified otherwise, participants in this population will be classified according to the assigned treatment.	Main	Efficacy data
PK Set	This population will consist of all participants in Safety Set 1 with at least one post-dose quantifiable serum PK concentration for any mAb component. Participants with protocol deviations outlined in the PDMP that may interfere with serum PK concentrations or interpretation of PK parameters may be excluded or have data collected on or after the protocol deviations be set to missing. Participants in this population will be classified according to the actual mAb components received regardless of their assigned treatment.	Sentinel Safety & Main	Serum PK data
Safety Laboratory / NLF Sets	This population will include all participants for whom safety laboratory / NLF data were collected in Safety Set 1 and the PK Set, respectively. Participants in these populations will be classified according to the actual mAb components received regardless of their assigned treatment.	Sentinel Safety & Main	Safety laboratory / NLF PK data
ADA Sets	This population will consist of all Safety Set 1 participants with a non-missing baseline and at least one non-missing post-baseline ADA result of the same mAb component. For example, the AZD1061 ADA Set consists of participants in Safety Set 1 with a non-missing baseline AZD1061 ADA result and at least one non-missing post-baseline AZD1061 ADA result. The AZD7442 or AZD5156 ADA Set is considered ADA-evaluable for either one or both of the respective mAb components. For example, the AZD7442 ADA Set consists of participants in Safety Set 1 who are AZD8895 ADA-evaluable and/or AZD1061 ADA-evaluable. The AZD5156 ADA Set, AZD3152 ADA Set, and AZD1061 ADA Set apply to the Sentinel Safety Cohort, whereas the AZD3152 ADA Set, AZD7442 ADA Set, AZD1061 ADA Set, and AZD8895 ADA Set apply to the Main Cohort. Participants with protocol deviations outlined in the PDMP that may interfere with ADA assessments may be excluded or have data collected on or after the protocol deviations be set to missing. Participants in this population will be classified according to the actual mAb components received regardless of their assigned treatment.	Sentinel Safety & Main	ADA data

ADA = anti-drug antibody; AE = adverse event; FAS = Full Analysis Set; mAb = monoclonal antibody; nAb = neutralizing antibody; NLF = nasal lining fluid; PDMP = protocol deviation management plan; PK = pharmacokinetics; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

3.3 Statistical Hypotheses

The dual primary efficacy objectives are:

- Compare the efficacy of AZD3152 to AZD7442 and/or Placebo in the Main Cohort to prevent symptomatic COVID-19 caused by any SARS-CoV-2 variant observed at any time up to 181 days after the last dose (i.e., Visit 9 [Day 361] for participants who receive both planned treatment administrations).
- Compare the efficacy of AZD3152 to AZD7442 and/or Placebo in the Main Cohort to prevent symptomatic COVID-19 attributable to matched variants observed at any time up to 181 days after the last dose (i.e., Visit 9 [Day 361] for participants who receive both planned treatment administrations).

The hypotheses for each endpoint are as follows:

- For the dual primary efficacy endpoint based on all confirmed events (or any variants):

$$H_0: \quad \frac{\lambda_{\mathrm{AZD3152_{any}}}}{\lambda_{\mathrm{comparator_{any}}}} \geq 1.0,$$

$$H_A: \quad \frac{\lambda_{\mathrm{AZD3152_{any}}}}{\lambda_{\mathrm{comparator_{any}}}} < 1.0.$$

- For the dual primary efficacy endpoint based on matched variants:

$$H_0: \quad \frac{\lambda_{\mathrm{AZD3152_{matched}}}}{\lambda_{\mathrm{comparator_{matched}}}} \geq 1.0,$$

$$H_A: \quad \frac{\lambda_{\mathrm{AZD3152_{matched}}}}{\lambda_{\mathrm{comparator_{matched}}}} < 1.0.$$

where $\lambda_{\mathrm{AZD3152_{any}}}$ and $\lambda_{\mathrm{comparator_{any}}}$ represent the risk of symptomatic COVID-19 for the AZD3152 and comparator arms, respectively, in the context of dual primary efficacy endpoint based on all confirmed events (or any variants). Similarly, $\lambda_{\mathrm{AZD3152_{matched}}}$ and $\lambda_{\mathrm{comparator_{matched}}}$ denote the risk for the same arms but in the context of dual primary efficacy endpoint based on matched variants.

A superiority test will be performed for each dual primary endpoint to compare the relative risk of symptomatic COVID-19 between treatment arms using a two-sided test. In order to maintain a Type I error rate of 5% ($\alpha = 5\%$) within the two primary endpoints, Holm's step-down procedure will be applied. This procedure adjusts the alpha levels by the number of tests conducted: the alpha for the endpoint with the smallest p-value will be 2.5%, while the alpha for the endpoint with the largest p-value will remain at the standard 5%. A positive

outcome will be declared if either one of the dual primary endpoints is statistically significant at the first step of the testing procedure.

The testing procedure of the secondary efficacy endpoints in Section 1.1 is outlined in Section 3.4.4.4.

3.4 General Considerations

Data from the Sentinel Safety Cohort will be presented separately from the Main Cohort as follows:

- In the Sentinel Safety Cohort, participants will be grouped according to their study intervention on Day 1 for analysis purposes, namely "AZD5156" and "Placebo."
- In the Main Cohort, participants will be classified based on their study interventions at two distinct time points: Day 1 and Day 181. The groupings will represent different study interventions administered on Day 1 and Day 181, denoted as follows: "AZD3152/AZD3152," "AZD7442/Placebo," and "Placebo/Placebo." Each pair signifies the interventions received on Day 1 and Day 181, respectively. For summaries presenting data up to Day 181, the Day 1 study intervention will only be used as the grouping.
- The following additional group will be included in selected tables:
  - A "Comparator" group will be established, which encompasses participants from "AZD7442/Placebo," and "Placebo/Placebo" groups.

This SAP distinguishes between "planned" and "received" study interventions. The "planned" treatment refers to the IP a participant was intended to receive according to the study protocol, specifically following randomization, while the "received" treatment is what the participant actually received. If a participant misses the first IP dose but receives the second IP dose, the second IP dose will be considered the Day 1 IP dose received for analysis purposes.

Table 7 explains the different groups in the study based on their planned IP interventions. It details how many doses of each IP (AZD3152, AZD7442, and Placebo) the Main Cohort participants were intended to receive and in what sequence.

Table 7 Planned Intervention Description

Planned Intervention (Day 1/Day 181)	Description
AZD3152/AZD3152	Participants planned to receive AZD3152 as both the first and second IP doses.

Table 7 Planned Intervention Description

Planned Intervention (Day 1/Day 181)	Description
AZD7442/PbO	Participants planned to receive AZD7442 as the first IP dose, followed by PbO as the second IP dose.
PbO/PbO	Participants planned to receive PbO as both the first and second IP doses.
Comparator	This group includes participants who were planned to receive either AZD7442 or Placebo.

IP = investigational product; PbO = Placebo

Table 8 describes the interventions the Main Cohort participants will receive, factoring in missed second doses and variations in the IP given for the second dose. It further categorizes these interventions according to various data domains to indicate their applicability in each data category.

Table 8 Received Intervention Description

Received Intervention (Day 1/Day 181)	Description	Data Category							
		Efficacy*	Viral Lineage	nAb	ADA	PK	AE	LB	VS
AZD3152/AZD3152	Participants received AZD3152 as both the first and second IP doses.	✓	✓	✓	✓	✓	✓		✓
AZD3152/-	Participants received AZD3152 as the first IP dose but missed the second IP dose.	✓	✓	✓	✓	✓			
AZD7442/PbO	Participants received AZD7442 as the first IP dose and PbO as the second IP dose.						✓		
AZD7442/-	Participants received AZD7442 as the first IP dose but missed the second IP dose.								
PbO/PbO	Participants received PbO as both the first and second IP doses.						✓		
PbO/-	Participants received PbO as the first IP dose but missed the second PbO dose.								
Comparator	The "Comparator" group includes participants who received any of the following combinations: • AZD7442 for the first IP dose followed by PbO or no second IP dose (AZD7442/PbO, AZD7442/-) • Both IP doses as PbO (PbO/PbO) • PbO for the first IP dose with no second IP dose (PbO/-)	✓					✓		

ADA = anti-drug antibody; AE = adverse event; IP = investigational product; LB = laboratory; nAb = neutralizing antibody; PbO = Placebo; PK = pharmacokinetic(s); VS = vital sign
* Applicable to sensitivity analyses of efficacy outcomes. Primary COVID-19 Efficacy endpoints will be evaluated as randomized.

In the event of a medication error that results in protocol deviations, such as a participant receiving "Placebo/AZD7442", “AZD7442/AZD7442”, or "AZD3152/AZD7442" (Day 1 vs. Day 181 IP doses), these cases will not be categorized into exclusive treatment categories for group summaries but presented in listings.

Categorical variables will be summarized through frequencies and percentages, where the denominator for calculation is the relevant analysis set unless otherwise stated. A row denoted as "Missing" will be included in the count tabulations (where necessary) to account for missing values. Continuous variables will be summarized through descriptive statistics, including the number of available data (n), mean, standard deviation (SD), median, minimum, and maximum. Descriptive statistics will include the n < lower limit of quantification (LLOQ) [number of participants with results below the LLOQ], n > upper limit of quantification (ULOQ) [number of participants with results above the ULOQ], geometric mean, geometric standard deviation (GSD), geometric coefficient of variation (GCV), median, minimum, and maximum for general concentration data. Point estimates will be presented with a 95% CI, and the reporting of p-values will correspond to a two-sided test unless otherwise stated. The summaries will be presented per treatment group and visit (where applicable).

Subgroup analyses not specified in this document will be added to the exploratory SAP.

Data will be provided in data listings sorted per treatment group and participant number.

All statistical analyses will be conducted using entimICE AZ 4.4 – Service Pack 8.

3.4.1 General Study Level Definitions

Study days will be calculated relative to the first dose of the IP unless otherwise stated. The study day corresponding to "Date" is expressed as "Date – First IP dose date" if the date is before the first IP dose and calculated as "Date – First IP dose date + 1" for dates on or after the first IP dose. When an event date is partial or missing, the listings will display the study day and any corresponding durations as missing; the imputed dates will not be presented in the listings.

"Baseline" is the last non-missing measurement taken before the first IP dose. Pre-dose measurements specified in the SoA taken on the same date as the first dose of the IP (Day 1) will be considered baseline regardless of the timing recorded. The change from baseline will be calculated as (Post-baseline – Baseline), and, if applicable, the percentage change from baseline will be calculated as (100×[Change from baseline]/Baseline).

3.4.2 Analysis Visit Windows

A windowing convention will be used to determine the analysis value for a given study visit for visit-based assessments, as specified in Table 9, Table 10, and Table 11.

Table 9 Analysis Visit Windows of Sentinel Safety Cohort

Nominal Visit	Visit Window*	
	nAb/PK Data	Non-nAb/PK Data
Screening	≤ -1	≤ -1
Day 1	1	1
Day 3	2 – 4	2 – 4
Day 5	5 – 7	5 – 7
Day 8	8 – 10	8 – 10
Day 15	11 – 21	11 – 21
Day 29	22 – 36	22 – 36
Day 58	51 – 65	37 – 78
Day 91	84 – 98	79 – 103
Day 181	169 – 193	104 – 258
Day 271	259 – 283	259 – 283
Day 361	345 – 377	284 – 438

nAb = neutralizing antibody; PK = pharmacokinetic(s)
* Windowing is done relative to the first investigational product dosing date (Section 3.4.1).

Table 10 Analysis Visit Windows of Main Cohort

Nominal Visit	Visit Window*	
	nAb/PK Data	Non-nAb/PK Data
Screening	≤ -1	≤ -1
Day 1	1	1
Day 8	8 – 12	2 – 12
Day 15	15 – 19	13 – 22
Day 29	22 – 36	23 – 60
Day 91	84 – 98	61 – 136
Day 181 predose#	181 – 188	137 – 188 (prior to second dose)
Day 181 post-dose	NA	181 – 188 (post second dose)
Day 189	189 – 196	189 – 200
Day 210	203 – 217	201 – 241

Table 10 Analysis Visit Windows of Main Cohort

Nominal Visit	Visit Window*	
	nAb/PK Data	Non-nAb/PK Data
Day 271	264 – 278	242 – 316
Day 361	354 – 368	317 – 405
Day 451	NA	NA

NA = not applicable; nAb = neutralizing antibody; PK = pharmacokinetic(s)
* Windowing is done relative to the first investigational product (IP) dosing date (Section 3.4.1).
# Collections up to and including the Day 181 predose visit must occur before the second IP dose (if received) to be included in the analysis.

Table 11 Illness Visits Analysis Windows

Nominal Visit*	Visit Window (All Data)#
IL-D1	1
IL-D3	2 – 4
IL-D5	5 – 6
IL-D8	7 – 9
IL-D11	10 – 12
IL-D14	13 – 16

ID-*X* = Illness Visit Day *X* of the first confirmed Coronavirus disease 2019 (COVID-19) illness episode
* If an illness series has been triggered but is later confirmed as not COVID-19-related, the period will be assigned as "Unconfirmed Illness."
# Windowing is done relative to IL-D1.

When one or more results are available for the same visit window, the result with the date closest to the expected visit date will be used in the analysis. If two observations are equidistant from the expected visit date, the later observation will be used in the analysis. Visits outside the specified visit windows will not be part of the by-visit summaries (i.e., no mapping will be applied to such data points).

Only the first confirmed COVID-19 illness episode will be summarized.

3.4.3 Handling of Unscheduled Visits

Unscheduled, retest (with the same visit number assigned), and early discontinuation measurements will be included in by-visit summaries when presented by analysis visit.

3.4.4 Multiplicity/Multiple Comparisons

This study aims to assess the efficacy estimands relating to the dual primary efficacy endpoints in the Main Cohort, with the goal of controlling the Type I error rate at 5%. These efficacy estimands are centered on comparing AZD3152 to AZD7442 and/or Placebo

("AZD3152/AZD3152" vs. "Comparator," as specified in Table 7) regarding their impact on symptomatic COVID-19 outcomes. The specific statistical hypotheses associated with these efficacy estimands and endpoints are detailed in Section 3.3. The two primary efficacy endpoints under consideration are as follows:

- The incidence of symptomatic COVID-19 caused by any SARS-CoV-2 variant
- The incidence of symptomatic COVID-19 attributable to matched variants

Both endpoints will be evaluated based on event data up to Day 361 by making a superiority comparison based on the ratio of the risk of symptomatic COVID-19 for participants receiving AZD3152 vs. the comparator ("AZD3152/AZD3152" vs. "Comparator," as specified in Table 7). In order to manage multiple comparisons arising from the dual primary endpoints and maintain the overall Type I error rate of 5%, Holm's step-down procedure will be applied, as detailed in Section 3.3.

The analysis will present the relative risk reduction with CIs interpreted in the context of the *adjusted* alpha level according to Holm's step-down procedure for each endpoint. Specifically, the alpha level for the endpoint with the smallest p-value will be adjusted to 2.5%, and for the endpoint with the largest p-value, the alpha level will remain at 5%. A positive study result will be declared if either one of the two endpoints achieves significance, a p-value smaller than its corresponding adjusted alpha level (2.5% for the endpoint with the smallest p-value and 5% for the other endpoint).

Following the dual primary endpoint testing, the secondary efficacy endpoints outlined in Section 1.1 will be evaluated hierarchically. This sequential testing approach will preserve the overall Type I error rate at 5%. Each null hypothesis in the hierarchy will be tested at the 5% level only if all preceding hypotheses have been rejected. If any null hypothesis is not rejected, subsequent tests will be treated as nominal. The specific order of these hierarchical tests is detailed in Figure 1. Any tests for endpoints not included in Figure 1 will be considered exploratory and interpreted nominally.

Figure 1 Hierarchical Hypothesis Testing Order of Efficacy Endpoints Controlling Type I Error at 5% (SARS-CoV-2-Negative Set)

Dual primary endpoint: first occurrence of a symptomatic COVID-19 case up to Month 12 caused by any SARS-CoV-2 variant (Endpoint 1) and/or attributable to matched variants (Endpoint 2)[*]	Superiority comparison based on Relative Risk (Section 4.4.1)
⇩	
Incidence of post-treatment symptomatic COVID-19 cases in the following order[#]*:* 1. Symptomatic COVID-19 case (negative RT-PCR at baseline to positive at any time up 12 months with all observed events at final readout) caused by any SARS-CoV-2 matched variant 2. Symptomatic COVID-19 case (negative RT-PCR at baseline to positive at any time up to 12 months with all observed events at final readout) caused by any SARS-CoV-2 variants 3. Severe COVID-19 caused by any SARS-CoV-2 variant any time up to 12 months 4. Severe COVID-19 caused by any SARS-CoV-2 matched variants at any time up to 12 months 5. Composite of COVID-19-related hospitalization and/or COVID-19-related death (WHO COVID-19 Clinical Progression Scale score ≥ 4) any time up to 12 months 6. COVID-19-related hospitalization any time up to 12 months 7. COVID-19-related death any time up to 12 months 8. Symptomatic COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 months) caused by any SARS-CoV-2 variant 9. Symptomatic COVID-19 case (negative RT-PCR at baseline to positive at any time up to 6 months) caused by any SARS-CoV-2 matched variants	Superiority comparison based on relative risk reduction (Section 4.4.2)

COVID-19 = Coronavirus disease 2019; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

* Holm's step-down procedure will be applied to manage multiple comparisons arising from the dual primary endpoints and maintain the overall Type I error rate of 5%.

Should either of the primary endpoints be non-significant, they will be removed from the testing order.

4 STATISTICAL ANALYSIS

This section provides definitions and information on derivations, analyses, and data presentations per data domain.

4.1 Study Population

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

For the Sentinel Safety Cohort, summaries will be provided by treatment ("AZD5156" or "Placebo") and the "Total," which includes all treatments combined.

For the Main Cohort, summaries will be provided for each specific treatment group: "AZD3152/AZD3152," "AZD7442/Placebo," "Placebo/Placebo," and "Comparator," as specified in Table 7. The "Total" will represent the sum of all participants within the Main Cohort, irrespective of the treatment groups.

4.1.1 Participant Disposition and Completion Status

4.1.1.1 Definitions and Derivations

For determining the stratification factors in Section 1.2, the imputation rules of the date of COVID-19 vaccination status and prior SARS-CoV-2 infection and AZD7442 use are as follows:

- In cases where the day is missing, the day will be imputed as the first of the month.
- In cases where the month is missing, the month will be imputed as January.

The duration of follow-up will be categorized as follows:

- Duration of on-study follow-up from the date of the first IP dose until the earliest of the following events: data cutoff (DCO), study discontinuation, last follow-up, death, or study completion date
- Duration of safety follow-up from the date of the first IP dose to either the DCO date or the date of the last safety assessment, whichever occurs first
- Duration from the date of the first IP dose to the occurrence of each dual primary endpoint events or censoring
- Duration from the date of the first IP dose to unblinding
- Duration from the date of the first IP dose to administering a COVID-19 vaccine or receipt of another COVID-19-preventive measure
- Duration from the date of the second IP dose until the earliest of the following events: DCO, study discontinuation, last follow-up, death, or study completion date

4.1.1.2 Presentation

The number and percentage of participants who were screened, randomized, initiated treatment, received both IP doses (on Day 1 and Day 181), and completed or withdrew from the study will be presented separately for each cohort and the planned treatment group. These summaries will be presented for the Screened Set.

The following study population characteristics will be summarized per cohort and treatment group:

- Recruitment per country and site for the Screened Set and the Full Analysis Set (FAS)
- Stratification factors at randomization (see Section 1.2), derived from the eCRF, for the FAS
- Duration of follow-up for the FAS

Other key information to understand the integrity of the study may be summarized.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

The analysis population definitions are presented in section 3.2Table 6.

4.1.2.2 Presentation

The number of participants included in each analysis set will be reported per cohort and treatment group. In addition, for each analysis set, the number of participants excluded, including the reasons, will be reported.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

A detailed list of possible important protocol deviations (IPDs) and the process for reviewing them by the clinical study team will be outlined in the protocol deviations management plan (PDMP).

The medical and statistical team members will review the protocol deviation categories in a blinded fashion before the clinical database locks, and they are classified as important per the PDMP.

At a minimum, the following deviation categories will be reviewed and considered for classifying the importance of PDs:

- Inclusion criteria
- Exclusion criteria
- Study withdrawal
- Investigational product deviation
- Concomitant use of disallowed medications
- Planned study procedures
- Possible impact on safety assessments

- Potential to interfere with PK concentrations or interpretation of PK parameters
- Potential to interfere with the generation or interpretation of an antibody response

4.1.3.2 Presentation

The number and percentage of participants with IPDs will be provided per cohort, treatment group, and protocol deviation category. The summary will be based on the FAS.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

The demographic characteristics include the following:

- Age (years)
- Age category (< 65 years, ≥ 65 years)
- Sex
- Hispanic/Latino (Yes, No)
- Race
- Ethnicity

4.1.4.2 Presentation

A summary of demographic characteristics will be provided for the FAS. Demographics will be summarized for the Main cohort by treatment group through descriptive statistics. The Sentinel cohort will be summarized by injection site and treatment group.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

The baseline characteristics include the following:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- First IP dose injection site
- Central SARS-CoV-2 RT-PCR result
- SARS-CoV-2 serology (anti-nucleocapsid) result
- SARS-CoV-2 variant nAb titers
- Subgroups listed in Section 4.4.1.4
- Disease histories not part of the medical history summaries (see Section 4.1.6) and the subgroups in Section 4.4.1.4

4.1.5.2 Presentation

Baseline characteristics will be summarized similarly to demographic characteristics for the FAS.

4.1.6 Medical History

4.1.6.1 Definitions and Derivations

The medical history will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) dictionary version.

Clinically significant abnormal physical examination findings at screening will be recorded as medical history.

4.1.6.2 Presentation

The medical history will be summarized per System Organ Class (SOC), the preferred term (PT), cohort, and treatment group for the FAS. A participant having more than one condition within the same SOC or PT will be counted only once for the particular SOC or PT.

4.1.7 Prior and Concomitant Medications

4.1.7.1 Definitions and Derivations

All medications will be coded using the latest WHO Drug Global dictionary version.

Medication is regarded as prior if stopped before the first IP dosing date. Medication is considered concomitant if the start date is on or after the first IP dosing date or if it started before the IP dose and is ongoing after the IP dose. The algorithm for imputing missing or partial medication start and stop dates is provided in 0.

4.1.7.2 Presentation

Prior and concomitant medications will be summarized per Anatomical Therapeutic Class (ATC) Level 2, the preferred drug name, cohort, and treatment group for 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 the particular ATC Level 2 or preferred drug name.

Prohibited and restricted concomitant medications will be summarized separately.

4.1.8 Study Drug Compliance

4.1.8.1 Definitions and Derivations

Treatment adherence will be determined based on the exposure data in the eCRF.

4.1.8.2 Presentation

Treatment compliance with administering the first and second IP doses per the CSP (Yes, No) will be summarized for the FAS; data on medication errors will be listed.

4.2 Neutralizing Activity Endpoints

4.2.1 Analysis Variables and Derivations

The SARS-CoV-2 nAb responses include the nAb titer levels and fold rise of nAb titers collected over time. The fold rise will be calculated as the ratio of the post-dose titer and the baseline nAb titer levels. The handling of missing titer values and values below and above the lower and upper limits of quantification is outlined in Section 4.2.3.

4.2.2 Analyses and Presentation

The SARS-CoV-2 nAb responses will be summarized descriptively for both the Sentinel Safety Cohort and the Main Cohort as follows:

1. **For the Sentinel Safety Cohort**, the nAb responses will be summarized for participants in the SARS-CoV-2 nAb Set by SARS-CoV-2 variant, visit, and treatment group, including "AZD5156" and "Placebo."

2. **In the Main Cohort**, the nAb responses will be summarized for participants in the SARS-CoV-2 nAb Set by SARS-CoV-2 variant and visit.

    a. Up to the predose Day 181 visit, summaries will be generated for all treatment groups based on the Day 1 IP dose, including "AZD3152," "AZD7442," and "Placebo."

    b. After the Day 181 predose visit, the nAb responses will be summarized by SARS-CoV-2 variant and visit for the following Day 1/Day 181 treatment combinations: "AZD3152/AZD3152," "AZD3152/-," "One Dose: AZD7442" (AZD7442/Placebo or AZD7442/-), and "Both/One Dose: Placebo" (Placebo/Placebo or Placebo/-), as specified in Table 8.

The nAb titers over time will be presented in a box and whisker plot per cohort and SARS-CoV-2 variant.

The geometric mean titers (GMTs) and geometric mean fold rises (GMFRs) of nAb titers will be calculated for each SARS-CoV-2 variant and treatment group and summarized at each scheduled visit for Main Cohort participants in the SARS-CoV-2 nAb Set. Inferences about the GMT and GMFR ratio of nAb responses to each SARS-CoV-2 variant will be drawn. These calculations will be conducted separately per visit.

1. Up to the predose Day 181 visit, the comparisons will be conducted between "AZD7442," "AZD3152," and "Placebo."

2. After the Day 181 predose visit, comparisons will be conducted among the treatment groups "AZD3152/AZD3152," "AZD3152/," "One Dose: AZD7442" (AZD7442/Placebo or AZD7442/), and "Both/One Dose: Placebo" (Placebo/Placebo or Placebo/).

The inferences will be based on model-adjusted titer levels. The statistical methodology will be based on a two-sided 95% CI of the ratio of the GMTs and GMFRs. A two-sided 95% CI will be constructed for the ratio $\frac{\text{GMT}_{\text{Group A}}}{\text{GMT}_{\text{Group B}}}$, where $\text{GMT}_{\text{Group A}}$ and $\text{GMT}_{\text{Group B}}$ are the geometric mean nAb titer of Groups A and B, respectively. The 95% CI will be calculated using the normal approximation of log-transformed nAb titers. The 95% CI for the GMFR ratio will be constructed similarly to that of the GMT ratio.

The log-transformed values of the titers and fold rises will be analyzed per time point using an analysis of covariance (ANCOVA), including baseline nAb concentrations on the log scale, age (< 65 years, ≥ 65 years), COVID-19 vaccination status within six months prior to randomization and SARS-CoV-2 infection within six months prior to randomization as fixed effects. The 95% CI of the GMT, GMT ratio, and GMFR ratio will be calculated from the fitted model as the anti-logarithm transformation of the log-transformed mean titer, mean titer difference, and mean fold rise difference's two-sided 95% CI, respectively.

Additional SARS-CoV-2 variants other than those listed in Table 1 may also be assessed to support study activities and the evaluation of AZD3152.

The nAb analysis may be repeated for additional analysis sets, including those with SARS-CoV-2 infections.

4.2.3 Handling of Missing Data

The analysis of GMTs will use the following imputation method:

- Missing titer values will not be imputed.
- Titer values measured below the LLOQ will be imputed with half the LLOQ in summaries and analyses but will be listed as reported in the raw data listings.

- Titer values measured above the ULOQ will be imputed at the ULOQ value.

The LLOQ value for specific SARS-CoV-2 variants is presented in Table 12. The LLOQ values will be used to impute measured nAb results below the LLOQ.CCI
CCI

Table 12 SARS-CoV-2 Variant Lower Limit of Quantification Values

Variant	LLOQ (Titer, 1/Dilution)
Alpha/B.1.1.7	CCI
BA.2	
BA.4/5	
XBB.1.5	

LLOQ = lower limit of quantification; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

4.3 4.2.21.2Anti-Drug Antibody Endpoints

4.3.1 Analysis Variables and Derivations

The presence or absence of anti-drug antibodies (ADAs) will be determined in the serum samples using validated bioanalytical methods in a tiered testing scheme. Initially, the screening step is carried out, followed by a confirmatory step only if the screening result is positive. The overall ADA outcome for a sample is defined according to the following criteria:

- If the screening result is negative, the ADA outcome is considered negative, and no further confirmatory testing is required.
- The ADA outcome is considered positive if the screening result and the confirmatory test are positive.
- The ADA outcome is considered negative if the screening result is positive, but the confirmatory test is negative.
- If the screening result is positive, but the confirmatory test is missing (not available), the ADA status of that sample is considered missing.

ADA data for the mAb components AZD1061, AZD3152, and AZD8895 will be collected at the scheduled visits per the CSP's SoA. According to the rules described above, ADA results from each sample will be reported as either positive or negative. If the sample is confirmed positive for ADA, endpoint titer determination and anti-drug nAbs analysis will be performed (anti-drug nAbs – Main Cohort only). The neutralizing ADA results will be reported as positive or negative.

A participant is considered ADA-positive if "ADA-evaluable" (see Section 3.2) and a positive ADA result in the confirmatory assay is available at any time (including baseline and all post-baseline measurements); otherwise, the participant is considered ADA-negative if *ADA-evaluable*.

The ADA data for AZD5156 and AZD7442 (respectively only applicable to the Sentinel Safety and Main Cohorts) will be classified ADA-positive or ADA-negative as follows:

- ADA-positive to AZD5156 is defined as having a positive ADA result for AZD1061 or AZD3152 at any time (including baseline and all post-baseline measurements). Conversely, ADA-negative to AZD5156 is defined as having negative ADA results for AZD1061 and AZD3152 at all times (including baseline and all post-baseline measurements).
- ADA-positive to AZD7442 is defined as having a positive ADA result for AZD1061 or AZD8895 at any time (including baseline and all post-baseline measurements). Conversely, ADA-negative to AZD7442 is defined as having negative ADA results for AZD1061 and AZD8895 at all times (including baseline and all post-baseline measurements).

Summaries will include only ADA-evaluable participants for the respective agent (see definitions of various ADA analysis sets in Section 3.2).

The ADA endpoints are the number and percentage of participants in the following categories:

- Positive ADA response at any visit, including baseline (excluding screening) in the particular ADA analysis set – The percentage is known as ADA prevalence.
- ADA-positive post-baseline and positive at baseline
- ADA-positive at baseline and not detected post-baseline
- **Treatment-emergent ADA-positive (TE-ADA+)**: Either treatment-induced ADA or treatment-boosted ADA in the particular ADA analysis set. The percentage is known as ADA incidence.
- **Treatment-induced ADA-positive**: ADA-negative at baseline and ADA-positive for at least one post-baseline assessment with ADA titer ≥ 160 for AZD8895, ≥ 80 for AZD1061, and ≥ 200 for AZD3152. For AZD5156 and AZD7442: either mAb component is treatment-induced ADA-positive in the AZD5156 or AZD7442 ADA Sets.
- **Treatment-boosted ADA-positive**: Baseline-positive ADA titer boosted to ≥ 4-fold during the study period – For AZD5156 and AZD7442: either the mAb component is treatment-boosted ADA-positive in the AZD5156 or AZD7442 ADA Sets.

- **Non-treatment-emergent ADA-positive**: ADA-positive and not fulfilling the conditions for TE-ADA+. For AZD5156 and AZD7442: ADA-positive for AZD5156 or AZD7442 and not fulfilling the conditions of TE-ADA+ for either mAb component in the AZD5156 or AZD7442 ADA Sets.
- **Treatment-emergent ADA persistently positive**: Treatment-emergent ADA-positive and having post-baseline ADA-positive assessments with ADA titer ≥ 160 for AZD8895, ≥ 80 for AZD1061, and ≥ 200 for AZD3152 for at least two post-baseline assessments (with ≥ 16 weeks between first and last positive assessments) or positive with ADA titer ≥ 160 for AZD8895, ≥ 80 for AZD1061, and ≥ 200 for AZD3152 at last post-baseline assessment. For AZD5156 and AZD7442: If either mAb component is treatment-emergent ADA persistently positive in the AZD5156 or AZD7442 ADA Sets.
- **Treatment-emergent ADA transiently positive**: Treatment-emergent ADA-positive, and having at least one post-baseline ADA-positive assessment with ADA titer ≥ 160 for AZD8895, ≥ 80 for AZD1061, and ≥ 200 for AZD3152 and not fulfilling the conditions of persistently positive. For AZD5156 and AZD7442: If Treatment-emergent ADA-positive for AZD5156 or AZD7442 and not fulfilling the conditions of persistently positive for either mAb component in the AZD5156 or AZD7442 ADA Sets, respectively.
- Neutralizing ADA-positive at any time, including baseline (excluding screening). The percentage is known as nAb prevalence (Main Cohort only).

4.3.2 Analyses and Presentation

For the Sentinel Safety Cohort, the ADA endpoints for participants who received the IP dose (either "AZD5156" or "Placebo") will be summarized. For the Main Cohort, the treatment groups for this summary of the ADA endpoints will be as follows: "AZD3152/AZD3152", "AZD3152/-" and "One Dose: AZD7442" (AZD7442/Placebo or AZD7442/), as specified in Table 8.

ADA responses will be separately summarized for AZD1061, AZD3152, AZD5156, AZD8895, and AZD7442. Summary statistics of the maximum ADA titers in each category, displaying the minimum, first quartile (Q1), median, third quartile (Q3), and maximum, will be provided per treatment group based on the respective ADA analysis set for AZD1061, AZD3152, and AZD8895.

The maximum ADA titer per ADA category for AZD5156 and AZD7442 is calculated as follows:

- The ADA titer of AZD5156 is the maximum of the AZD1061 and AZD3152 titers over time.

- The ADA titer of AZD7442 is the maximum of the AZD1061 and AZD8895 titers over time.

The summary statistics will be calculated based on the maximum post-baseline titers for each ADA-positive participant within each treatment, except for the following categories: 'ADA-positive at baseline and not detected post-baseline' is based on the maximum titer at baseline only, and 'Non-treatment-emergent ADA-positive' is based on the maximum titer at baseline or post-baseline.

Table 13 details the rules for imputing ADA titers. The imputation strategy varies depending on the particular mAb (AZD1061, AZD3152, or AZD8895) and the observed ADA result.

Table 13 Imputation Rules for Anti-Drug Antibody Titers

Sample ADA Result		Observed ADA Titer	ADA Titer Imputation Strategy
Screening Step	**Confirmatory Step**		
Positive	Positive	< MRD	For AZD1061 and AZD3152, impute the ADA titer to the MRD value.
Positive	Positive	≤ MRD	For AZD8895, impute the ADA titer to the MRD value.
Positive	Positive	Missing	For AZD1061, AZD3152, and AZD8895, set the ADA titer to missing.

ADA = anti-drug antibody; MRD = minimum required dilution

The potential impact of ADA on safety, PK, and efficacy will be assessed descriptively (if data allow). This analysis will include descriptive summaries of serum PK concentrations, and the number and percentage of participants with adverse events (AEs) per SOC and PT will be provided for the following ADA categories by treatment group: treatment-emergent ADA-positive, non-treatment-emergent ADA-positive, and ADA-negative. AEs and serum PK concentrations will be summarized for participants in the Sentinel Safety Cohort based on the ADA status for AZD5156. In the Main Cohort, summaries will be provided based on the ADA status of AZD3152 for participants who received AZD3152 (AZD3152/AZD3152 and AZD3152/- [see Table 8]) and the ADA status of AZD7442 for those who received AZD7442 (One Dose: AZD7442 [see Table 8]).

All ADA results will be listed per participant regardless of ADA-evaluable status.

4.4 Coronavirus Disease Endpoints

4.4.1 First Symptomatic COVID-19 Cases

4.4.1.1 Analysis Variables and Derivations

The dual primary time-to-event COVID-19 outcomes will be derived using the participants' baseline and post-baseline central SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) tests up to Day 361, including the variant information of the SARS-CoV-2 infection, symptom occurrence reported by the investigator per the CSP, and the timing of symptom onset. For the dual primary efficacy endpoints, the analysis will differentiate between any RT-PCR-confirmed symptomatic COVID-19 events and those specifically attributable to matched variants that do not contain F456L substitution and are expected to be susceptible to AZD3152. Sequence analysis of RT-PCR-positive swabs will be performed using GenoSure SARS-CoV-2 spike NGS assay at Monogram Biosciences (South San Francisco, CA, USA). Sequences from SARS-CoV-2-positive swabs collected during the Illness Visits will be analyzed to determine the frequency of amino acid polymorphisms (consensus; reported at ≥ 25% frequency) and minor variants (minimum coverage > 1000X, reported at ≥ 3% frequency). In order to assess the presence of the F456L substitution, the consensus (reported at ≥ 25% frequency) sequence data from the first available RT-PCR-positive sample collected during the Illness Visits will be used to identify matched variant events for Endpoint 2 below. The participants will be considered as having met the dual primary time-to-event efficacy endpoint if the following criteria are met:

- For the **primary confirmed symptomatic COVID-19 endpoint caused by any variant** (Endpoint 1), the participant must develop symptoms associated with COVID-19 after the first IP dose at any time up to 181 days after the last dose (i.e., Visit 9 [Day 361] for participants who receive both planned treatment administrations). All Primary events are required to be confirmed by a positive central SARS-CoV-2 RT-PCR test. The specific window for a positive RT-PCR test in relation to the onset or continuation of COVID-19 symptoms is outlined below. Participants in the SARS-CoV-2-Negative Set must not have a positive central SARS-CoV-2 RT-PCR test at baseline. In contrast, participants in Safety Set 1 can be RT-PCR-positive or negative at baseline (see Section 4.4.1.5.3). These symptoms must satisfy the modified WHO definition of symptomatic COVID-19.
- The same criteria as the confirmed symptomatic COVID-19 endpoint caused by any variant apply for the **primary matched variant endpoint** (Endpoint 2), but the positive RT-PCR test and symptoms must be attributable to matched SARS-CoV-2 variants that do not have F456L substitution.

The presence of symptoms at each Illness Visit will be considered to link the onset of symptoms, as recorded in the COVID-19 initial assessment, with the central RT-PCR test results. This assessment will be based on the WHO COVID-19 Clinical Progression Scale score, where a score of 2 or higher, recorded during these Illness Visits, will be considered indicative of symptomatic COVID-19. Specifically, a positive nasopharyngeal (NP) swab central RT-PCR test must be collected within ten days of the initial onset or during the continuation of COVID-19 symptoms, as collected during the Illness Visits with the WHO score of 2 or higher. Local RT-PCR or rapid antigen tests will not be used to replace missing central RT-PCR tests. Participants without a positive central RT-PCR test within this window, relative to the ongoing symptoms, will be considered not to have met the dual primary time-to-event efficacy endpoint criteria.

The handling of dropouts and missing data for the dual primary time-to-event COVID-19 outcome is outlined in Section 4.4.1.3.

Participants who died due to COVID-19 or who are hospitalized for COVID-19 will be considered as having met the "all confirmed events" time-to-event efficacy endpoint criteria (Endpoint 1), even if no other qualifying symptoms have been recorded.

Any participant who meets the dual primary time-to-event efficacy endpoint criteria only after Day 361 will be considered as having not met the time-to-event efficacy endpoint criteria.

The *timing* variable that will be used for the dual primary COVID-19 outcome will be the relative day of symptom onset (i.e., Symptom onset day = Date of symptom onset – Date of first IP dose + 1). The *timing* variable of the "all confirmed events" endpoint (Endpoint 1) also includes COVID-19-related deaths and the first COVID-19-related hospital admissions.

4.4.1.2 Analyses and Presentation

The dual primary efficacy endpoints will be evaluated for the SARS-CoV-2-Negative Set with a Poisson regression model. Which will include study intervention as a covariate to compare the prophylactic efficacy of "AZD3152/AZD3152" vs. "Comparator", and the randomization stratification factors in Section 1.2 (COVID-19 vaccination status, SARS-CoV-2 infection status, and AZD7442 usage) derived from the eCRF as covariates. The model will use a robust variance (Zou 2004) and offset term to adjust for differential follow-up time. The censoring rules for the analysis of both dual primary efficacy endpoints are provided in Section 4.4.1.3. Based on the adjusted alpha levels as per Holm's procedure (2.5% for the test with the smallest p-value and 5% for the other), the estimated Relative Risk with corresponding CI for testing superiority will be calculated from the model.

Based on the log-link function, the model will be implemented with a REPEATED statement for participant ID and the log-follow-up time as an offset. Let parameter β represent the true log(RR), and L_β and U_β the lower and upper CLs of β's 95% CI. The estimated parameter $\hat{\beta}$, 95% CI for β, and the two-sided p-value will be obtained from the SAS output of the GENMOD procedure. The estimated RR and corresponding 95% CI will be calculated by exponentiating $\hat{\beta}$ and the CLs of β. The RRR estimate is given by $100 \times \left[1 - \exp\left(\hat{\beta}\right)\right]$, and the lower and upper CLs by $100 \times \left[1 - \exp\left(U_\beta\right)\right]$ and $100 \times \left[1 - \exp\left(L_\beta\right)\right]$, respectively.

The intercurrent event strategy of the dual primary efficacy endpoints is given in Table 1. These endpoints are the confirmed symptomatic COVID-19 endpoint caused by any variant (Endpoint 1) and the confirmed symptomatic COVID-19 endpoint attributable to matched variants (Endpoint 2). The dual primary efficacy endpoint analysis targets the efficacy estimands in Table 1.

See Section 3.3 on the hypothesis testing for each dual primary efficacy endpoint of superiority in symptomatic COVID-19 up to Day 361. Refer to Section 3.4.4 for the multiplicity adjustment approach, applying Holm's procedure to control the Type I error rate across the dual primary time-to-event efficacy endpoints.

In addition, Kaplan-Meier curves, will be presented for each dual primary efficacy endpoint per treatment group, and the follow-up days will be summarized descriptively.

A listing of all COVID-19 symptom assessments and the SARS-CoV-2 RT-PCR results will be provided.

4.4.1.3 Handling Dropouts, Missing Data, and Censoring

This section describes the handling of dropouts and missing data for the dual primary time-to-event efficacy endpoint, including censoring.

No data will be considered missing for the dual primary time-to-event efficacy endpoint. All participants will be considered as having been censored or having met the dual primary time-to-event efficacy endpoint.

For the **primary confirmed symptomatic COVID-19 endpoint caused by any variant** (Endpoint 1):

- Symptomatic COVID-19 events will be considered an "event" when dated on or before the earliest of the following censoring dates:
  - Intercurrent events, which include:
    - Participants becoming unblinded to the study intervention assignment.

        - Receipt of the first dose of any COVID-19-preventive product including COV-19 vaccinations and/or medications with indications for the prevention of COV-19.
    - Death not related to COVID-19
    - Early withdrawal/discontinuation
    - Day 181 for participants who did not receive the second dose of the IP (Day 361 analysis only)
    - Last assessment date for participants who are lost to follow-up
    - DCO date
    - End of the analysis period (i.e., Day 361)
- For the **primary matched variant endpoint** (Endpoint 2), in addition to the above criteria, the following is considered an intercurrent event for symptomatic COVID-19 events attributable to matched variants: The date of first occurrence of an RT-PCR-confirmed symptomatic COVID-19 case not attributable to a matched variant or undetermined variants, including COVID-19-related hospitalizations and COVID-19-related deaths.

Participants who did not meet the dual primary time-to-event efficacy endpoint criteria on or before the above censoring date will be right-censored at the earliest of these dates.

Participants may receive additional treatments per the standard of care to manage symptoms or prevent progression to severe COVID-19. Therefore, these participants may have met the definition of the COVID-19 endpoint, symptomatic COVID-19, and receiving such treatments will not necessarily lead to exclusion from the analysis.

4.4.1.4 Subgroup Analysis

The dual primary analysis in Section 4.4.1.2 will be extended to include the following subgroups.

Baseline and Demographics:

- Sex (Female, Male)
- Race (Asian, Black, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- BMI: ≥ 30 kg/m2 (Yes, No)
- Region (US, ROW)
- Region 2 (US, EU, ROW)
- ECG interpretation (Normal, Abnormal)
- Age group (≥ 65 years, < 65 years)

Randomization stratification factors derived from the eCRF:

- COVID-19 vaccination status within six months prior to randomization (Yes, No)

- Prior SARS-CoV-2 infection within six months prior to randomization (Yes, No)
- EVUSHELD use within 12 months prior to randomization (Yes, No)
- Prior COVID-19 vaccination or prior SARS-CoV-2 infection within six months prior to randomization (Yes, No)

Immunocompromised conditions:

- Solid organ or stem cell transplants (Yes, No)
- Solid tumor cancer and on active treatment (Yes, No)
- Taking immunosuppressive medicines (Yes, No)
- Hematological malignancies (Yes, No)
- Moderate or severe secondary Immunodeficiency eg, hemodialysis (Yes, No)

This analysis will incorporate both subgroup and subgroup-by-intervention interaction into the model for the estimation of efficacy measures and the corresponding 95% CIs for each subgroup. The estimated efficacy measures and 95% CIs will be plotted with forest plots for all subgroups. This model will not include the stratification factors used in the main analysis. If there is 0 event at any combined level of subgroup and intervention, then Poisson regression with subgroup-by-intervention cannot converge, exact conditional Poisson regression with adjustment of follow-up time will be used to estimate efficacy for each subgroup. If there is no event in one of two treatment groups in a subgroup, then 97.5% one-sided CI will be reported.

4.4.1.5 Sensitivity and Additional Analyses

Table 14 provides an overview of the planned sensitivity analyses, including their applicability to each dual primary endpoint.

Table 14 Sensitivity and Additional Analyses Summary

Sensitivity Analysis	Endpoint 1 – All Confirmed Events	Endpoint 2 – Matched Variant Events	Section
Treatment policy strategy for intercurrent events	Primary and final readouts	Primary and final readouts	Section 4.4.1.5.1
Symptomatic COVID-19 case confirmation, including local RT-PCR tests	Final readout	Not applicable	Section 4.4.1.5.2
Analysis by actual dose received	Final readout	Final readout	Section 4.4.1.5.3
Extended Cox model	Primary and Final readout*	Not applicable	Section 4.4.1.5.4
Matched variants analysis censoring	Not applicable	Primary and final readouts	Section 4.4.1.5.5
Missing sequence data imputation	Not applicable	Final readout	Section 4.4.1.5.6

Table 14 Sensitivity and Additional Analyses Summary

Sensitivity Analysis	Endpoint 1 – All Confirmed Events	Endpoint 2 – Matched Variant Events	Section
Delayed second IP dose censoring	Final readout	Final readout	Section 4.4.1.5.7
Short-term events	Final readouts*	Final readouts*	Section **Error! Reference source not found.**
Severe COVID-19 and COVID-19 Related Hospitalization and/or Death	Primary and final readouts	Not applicable	Section 4.4.1.5.9
Cox Porportional Hazzard Regression	Primary and final readouts	Primary and final readouts	Section 4.4.1.5.10
Variant Specific Analysis	Not applicable	Primary and final readouts	Section 4.4.1.5.11

COVID-19 = Coronavirus disease 2019; IP = investigational product; RT-PCR = reverse transcriptase polymerase chain reaction; * = may be produced.

4.4.1.5.1 Treatment Policy Strategy for Intercurrent Events

The treatment policy strategy will be applied in the sensitivity analyses for the primary and final readouts of both Endpoint 1 ("all confirmed events") and Endpoint 2 ("matched variant events"). Under this strategy, the usual censoring rules for intercurrent events will not be considered, meaning events such as unblinding to the study intervention assignment, receipt of the first dose of any COVID-19 preventive product, or the occurrence of symptomatic COVID-19 cases not attributable to matched variants or undetermined variants will not lead to censoring. Except for these intercurrent events, all other censoring criteria will still apply as specified in Section 4.4.1.3.

4.4.1.5.2 Symptomatic COVID-19 Case Confirmation Including Local RT-PCR Tests

In a sensitivity analysis for the final readout, the primary efficacy analysis will be repeated using both positive central and local SARS-CoV-2 RT-PCR tests to establish Endpoint 1 ("all confirmed events"). Specifically, both types of RT-PCR tests, central and local, will be employed to confirm symptomatic COVID-19 cases.

4.4.1.5.3 Analysis by Actual Dose Received

In a sensitivity analysis for the final readout, the primary efficacy analysis of the dual primary time-to-event efficacy endpoints, as detailed in Section 4.4.1.2, will be repeated for participants included in Safety Set 1. In this analysis, participants will be categorized based on their treatment received. The categories for treatment are "AZD3152/AZD3152" and "Comparator," as outlined in Table 8. These reanalyses will be conducted if it is determined

that at least 10% of participants have deviated in a way that results in a change between the "AZD3152/AZD3152" vs. "Comparator" groupings due to protocol violations (e.g., dose administration errors).

4.4.1.5.4 Extended Cox Model

In a sensitivity analysis that may be conducted at the primary and final readout, Endpoint 1 ("all confirmed events") may be evaluated using alternative extended Cox models that may include stratification or time-varying treatment effects such as a binary variable grouped by time at risk prior to and post 16th December, 2023. This date was selected (based on GISAID database accessed on 13Mar2024, with sequence quality cutoffs of <= 8% ambiguous bases and >= 29000 bases) to reflect when variants with the F456L mutation observed became non-dominant. Inclusion of a time-varying treatment effect and/or stratification may reduce violation of the proportional hazards assumption caused by variant changes observed in the study.

4.4.1.5.5 Matched Variants Analysis Censoring

In a sensitivity analysis for Endpoint 2 ("matched variant events"), during both the primary and final readouts, the censoring rule applied to cases not attributable to matched or undetermined variants will not be applied. This approach will assess the impact of excluding this specific censoring rule on the primary analysis outcomes while all other censoring criteria from Endpoint 1 ("all confirmed events") remain unchanged.

4.4.1.5.6 Missing Sequence Data Imputation

When more than 10% of sequencing data needed to determine the viral variant for a symptomatic COVID-19 event is absent, imputation techniques will be implemented for a robust analysis of Endpoint 2 ("matched variant events") for the final readout. One method may attribute variants according to their prevalence during distinct periods, matching missing sequences to the dominant variant at those times based on regional prevalence data (GISAID). Alternatively, any unidentified sequences will be presumed susceptible to the IP.

4.4.1.5.7 Delayed Second Investigational Product Dose Censoring

In the final readout of the study, a sensitivity analysis will be performed to evaluate the impact of censoring at Day 181 for participants who received their second IP dose beyond the expected scheduling window. This analysis will consider the effect of late dosing on the dual primary time-to-event efficacy endpoints. Specifically, participants who receive their second IP dose later than 195 days (181 days plus a 14-day window) will have their data censored at Day 195, similar to participants who did not receive the second dose.

4.4.1.5.8 COVID-19 Analysis within three months

Sensitivity analysis for may be performed to focus on events occurring within three months (90 days) following each IP dose. The initial model will incorporate interaction of treatment and a categorical time-varying covariate that separates time at risk into two groups: <=90 days post any dose and >90 days post any dose. This model assumes a constant treatment effect for each of the two time periods where proportional hazards are more likely to be observed. Additional covariates maybe included to create smaller periods of time at risk at the final analysis.

4.4.1.5.9 Severe COVID-19 and COVID-19 Related Hospitalization and/or Death

The primary and final readouts two endpoints will repeat the primary analysis of the dual primary efficacy endpoints but for Severe COVID-19 and the composite endpoint of COVID-19-related hospitalization or COVID-19-related death. The analysis will apply the same censoring rules as the primary endpoints based on intercurrent events that occur prior to symptom onset date. The time at risk will be based on the minimum date of disease progression; for Severe COVID the date the event became severe and for COVID-19 Related hospitalization and/or Death the first date either component occurred.If there is no event at any level of any stratification factor, then that stratification factor will be dropped from Poisson regression with robust variance. If there is no event in one of two treatment groups, then the two-sided p-value and 97.5% one-sided CI from exact conditional Poisson regression with adjustment of follow-up and without stratification will be used.

4.4.1.5.10 Time to Symptomatic COVID-19

To support the primary readout Cox proportional hazards regression will be used to estimate hazard of Symptomatic COVID-19 with similar methodology as the primary endpoints. Where the statistical model will include study intervention, stratification factors and apply similar rules for censoring and intercurrent events. The Efron method will be used to control for ties. The efficacy estimate will be presented as $1 - \widehat{HR}$, where $\widehat{HR}$ is the estimate of the HR. The CI's lower and upper bound of efficacy will be presented as 1 – UCL and 1 – LCL, respectively, where UCL and LCL are the upper and lower confidence limits (CLs) of the HR's CI, respectively.

4.4.1.5.11 Variant Specific

First symptomatic COVID-19 cases attributable to each specific variant group will be analysed with similar methodology as the primary matched variant endpoint, which includes study intervention and stratification factors as covariates. Censoring rules will be followed as described in section 4.4.1.3 for each variant specific endpoint. Lineage groups

may be updated throughout the study and presented in subsequent readouts to reflect changes in variants.

Lineage groups to be evaluated at the primary readout:

BA.2_4	JN.1|JN.1.1|JN.1.19|JN.1.22|JN.1.3|JN.1.4|JN.1.5|JN.1.8|JN.2.5| XDD|XDP|XDR
BA.2.86_1	BA.2.86|BA.2.86.1|BA.2.86.2|BA.2.86.3|JN.2|JN.3|JN.3.2
BA.2_11	JN.1.1.1|JN.1.4.3|JN.1.8.1|XDK

4.4.2 Incidence of COVID-19 Cases

4.4.2.1 Analyses Variables and Derivations

Each outcome will be evaluated through Day 181 and Day 361, where a participant can become positive at any time between the baseline and evaluation point at the final analysis. The incidence efficacy endpoints are the incidence of the following COVID-19 cases after the first IP dose:

- Confirmed symptomatic SARS-CoV-2 infection attributable to any SARS-CoV-2 variant (see Section 4.4.1.1)
- Confirmed symptomatic SARS-CoV-2 infection attributable to a matched variant
- Severe symptomatic COVID-19 determined by the investigator attributable to any SARS-CoV-2 variant
- Severe symptomatic COVID-19 determined by the investigator attributable to a matched variant
- Composite of COVID-19-related hospitalization or COVID-19-related death
- COVID-19-related hospitalization
- COVID-19-related death

Efficacy is the incidence of infection of "AZD3152/AZD3152" vs. "Comparator," as specified in Table 7, expressed as a percentage, i.e., the relative risk reduction (RRR) per the following formula: RRR = 100×(1 – Risk ratio [RR]).

Days 361 and 181 are the end of the analysis period (see Section 4.4.1.1) for the 12-month and 6-month analyses, respectively.

4.4.2.2 Analyses and Presentation

The incidence efficacy endpoints for the SARS-CoV-2-Negative Set will be analyzed.

The Poisson regression model by Zou (2004) with robust variance, adjusting for follow-up time, will be used as the analysis model to estimate the relative risk (RR), comparing "AZD3152/AZD3152" vs. "Comparator" on the incidence of the endpoint. As covariates, the model will include study intervention and randomization stratification factors in Section 1.2, derived from the eCRF. The logarithm of the participant's corresponding follow-up time at risk starting from the first IP dose up to the event or censoring date (see Section 4.4.1.1 and Section 4.4.1.3) will be used as an offset variable in the model to adjust for participants having different exposure times during which the events occur. The follow-up time for those participants will be relative to the first IP dose. The RRR estimate and corresponding 95% CI and two-sided p-value, will be calculated from the regression model. Based on the log-link function, the model will be implemented using the `GENMOD` procedure in SAS and specifying the `REPEATED` statement for participant ID and the log-follow-up time as an offset.

Let parameter β represent the true log(RR), and L_β and U_β the lower and upper CLs of β's 95% CI. The estimated parameter $\hat{\beta}$, 95% CI for β, and the two-sided p-value will be obtained from the SAS output of the `GENMOD` procedure. The estimated RR and corresponding 95% CI will be calculated by exponentiating $\hat{\beta}$ and the CLs of β. The RRR estimate is given by $100 \times \left[1 - \exp\left(\hat{\beta}\right)\right]$, and the lower and upper CLs by $100 \times \left[1 - \exp\left(U_\beta\right)\right]$ and $100 \times \left[1 - \exp\left(L_\beta\right)\right]$, respectively.

Fisher's exact test may be an alternative if the chi-square test assumptions are unmet due to small sample size issues.

4.4.2.3 Handling of Missing Data

Following the censoring rules as below, no data will be considered missing for the incidence efficacy endpoints after an intercurrent event.

For the following incidence efficacy endpoints, censoring rules will be same as **primary confirmed symptomatic COVID-19 endpoint caused by any variant** as described in Section 4.4.1.3:

- Confirmed symptomatic SARS-CoV-2 infection attributable to any SARS-CoV-2 variant (see Section 4.4.1.1)
- Severe symptomatic COVID-19 determined by the investigator attributable to any SARS-CoV-2 variant
- Composite of COVID-19-related hospitalization or COVID-19-related death
- COVID-19-related hospitalization
- COVID-19-related death

For confirmed symptomatic SARS-CoV-2 infection attributable to a matched variant, censoring rules will be same as **primary matched variant endpoint** as described in Section 4.4.1.3.

For severe symptomatic COVID-19 determined by the investigator attributable to a matched variant, censoring rules will be same as **primary matched variant endpoint** as described in Section 4.4.1.3 except that the date of **non-severe** symptomatic COVID-19 case not attributable to a matched variant or undetermined variants will be excluded from censoring dates.

4.4.2.4 Additional Analyses

The exploratory analysis of the Illness Visits (e.g., e-Diary symptoms data), including the duration of COVID-19 symptoms, will be detailed in the exploratory SAP.

4.5 Pharmacokinetic Endpoints

This section covers details related to the serum and nasal lining fluid (NLF) PK endpoints and analyses. Serum and NLF PK samples will be collected per the CSP's SoA.

The serum PK samples will be analyzed for the PK Set, whereas the NLF PK samples will be analyzed for the NLF Set.

A non-compartmental serum PK data analysis will be performed for AZD5156-treated participants in the Sentinel Safety Cohort. Details of the non-compartmental serum PK analysis are summarized in Appendix A.

A population PK analysis will be performed on serum PK data for participants in the Main Cohort. The population PK analysis will be detailed in a separate analysis plan.

Similar to the analysis of serum PK concentrations, the NLF PK concentrations will be summarized per treatment group and time point for each mAb component. NLF concentration results may be reported separately from the CSR.

4.6 Viral Sequencing Endpoint

Viral sequencing will be conducted through genotypic analyses of SARS-CoV-2 virus sequences obtained from NP swab samples collected from participants during Illness Visits.

Sequence analysis of RT-PCR-positive swabs will be performed using GenoSure SARS-CoV-2 spike NGS assay at Monogram Biosciences (South San Francisco, CA, USA). Sequences from SARS-CoV-2-positive swabs collected during the Illness Visits will be analyzed to determine the frequency of amino acid polymorphisms (consensus; reported

at ≥ 25% frequency) and minor variants (minimum coverage > 1000X; reported at ≥ 3% frequency). Consensus sequencing analysis (> 25% frequency) will be used to identify matched variants. The minor variant analysis will be summarized descriptively.

The sequencing data, corresponding to the "all confirmed events" efficacy endpoint up to Day 361, will be descriptively summarized for participants in the SARS-CoV-2-Negative Set for the following Day 1/Day 181 treatment combinations specified in Table 8: "AZD3152/AZD3152," "AZD3152/-," "One Dose: AZD7442," and "Both/One Dose: Placebo." This analysis will be based on the treatment actually received by the participants rather than the treatment to which they were randomized. Additionally, viral lineage data will be summarized for Safety Set 1. A similar analysis will also be conducted for the efficacy endpoint up to Day 181, based on the treatment received on Day 1, which includes the groups "AZD3152," "AZD7442," and "Placebo."

4.7 Safety Endpoints

Pregnancy data will be provided in the data listings.

4.7.1 Adverse Events

4.7.1.1 Definitions and Derivations

AEs will be coded using the latest version of the MedDRA dictionary. The algorithm for imputing missing or partial medication start and stop dates is provided in Appendix A.

4.7.1.1.1 Adverse Events and Serious Adverse Events

The definition of AEs and serious adverse events (SAEs) is presented in the CSP. All AEs will be collected in the eCRF from the time of study intervention administration through 90 days following the administration of the two IP doses and during the Illness Visits. SAEs are those events recorded as "serious" on the AE page of the eCRF. Immediate AEs will be collected for a 1-hour observation period after the IP doses. SAEs, including COVID-19-related and other deaths, will be recorded from signing the informed consent form through the end of the study.

Listings of all AEs and SAEs recorded in the database, including COVID-19-related and other deaths, will be provided. For SAEs with partial dates, if the known part of the date indicates that the SAE stopped before the IP dose, it will be considered an SAE before the IP dose; otherwise, it will be considered an SAE post-dose of the first IP.

Clinically significant abnormal physical examination findings at screening will be recorded as medical history, while clinically significant findings following vaccination will be

recorded as AEs. Similarly, injection site reactions and abnormal laboratory and vital signs findings will be recorded as AEs.

Diagnoses of suspected or confirmed COVID-19, confirmed asymptomatic SARS-CoV-2 infection, and recurrence of COVID-19 (or SARS-CoV-2 reinfection) will be collected and recorded in the eCRF as AEs.

4.7.1.1.2 Adverse Events of Special Interest

AESIs are events of scientific and medical interest that are specific to further understanding the IP safety profile. These events will be assessed from the time of study intervention administration until the study's last visit. AESIs for this study include, but are not limited to:

- Anaphylaxis and other serious hypersensitivity reactions, including immune-complex disease, as defined in the CSP
- Cardiovascular and thrombotic events as assessed by a cardiovascular events adjudication committee

Both serious and non-serious AESIs will be monitored and recorded throughout the duration of the study, from the time of study intervention until the final visit, unless otherwise specified.

AESIs will be programmatically identified by reviewing the prespecified preferred terms and classified into categories for serious hypersensitivity reactions, including anaphylaxis, immune complex disease, and cardiovascular and thrombotic events. Serious hypersensitivity reactions, including anaphylaxis, must additionally be classified as an SAE and/or have a CTCAE grade of 3 or higher within 30 days of the IP doses to meet the criteria for an AESI. In order to meet the criteria for AESIs, cardiovascular and thrombotic events 1) must be adjudicated as positive for the Main Cohort and 2) considered serious for the Sentinel Safety Cohort with no adjudication requirements.

The list of preferred terms to identify AESIs based on MedDRA terms is not included in this SAP to accommodate updates to the MedDRA dictionary version and for convenience in using them directly in SAS programming. Listings used to identify AESIs will be stored with the Biostatistics team. Terms and versions used for each clinical database lock will be reported.

4.7.1.1.3 Medically Attended Adverse Events

Medically attended adverse events (MAAEs) are defined as AEs leading to medically attended visits that were not routine physical examinations or vaccination visits. MAAEs will be collected throughout the study.

4.7.1.1.4 Severity

The severity of AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 as "Mild (Grade 1)," "Moderate (Grade 2)," "Severe (Grade 3)," "Potentially life-threatening (Grade 4)," and "Fatal" (Grade 5). The severity of AEs will be collected on the eCRF.

4.7.1.1.5 Relationship to Investigational Product

As indicated by the investigator, the relationship of AEs to IP will be classified as unrelated or related.

4.7.1.1.6 Participant Time-Adjusted Rate

The participant time-adjusted rate is calculated as the number of participants with AEs per category divided by the total participant years in a given collection period (see Section 4.7.1.2). The participant years are determined by summing all participants' total number of follow-up days divided by 365.25.

4.7.1.2 Presentation

4.7.1.2.1 Adverse Events (90 Days Post-Dose)

The "90 days post-dose" AEs will be summarized as follows:

1. For the Sentinel Safety Cohort, AEs that started, worsened, or became serious on or after the IP dosing date up to and including 90 days following the IP dosing date will be summarized for participants who received the IP dose (either "AZD5156" or "Placebo"; Safety Set 1).

2. For the Main Cohort:

    a. AEs that started, worsened, or became serious on or after the first IP dosing date up to and including 90 days following the first IP dosing date will be summarized for participants in Safety Set 1. Participants will be categorized into groups based on the first IP dose received on Day 1: "AZD3152," "AZD7442," and "Placebo."

    b. AEs that started, worsened, or became serious on or after the second IP dosing date up to and including 90 days following the second IP dosing date will be summarized for participants in Safety Set 2. The treatment groups for this summary will be as follows: "AZD3152/AZD3152," "AZD7442/Placebo," and "Placebo/Placebo," as specified in Table 8.

Table 15 summarizes the analyses of "90 days post-dose" AEs. These AEs will be summarized for the categories listed in Table 15.

Table 15 Adverse Events (90 Days Post-Dose) by Category

Cohort	Population	Started, Worsened, or Became Serious	Treatment Groups (per Table 8)	AEs	AEs ≥ 5% Incidence Rate in Any Treatment	AEs per Maximum Severity	IP-related AEs	IP-related AEs per Maximum Severity	Immediate AEs	COVID-19-related AEs	AESIs	IP-related AESIs	MAAEs	IP-related MAAEs	SAEs Leading to Death	IP-related SAEs Leading to Death	SAEs	IP-related SAEs	Serious AESIs	IP-related Serious AESIs	Serious MAAEs	IP-related Serious MAAEs	AEs Leading to Study Discontinuation	IP-related AEs Leading to Study Discontinuation	IP-related SAEs Leading to Study Discontinuation
Sentinel Safety Cohort	Safety Set 1	IP dosing date (90 days)	Day 1 IP dose: • AZD5156 • Placebo	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Main Cohort	Safety Set 1	First IP dosing date (90 days)	Day 1 IP dose: • AZD3152 • AZD7442 • Placebo	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Main Cohort	Safety Set 2	Second IP dosing date (90 days)	Intervention (Day 1/Day 181): • AZD3152/AZD3152 • AZD7442/Placebo • Placebo/Placebo	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

AESI = adverse event of special interest; COVID-19 = Coronavirus disease 19; IP = investigational product; MAAE = medically attended adverse event

For the analysis of "90 days post-dose" AEs, a visit window of 13 days will be used for AE data from both the Sentinel Safety and Main Cohort, allowing for the collection and analysis of AEs that started, worsened, or became serious up to Day 103 following the intervention.

4.7.1.2.2 Adverse Events Collected During Full Study Duration (451 Days)

The "full study duration" AEs (throughout the entire study duration of 451 days) will be summarized as follows:

1. For the Sentinel Safety Cohort, AEs that started, worsened, or became serious on or after the first IP dosing date up to and including the end of the study will be summarized for participants who received the IP dose (either "AZD5156" and "Placebo"; Safety Set 1).

2. For the Main Cohort:

    a. AEs that started, worsened, or became serious on or after the first IP dosing date up to and including one day prior to the second IP dosing date or Day 180 (relative to the first IP dose) if no second IP dose was received will be summarized for participants in Safety Set 1. Participants will be categorized into groups based on the IP dose received on Day 1: "AZD3152," "AZD7442," and "Placebo."

    b. AEs that started, worsened, or became serious on or after the second IP dosing date up to and including the end of the study will be summarized for participants in Safety Set 2. The treatment groups for this summary will be as follows: "AZD3152/AZD3152," "AZD7442/Placebo," and "Placebo/Placebo," as specified in Table 8.

    c. AEs that started, worsened, or became serious on or after the first IP dosing date up to and including the end of the study will be summarized for participants in Safety Set 1. The treatment groups for this summary will be as follows: "Both/One Dose: AZD3152," "One Dose: AZD7442," "Both/One Dose: Placebo," and "Comparator," as specified in Table 8.

Table 16 summarizes the analyses of "full study duration" AEs. These AEs will be summarized for the categories listed in Table 16.

Table 16 Adverse Events Collected During Full Study Duration (451 Days) by Category

Cohort	Population	Started, Worsened, or Became Serious		Treatment Groups (per Table 8)	AEs	AEs ≥ 5% Incidence Rate in Any Treatment	AEs per Maximum Severity	IP-related AEs	IP-related AEs per Maximum Severity	Immediate AEs	COVID-19-related AEs	AESIs	IP-related AESIs	MAAEs	IP-related MAAEs	SAEs Leading to Death	IP-related SAEs Leading to Death	SAEs	IP-related SAEs	Serious AESIs	IP-related Serious AESIs	Serious MAAEs	IP-related Serious MAAEs	AEs Leading to Study Discontinuation	IP-related AEs Leading to Study Discontinuation	IP-related SAEs Leading to Study Discontinuation
		From	Up to																							
Sentinel Safety Cohort	Safety Set 1	IP dosing date	End of study	Day 1 IP dose: • AZD5156 • Placebo	N/A	N/A	N/A	✓	✓	N/A	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	N/A	✓	✓
Main Cohort	Safety Set 1	First IP dosing date	One day prior to the second IP dosing date	Day 1 IP dose: • AZD3152 • AZD7442 • Placebo	N/A	N/A	N/A	✓	✓	N/A	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	N/A	✓	✓
Main Cohort	Safety Set 2	Second IP dosing date	End of study	Intervention (Day 1/Day 181): • AZD3152/AZD3152 • AZD7442/Placebo • Placebo/Placebo	N/A	N/A	N/A	✓	✓	N/A	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	N/A	✓	✓

Table 16 Adverse Events Collected During Full Study Duration (451 Days) by Category

Cohort	Population	Started, Worsened, or Became Serious		Treatment Groups (per Table 8)	AEs	AEs ≥ 5% Incidence Rate in Any Treatment	AEs per Maximum Severity	IP-related AEs	IP-related AEs per Maximum Severity	Immediate AEs	COVID-19-related AEs	AESIs	IP-related AESIs	MAAEs	IP-related MAAEs	SAEs Leading to Death	IP-related SAEs Leading to Death	SAEs	IP-related SAEs	Serious AESIs	IP-related Serious AESIs	Serious MAAEs	IP-related Serious MAAEs	AEs Leading to Study Discontinuation	IP-related AEs Leading to Study Discontinuation	IP-related SAEs Leading to Study Discontinuation
		From	Up to																							
Main Cohort	Safety Set 1	First IP dosing date	End of study	Intervention (Day 1/Day 181): • Both/One Dose: AZD3152 • One Dose: AZD7442 • Both/One Dose: Placebo • Comparator	N/A	N/A	N/A	✓	✓	N/A	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	N/A	✓	✓

AESI = adverse event of special interest; COVID-19 = Coronavirus disease 19; IP = investigational product; MAAE = medically attended adverse event

"Full study duration" AEs before the first IP dose will be presented in listings but will not count toward the incidence counts in summary tables.

For the analysis of "full study duration" AEs, a visit window of 13 days will be used for AE data from both the Sentinel Safety and Main Cohort, allowing for the collection and analysis of AEs that started, worsened, or became serious up to Day 464 following the intervention.

Summaries of AEs per SOC and PT will include the number and percentage of participants reporting at least one event and the participant time-adjusted rates of AEs calculated as the number of participants reporting at least one event divided by the total participant time at risk for each treatment group, multiplied by 100. The total participant time at risk starts from the dosing date to the end of the relevant observation period and considers any discontinuations or loss to follow-up. The incidence rates will be presented per 100 participant years (365.25 days).

AEs that started, worsened, or became serious during a given study period will count toward the incidence summaries. For the summary of the incidence rates, should a participant experience multiple events within a category, the participant will be counted only once. For AEs per maximum severity, should a participant experience multiple AEs within a SOC or PT, the maximum severity grade will be counted for the particular SOC or PT.

In addition, the overview and the main SOC/PT AE tables will present the binomial *exact* 95% CI for the AE incidence rates of Clopper and Pearson (1934) per treatment group.

4.7.1.3 Subgroup Analysis

Select descriptive analyses of the Main Cohort adverse event data in Section 4.7.1 may be repeated for the following subgroups:

- Sex (Female, Male)
- Race (Asian, Black, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Age (< 18 years, 18 to < 65 and ≥ 65 years)
- BMI: ≥ 30 kg/m2 (Yes, No)

4.7.2 Clinical Laboratory Blood Samples

4.7.2.1 Definitions and Derivations

Hematology, serum chemistry, and coagulation will be performed per the CSP's SoA only for the Sentinel Safety Cohort and for at least the first 600 participants in the Main Cohort. Since safety laboratory data are not collected post-second IP dose, all associated summaries reflect the effects of only the initial treatment, simplifying the analysis by linking the laboratory results to a single intervention.

Quantitative laboratory parameters reported as "< X" (below the LLOQ) or "> X" (above the ULOQ)" will be converted to X for quantitative summaries but will be presented as recorded (i.e., as "< X" or "> X") in the listings.

Quantitative laboratory parameters with available CTCAE toxicity grades (Version 5.0) will be categorized as "no event" or Grades 1 to 4. A higher grade represents more severe toxicity. Refer to 0 for each parameter toxicity grade criteria.

4.7.2.2 Presentations

4.7.2.2.1 Descriptive Analysis

The safety laboratory results will be summarized descriptively for both the Sentinel Safety Cohort and the Main Cohort as follows:

1. For the Sentinel Safety Cohort, the safety laboratory results will be summarized for participants in the Safety Laboratory Set by visit and treatment group, including "AZD5156" and "Placebo."

2. In the Main Cohort, the safety laboratory results will be summarized for participants in the Safety Laboratory Set by visit. Summaries will be generated for all treatment groups based on the Day 1 IP dose, including "AZD3152," "AZD7442," and "Placebo."

The descriptive summaries of the laboratory parameters include summaries of the observed and change from baseline per visit (quantitative parameters).

4.7.2.2.2 Abnormalities Incidence

The incidence of treatment-emergent abnormal results will be assessed based on the CTCAE grading system (toxicity grades). The number of participants in the Safety Laboratory Set with at least one treatment-emergent abnormal laboratory result per parameter will be calculated for each treatment group. The incidence rates of treatment-emergent abnormal laboratory results will be presented as the percentage of participants

with abnormal values out of the total number of participants in each treatment group with data.

Participants' laboratory data with at least one treatment-emergent abnormal result will be listed per laboratory domain (hematology, serum chemistry, and coagulation).

4.7.2.2.3 Liver Toxicities

Summaries of liver toxicity for each treatment group will be provided, similar to the presentations of treatment-emergent abnormal results in the Safety Laboratory Set. These summaries will include:

- The highest recorded values of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) after baseline, grouped into the following categories: less than 3 times the upper limit of normal (ULN), from 3 up to but not including 5 times the ULN, from 5 up to but not including 10 times the ULN or 10 times or greater than the ULN. These values will be cross-referenced with the highest recorded total bilirubin (TBL) values post-baseline, categorized as less than 2 times the ULN or 2 times the ULN and above.
- A list of participants who had at least one recorded post-baseline value of ALT or AST 3 times the ULN or greater or a TBL value 2 times the ULN or greater
- A list of participants who had at least one recorded post-baseline value of ALT or AST 3 times the ULN or greater and simultaneously a TBL value 2 times the ULN or greater

4.7.3 Vital Signs

4.7.3.1 Definitions and Derivations

Vital signs, including heart rate, respiratory rate, systolic and diastolic blood pressure, body temperature, pulse oximetry, weight, and BMI, will be performed at time points specified in the CSP.

0 presents the severity grades of abnormal vital signs.

4.7.3.2 Presentations

4.7.3.2.1 Descriptive Analysis

The vital signs measurements will be summarized descriptively for both the Sentinel Safety Cohort and the Main Cohort as follows:

1. For the Sentinel Safety Cohort, the vital signs measurements will be summarized for participants in Safety Set 1 by visit and treatment group, including "AZD5156" and "Placebo."

2. In the Main Cohort, the vital signs measurements will be summarized for participants in Safety Set 1 by visit. Up to the predose Day 181 visit, summaries will be generated for all treatment groups based on the Day 1 IP dose, including "AZD3152," "AZD7442," and "Placebo."

3. After the Day 181 predose visit in the Main Cohort, the vital signs measurements will be summarized for participants in Safety Set 1 by visit for the following Day 1/Day 181 treatment combinations: "AZD3152/AZD3152," "Both/One Dose: AZD3152," "One Dose: AZD7442," and "Both/One Dose: Placebo," as specified in Table 8.

The descriptive summaries of the vital signs parameters include summaries of the observed and change from baseline per visit.

4.7.3.2.2 Abnormalities Incidence

The incidence of treatment-emergent abnormal results will be assessed based on the criteria in 0, similar to the analysis approach used for the "full study duration" AE analysis (451-day events). The number of participants in Safety Set 1 with at least one treatment-emergent abnormal vital sign result per parameter will be calculated for each treatment group. The treatment groups for the incidence analysis of treatment-emergent abnormal vital signs results are as follows: "AZD5156" and "Placebo" for the Sentinel Safety Cohort, and "Both/One Dose: AZD3152," "One Dose: AZD7442," and "Both/One Dose: Placebo" for the Main Cohort, as specified in Table 8. The incidence rates of treatment-emergent abnormal vital signs results will be presented as the percentage of participants with abnormal values out of the total number of participants in each treatment group with data.

Participants' vital signs data with at least one treatment-emergent abnormal result will be listed.

4.7.4 Electrocardiogram

ECG will be performed at screening; the ECG findings will be summarized as part of the baseline characteristics summaries.

5 REFERENCES

Clopper, C.J. and Pearson, E.S., 1934. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*, 26(4), 404-413.

Zou, G., 2004. A modified Poisson regression approach to prospective studies with binary data. *American Journal of Epidemiology*, 159(7), 702-706.

MISSING MEDICATION AND ADVERSE EVENTS DATES IMPUTATION

The imputation rules for missing or partial medication start/stop dates are as follows:

- Missing or partial medication start dates:
  - If only the day is missing, use the first day of the month.
  - If both the day and month are missing, use the first day of the year.
  - If only the month is missing, use the year's first month.
  - If day and month are present and the year is missing, use the year of the informed consent date.
  - Use the informed consent date if the day, month, and year are missing.
- Missing or partial medication end dates:
  - Use the earliest of the data cutoff date and the end-of-study date as the reference date for the imputation rules below.
  - If the year is the same as the reference date's year:
    - If the day is missing and the month is the same as the reference date's month, use the day of the reference date.
    - If the day is missing and the month is different from the reference date's month, use the last day of the month.
    - If the day is present and the month is missing, use the month of the reference date.
  - If the year is different from the reference date's year:
    - If only the day is missing, use the last day of the month.
    - If both the day and month are missing, use the last day of the year.
  - If the date is completely missing, use the reference date.

The imputation rules for missing or partial adverse events start/stop dates/times are as follows:

- AEs with unknown start times, but with start date known, will be imputed with a time of 00:00, unless the start date corresponds to any given dosing date. In this case the start time will be imputed with the time of dosing. If this results in a start date/time after the end date/time of the AE, then the time will also be imputed with 00:00.
- AEs with completely unknown start dates will be imputed with the date and time of the first IP dose unless the end date is known and prior to first IP dose. In this case the start date will be imputed as the date of Screening and a time of 00:00.
- AEs with partially know start dates/times will be treated as follows:
  - If only the day is missing, then the day will be imputed with the first day of the month, unless the month and year in which the AE started is a month and

year in which treatment was administered (either the first or second IP dose), then the day will be imputed with the first day of the applicable treatment. If this results in a start date after the end date, then the day will be imputed with the first day of the month.

- If only the month is missing and the year is a year in which treatment was administered (either the first or second IP dose), then the month will be imputed with the first month in which the applicable treatment was administered. If this results in a start date after the end date of the AE, then the month will be imputed with JAN. If the known year part is not a year in which treatment was administered, then the month will also be imputed with JAN.
- If both the day and month are missing and the year is a year in which treatment was administered (either the first or second IP dose), then the day and month will be imputed with the day and month of dosing. If this results in a start date after the end date, then the day and month will be imputed with 01JAN. If the year is not a year in which treatment was administered, then the day and month will also be imputed with 01JAN.
- If only the year is missing, then the year will be imputed with the year of dosing (either the first or second IP dose).
- Missing times will be imputed as 00:00 h or with the time of dosing for events starting on day of dosing (either the first or second IP dose).

There will be no imputation of AE data for the data listing.

APPENDIX A PHARMACOKINETIC ANALYSES

Pharmacokinetic Parameters

For the Sentinel Safety Cohort, the PK parameters of the serum PK concentration data for AZD51516 and its component antibodies (AZD1061 and AZD3152) will be derived using non-compartmental methods in Phoenix® WinNonlin® Version 8.4 or higher (Certara) by AstraZeneca. No PK parameters will be determined from the NLF concentrations.

Where data allows, the PK analysis will be carried out using "actual" elapsed times determined from the PK sampling and dosing times recorded in the database. If "actual" elapsed times are missing, nominal times may be used at the discretion of the PK scientist with approval from the AstraZeneca clinical pharmacology scientist (CPS). Nominal sampling times may be used for any agreed interim PK parameter calculations.

For each PK sampling period, PK concentrations that are not quantifiable (NQ) from the time of pre-dose sampling (t = 0) up to the time of the first quantifiable PK concentration will be set to zero. After this time point, NQ PK concentrations will be set to missing for all PK concentration profiles. Where two or more consecutive PK concentrations are NQ at the end of a profile, the profile is deemed to have terminated. Therefore, any further quantifiable PK concentrations will be set to missing for calculating the PK parameters unless it is considered a true characteristic of the drug profile.

If an entire PK concentration-time profile is NQ, the profile will be excluded from the PK analysis.

C_{max} and t_{max} are taken directly from the PK concentration-time profiles.

The PK parameter described in Table 17 will be determined where data permits.

Table 17 Pharmacokinetic Parameters

Parameter	Definition	Derivation
AUC_{inf}	The area under the PK concentration-time curve from zero to infinity	Calculated by $AUC_{(0-t)}$ and then extrapolated by C_{last}/λ_z to infinity
AUC_{last}	The area under the PK concentration-time curve from zero to the last quantifiable PK concentration	Using the linear up/log down trapezoidal rule
$AUC_{(0-28d)}$	The partial area under the concentration-time curve from time 0 to 28 days post-dose	Using the linear up/log down trapezoidal rule

Table 17 Pharmacokinetic Parameters

Parameter	Definition	Derivation
$AUC_{(0\text{-}57d)}$	The partial area under the concentration-time curve from time 0 to 57 days post-dose	Using the linear up/log down trapezoidal rule
$AUC_{(0\text{-}90d)}$	The partial area under the concentration-time curve from time 0 to 90 days post-dose	Using the linear up/log down trapezoidal rule
$AUC_{(0\text{-}180d)}$	The partial area under the concentration-time curve from time 0 to 180 days post-dose	Using the linear up/log down trapezoidal rule
C_{max}	Maximum observed (peak) PK concentration	
t_{max}	Time to reach the peak or maximum observed PK concentration or response following drug administration	
$t_{1/2\lambda z}$	Half-life associated with terminal slope (λ_z) of a semi-logarithmic PK concentration-time curve	$\ln(2)/\lambda_z$
CL/F	Apparent total body clearance following extravascular administration	$Dose/AUC_{inf}$
Vz/F	The apparent volume of distribution during the terminal phase following extravascular administration	$Dose/(\lambda_z \times AUC_{inf})$

In addition, the diagnostic PK parameters described in Table 18 will also be determined.

Table 18 Diagnostic Pharmacokinetic Parameters

Parameter	Definition	Derivation
Rsq	Coefficient of determination, a statistical measure of fit for the regression used for λ_z determination	
Rsq_adj	Adjusted Rsq, a statistical measure of fit for the regression used for λ_z determination adjusted for the number of used data points	
λ_z	The terminal elimination rate constant	Estimated from linear regression of the terminal part of the log concentration vs. the time curve
λ_zN	Number of data points used for λ_z determination	
λ_z lower	Lower (earlier) time used for λ_z determination	
λ_z upper	Upper (later) time used for λ_z determination	
λ_z span ratio	The time period over which λ_z was determined as the ratio of $t_{1/2\lambda z}$	(λ_z upper – λ_z lower)/$t_{1/2\lambda z}$
$\%AUC_{extr}$	The extrapolated area under the curve from t_{last} to infinity (%)	
t_{last}	Time of last quantifiable concentration	

Additional pharmacokinetic parameters may be determined if deemed appropriate.

Points to consider for selecting data points for estimating the elimination rate constant:

The terminal elimination rate constant (lambda z [λ_z]) is calculated by log-linear regression of the terminal portion of the PK concentration-time profile. The following points should be considered and, in general, should ensure a good estimate of λ_z:

- If more than one phase is apparent, use only data points from the terminal phase.
- Use 3 to 6 measured PK concentrations spanning three half-lives.
- Include the last measurable PK concentration if possible.
- Include only observations after C_{max}.
- The coefficient of determination (Rsq) value shows the goodness-of-fit (the precision) in the choice of points. The Rsq adjusted value also shows the goodness-of-fit but considers the number of points used in the estimation. In order to achieve good precision in the estimation, the Rsq adjusted value should be high; e.g., a value larger than 0.8 indicates a good correlation.

Alternative approaches may meet study objectives. In such cases, reported diagnostic parameters should be referred to as the necessary precision discussed in the CSR.

Points to consider for AUC:

- The area under the PK concentration vs. the time curve is calculated using the trapezoidal rule. Generally, the 'linear up/log down' calculation method is appropriate.
- To ensure a robust estimate of AUC_{inf}, the extrapolation ($\%AUC_{extr}$) should be relatively small as a percentage of the whole AUC_{inf} (e.g., $\leq$ 20%).

Alternative approaches may adequately meet study objectives. In such cases, the reported diagnostic parameter $\%AUC_{extr}$ should be referred to, and accuracy and precision should be discussed in the CSR as necessary.

Derivation of AZD5156 and AZD7442 Concentrations

Serum and NLF concentrations of AZD5156 (Sentinel Safety Cohort only) and AZD7442 (Main Cohort only) will be derived from the concentrations of each constituent mAb for each time point based on the rules in Table 19. If the concentration of one or more constituent mAb is missing or not reportable for any individual time point, the concentration of AZD5156 or AZD7442 will not be derived for that time.

Table 19 Derivation of AZD5156 and AZD7442 Concentrations

Concentration of AZD1061	Concentration of AZD3152 or AZD8895	Concentration of AZD5156 or AZD7442
< LLOQ	< LLOQ	< LLOQ
X	< LLOQ	X
< LLOQ	Y	Y
X	Y	X + Y

The adjusted NLF concentrations and serum-to-NLF partition ratios will be calculated as follows:

- Adjusted NLF concentration (ng/mL) = Raw NLF concentration (ng/mL) × (1000 × Serum urea [mmol/L]) / (NLF urea [µmol/L])
- Serum:NLF partition (%) = 100 × (0.001 × Adjusted NLF concentration [ng/mL]) / (Serum concentration [µg/mL])

Pharmacokinetic Concentration Descriptive Statistics

The serum and NLF PK concentrations for each constituent mAb and derived AZD5156 or AZD7442 concentrations at each scheduled time point will be summarised by injection site (if applicable) (anterolateral thigh or gluteal; Sentinel Safety Cohort only) using appropriate descriptive statistics as follows:

1. For the Sentinel Safety Cohort, the PK concentrations will be summarized for participants in the PK Set who received "AZD5156" by visit and injection site.

2. In the Main Cohort, the PK concentrations will be summarized for participants in the PK Set by visit. Up to the predose Day 181 visit, summaries will be generated for all active treatment groups based on the Day 1 IP dose, including "AZD3152" and "AZD7442." Additionally, for the same time period, data will also be summarized for the following Day 1/Day 181 treatment combinations: "AZD3152/AZD3152," "AZD3152/," and "One Dose: AZD7442" (AZD7442/Placebo or AZD7442/), as specified in Table 8.

3. After the Day 181 predose visit in the Main Cohort, the PK concentrations will be summarized for participants in the PK Set by visit for the following Day 1/Day 181 treatment combinations: "AZD3152/AZD3152," "AZD3152/-," and "One Dose: AZD7442" (AZD7442/Placebo or AZD7442/-), as specified in Table 8.

The following descriptive statistics will be presented for PK concentrations: n, n below LLOQ, arithmetic mean and SD, geometric mean, GSD, GCV (%), median, minimum, and maximum.

The geometric mean will be calculated as exp(μ), where μ is the mean of the data on the natural log scale.

The GCV will be calculated as $100 \times \text{sqrt}[\exp(s^2) - 1]$, where s is the SD of the data on the natural log scale.

Where required for plots: The GSD will be calculated as exp(σ), where σ is the SD of the data on the natural log scale. The geometric mean ± GSD (geometric mean – GSD and geometric mean + GSD) will be calculated as exp[μ ± s].

Protocol scheduled times will be used to present the PK concentration summary tables and corresponding mean (arithmetic mean and geometric mean) PK concentration-time figures.

The descriptive analyses of the Main Cohort PK concentrations will be repeated for the subgroups in Section 4.4.1.4, with the addition of age group (>= 18 years, < 18 years).

Handling of Non-quantifiable Concentrations in Summaries

Individual serum and NLF PK 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 outputs. Individual PK concentrations that are 'not reportable' will be reported as 'not reportable' (NR), and those missing will be reported as 'no sample' (NS) in the listings. PK 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.
- When at most half of the PK concentration values are NQ (≤ 50%), all NQ values will be set to half the LLOQ, and all descriptive statistics will be calculated accordingly.
- When more than 50% (but not all) of the values are NQ, the geometric mean and GCV% will be set to 'not calculable (NC).' The maximum value will be reported from the individual data, and the minimum and median will be set to NQ.
- If all PK concentrations are NQ at a point in time, no descriptive statistics will be calculated for that particular time point. The geometric mean, minimum, median, and maximum will be reported as NQ and the GCV% as NC.
- The number of values below the LLOQ (n < LLOQ) will be reported for each time point, together with the total number of collected values (n).

Three observations above the LLOQ are required at a minimum for a PK concentration to be summarised. Two observations above the LLOQ will be presented as the minimum and maximum, with the other summary statistics as NC.

Pharmacokinetic Parameter Listings

All reportable PK parameters, including individual diagnostic parameters, will be listed separately for each participant (Sentinel Safety Cohort only) by injection site for each mAb.

Pharmacokinetic Parameter Descriptive Statistics

All PK and diagnostic parameters will be summarised for each mAb by injection site, using appropriate descriptive statistics.

The descriptive statistics for PK parameters will be presented as follows:

- PK parameters (except t_{max}): present n, arithmetic mean, arithmetic SD, geometric mean, GSD, GCV (%), median, minimum, and maximum
- Diagnostic PK parameters (except t_{last}, λ_z lower, and λ_z upper): present n, arithmetic mean, arithmetic SD, median, minimum, and maximum
- t_{max}, t_{last}, λ_z lower and λ_z upper: present n, median, minimum, and maximum

Three values are required at a minimum for PK parameters to be summarised. Two values are presented as minimum and maximum, with the other summary statistic as NC.

If one or more values for a given parameter are zero, no geometric statistics will be calculated for the particular parameter, and the results for geometric statistics will be set to 'not applicable (NA).'

Pharmacokinetic Parameter Comparisons

AUC_{inf}, AUC_{last}, $AUC_{(0\text{-}28d)}$, $AUC_{(0\text{-}57d)}$, $AUC_{(0\text{-}90d)}$, $AUC_{(0\text{-}180d)}$, and C_{max} will be compared (Sentinel Safety Cohort only) between injection sites for each mAb using an analysis of variance (ANOVA). The geometric mean ratio of the PK parameters and the corresponding 90% CIs will be reported. The gluteal injection site will be used as the reference. Additional comparisons between treatment arms may be conducted and reported in the final CSR.

Graphical Presentation of Pharmacokinetic Data

All mean (arithmetic mean and geometric mean) plots or combined plots showing all participants will be based on the PK Set. Individual plots per participant will be based on Safety Set 1.

For consistency, the PK concentration values used in the mean (arithmetic mean and geometric mean) data graphs will be those given in the descriptive statistics summary table for each time point.

NQ values will be handled as described for the descriptive statistics for geometric mean PK concentration-time plots. If the geometric mean is NQ, it will be set to zero for linear plots and a nominal value of 0.00001 for semi-logarithmic plots instead of being plotted as missing. Any negative geometric mean ± GSD error bar values will be truncated at zero on linear PK concentration-time plots and represented by the nominal value 0.00001 on semi-logarithmic plots.

Before the first quantifiable PK concentration, NQ PK concentrations will be set to zero (linear plots only) for individual plots. After the first quantifiable PK concentration, any NQ PK concentrations will be regarded as missing.

The following figures will be presented, as appropriate, for both the serum and NLF concentrations of participants in the Sentinel Safety Cohort:

- Figures for the arithmetic and geometric mean PK concentration-time data (with ± SD or ± GSD error bars) presented on both linear and semi-logarithmic scales using scheduled post-dose time for the following:
  - For each injection site with both mAbs and AZD5156 overlaid on the same plot
  - For each mAb and AZD5156 with all injection sites overlaid on the same plot
- Individual participant PK concentrations over time will be graphically presented on both linear and semi-logarithmic scales using "actual" time post-dose as follows:
  - Per participant with both mAbs and AZD5156 overlaid on the same plot
  - Combined individual plots with all participants overlaid on the same plot separated by injection site for each mAb and AZD5156
- Individual and geometric mean AUC_{inf}, AUC_{last}, and C_{max} vs. injection site for each mAb and AZD5156

Precision and Rounding Rules for Pharmacokinetic Data

Pharmacokinetic Concentration Data

The PK concentration data listings present the same number of significant figures as the data from the bioanalytical laboratory (usually but not always to three significant figures) and against the same units received.

The PK concentration descriptive statistics will be presented using four significant figures except for the minimum and maximum, which will be presented using three significant figures, and n and n < LLOQ, which will be presented as integers.

Pharmacokinetic Parameter Data

The PK parameter and diagnostic PK listings will be presented to three significant figures apart from the following:

- C_{max}: presented the same number of significant figures as received from the bioanalytical laboratory
- t_{max}, t_{last}, λ_z lower, and λ_z upper: presented as received in the data, usually to two decimal places
- λ_zN: presented as an integer (no decimals)

The descriptive statistics for the PK parameters and diagnostic parameters will be presented to four significant figures except for the minimum and maximum, which will be presented to three significant figures apart from the following:

- t_{max}, t_{last}, λ_z lower, and λ_z upper: presented as received in the data, usually to two decimal places
- Number of values (n) and λ_zN: presented as an integer

LABORATORY CTCAE TOXICITY GRADES

CTCAE Term	Laboratory Test	Grade 0 (No Event)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-threatening)
Anemia	Hemoglobin	≥ LLN	≥ 100 g/L – < LLN	≥ 80 – < 100 g/L	< 80 g/L	N/A
Hemoglobin increased	Hemoglobin	No increase above ULN	Increase above ULN > 0 – ≤ 20 g/L	Increase above ULN > 20 – ≤ 40 g/L	Increase above ULN > 40 g/L	N/A
Platelet count decreased	Platelet count	≥ LLN	≥ 75 × 10E9/L – < LLN	≥ 50 – < 75 × 10E9/L	≥ 25 – < 50 × 10E9/L	< 25 × 10E9/L
White blood cell (WBC) decreased	WBC	≥ LLN	≥ 3.0 × 10E9/L – < LLN	≥ 2.0 – < 3.0 × 10E9/L	≥ 1.0 – < 2.0 × 10E9/L	< 1.0 × 10E9/L
Leukocytosis	WBC	≤ 100 × 10E9/L	N/A	N/A	> 100 × 10E9/L	N/A
Absolute neutrophil count decreased	Absolute neutrophils count	≥ LLN	≥ 1.5 × 10E9/L – < LLN	≥ 1.0 – < 1.5 × 10E9/L	≥ 0.5 – < 1.0 × 10E9/L	< 0.5 × 10E9/L
Absolute lymphocyte count decreased	Absolute lymphocytes count	≥ LLN	≥ 0.8 × 10E9/L – < LLN	≥ 0.5 – < 0.8 × 10E9/L	≥ 0.2 – < 0.5 × 10E9/L	< 0.2 × 10E9/L
Absolute lymphocyte count increased	Absolute lymphocytes count	≤ 4 × 10E9/L	N/A	> 4 – ≤ 20 × 10E9/L	> 20 × 10E9/L	N/A
Eosinophilia	Absolute eosinophils	≤ ULN or ≤ baseline	> ULN and > baseline	N/A	N/A	N/A
Hypernatremia	Sodium	≤ ULN	> ULN – ≤ 150 mmol/L	> 150 – ≤ 155 mmol/L	> 155 – ≤ 160 mmol/L	> 160 mmol/L
Hyponatremia	Sodium	≥ LLN	≥ 130 mmol/L – < LLN	≥ 125 – < 130 mmol/L	≥ 120 – < 125 mmol/L	< 120 mmol/L
Hyperkalemia	Potassium	≤ ULN	> ULN – ≤ 5.5 mmol/L	> 5.5 – ≤ 6.0 mmol/L	> 6.0 – ≤ 7.0 mmol/L	> 7.0 mmol/L
Hypokalemia	Potassium	≥ LLN	≥ 3.0 mmol/L – < LLN	N/A	≥ 2.5 – < 3.0 mmol/L	< 2.5 mmol/L
Hypercalcemia	Serum calcium	≤ ULN	> ULN – ≤ 2.9 mmol/L	> 2.9 – ≤ 3.1 mmol/L	> 3.1 – ≤ 3.4 mmol/L	> 3.4 mmol/L
Hypocalcemia	Serum calcium	≥ LLN	≥ 2.0 mmol/L – < LLN	≥ 1.75 – < 2.0 mmol/L	≥ 1.5 – < 1.75 mmol/L	< 1.5 mmol/L
Hypoglycemia	Glucose	≥ LLN	≥ 3.0 mmol/L – < LLN	≥ 2.2 – < 3.0 mmol/L	≥ 1.7 – < 2.2 mmol/L	< 1.7 mmol/L
Creatinine increased	Creatinine	≤ ULN	> ULN – ≤ 1.5 × ULN	> 1.5 – ≤ 3.0 × ULN or > 1.5 – ≤ 3.0 × baseline	> 3.0 – ≤ 6.0 × ULN or > 3.0 × baseline	> 6.0 × ULN

CTCAE Term	Laboratory Test	Grade 0 (No Event)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially Life-threatening)
Alkaline phosphatase (ALP) increased	ALP	≤ ULN if baseline normal; ≤ 2.0 × baseline if baseline abnormal	> ULN – ≤ 2.5 × ULN if baseline normal; > 2.0 – ≤ 2.5 × baseline if baseline abnormal	> 2.5 – ≤ 5.0 × ULN if baseline normal; > 2.5 – ≤ 5.0 × baseline if baseline abnormal	> 5.0 – ≤ 20.0 × ULN if baseline normal; > 5.0 – ≤ 20.0 × baseline if baseline abnormal	> 20.0 × ULN if baseline normal; > 20.0 × baseline if baseline abnormal
Alanine transaminase (ALT) increased	ALT	≤ ULN if baseline normal; ≤ 1.5 × baseline if baseline abnormal	> ULN – ≤ 3.0 × ULN if baseline normal; > 1.5 – ≤ 3.0 × baseline if baseline abnormal	> 3.0 – ≤ 5.0 × ULN if baseline normal; > 3.0 – ≤ 5.0 × baseline if baseline abnormal	> 5.0 – ≤ 20.0 × ULN if baseline normal; > 5.0 – ≤ 20.0 × baseline if baseline abnormal	> 20.0 × ULN if baseline normal; > 20.0 × baseline if baseline abnormal
Aspartate transaminase (AST) increased	AST	≤ ULN if baseline normal; ≤ 1.5 × baseline if baseline abnormal	> ULN – ≤ 3.0 × ULN if baseline normal; > 1.5 – ≤ 3.0 × baseline if baseline abnormal	> 3.0 – ≤ 5.0 × ULN if baseline normal; > 3.0 – ≤ 5.0 × baseline if baseline abnormal	> 5.0 – ≤ 20.0 × ULN if baseline normal; > 5.0 – ≤ 20.0 × baseline if baseline abnormal	> 20.0 × ULN if baseline normal; > 20.0 × baseline if baseline abnormal
Blood bilirubin increased	Total bilirubin	≤ ULN if baseline normal; ≤ baseline if baseline abnormal	> ULN – ≤ 1.5 × ULN if baseline normal; > baseline – ≤ 1.5 × baseline if baseline abnormal	> 1.5 – ≤ 3.0 × ULN if baseline normal; > 1.5 – ≤ 3.0 × baseline if baseline abnormal	> 3.0 – ≤ 10.0 × ULN if baseline normal; > 3.0 – ≤ 10.0 × baseline if baseline abnormal	> 10.0 × ULN if baseline normal; > 10.0 × baseline if baseline abnormal
Gamma-glutamyl transferase (GGT) increased	GGT	≤ ULN if baseline normal; ≤ 2.0 × baseline if baseline abnormal	> ULN – ≤ 2.5 × ULN if baseline normal; > 2.0 – ≤ 2.5 × baseline if baseline abnormal	> 2.5 – ≤ 5.0 × ULN if baseline normal; > 2.5 – ≤ 5.0 × baseline if baseline abnormal	> 5.0 – ≤ 20.0 × ULN if baseline normal; > 5.0 – ≤ 20.0 × baseline if baseline abnormal	> 20.0 × ULN if baseline normal; > 20.0 × baseline if baseline abnormal
Hypoalbuminemia	Albumin	≥ LLN	≥ 30 g/L – < LLN	≥ 20 – < 30 g/L	< 20 g/L	N/A
Creatine phosphokinase (CPK) increased	Creatine kinase	≤ ULN	> ULN – ≤ 2.5 × ULN	> 2.5 – ≤ 5 × ULN	> 5 – ≤ 10 × ULN	> 10 × ULN
Activated partial thromboplastin time (aPTT) prolonged	aPTT	≤ ULN	> ULN – 1.5 × ULN	> 1.5 – 2.5 × ULN	> 2.5 × ULN	N/A

CLINICAL VITAL SIGN ABNORMALITIES

Vital Sign and Criterion	Vital Signs Grade				
	Grade 0 (No Event)	**Grade 1 (Mild)**	**Grade 2 (Moderate)**	**Grade 3 (Severe)**	**Grade 4 (Potentially Life-threatening)**
Fever (°C)	< 37.9	37.9 to 38.4	38.5 to 38.9	39.0 to 40	> 40
Tachycardia (beats/minute)	< 101	101 to 115	116 to 130	> 130	N/A
Bradycardia (beats/minute)	> 54	50 to 54	45 to 49	< 45	N/A
Hypertension; systolic (mmHg)	< 141	141 to 150	151 to 155	> 155	N/A
Hypertension; diastolic (mmHg)	< 91	91 to 95	96 to 100	> 100	N/A
Hypotension; systolic (mmHg)	> 89	85 to 89	80 to 84	< 80	N/A
Respiratory rate (breaths/minute)	< 17	17 to 20	21 to 25	> 25	N/A

SUB-STUDY STATISTICAL ANALYSIS PLAN

Study Code	D7000C00001
Edition Number	3.0
Date	26-Jan-2024

A Phase II Open Label Study to Evaluate the Safety, PK, and Neutralizing Activity of AZD3152 for Pre-exposure Prophylaxis of COVID-19

Brief Title: Study Understanding Pre-Exposure pRophylaxis of NOVel Antibodies (SUPERNOVA) Sub-study

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
AE	Adverse event
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Class
BMI	Body mass index
CDL	Clinical data lock
CI	Confidence interval
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DCO	Data cutoff
ECG	Electrocardiogram
FAS	Full analysis set
gCV	Geometric coefficient of variation
GMT	Geometric mean titer
GMFR	Geometric mean fold rise
gSD	Geometric standard deviation
IC50	Concentration required for 50% inhibition
IM	intramuscular
IP	Investigational Product
IPD	Important Protocol Deviation
IV	intravenous
LLOQ	Lower limit of quantification
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
nAb	Neutralizing antibody
NC	Not computed
NQ	Not quantifiable
NR	Not reportable
NS	No sample
PDMP	Protocol deviation management plan
PK	Pharmacokinetics

Abbreviation or Specialized Term	Definition
PT	Preferred term
RDMS	Regulatory Document Management System
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SIP	Study Integrity Plan
SoA	Schedule of activities
SOC	System organ class
ULOQ	Upper limit of quantification
VOC	Variant(s) of concern

AMENDMENT HISTORY

CATEGORY **Change refers to:**	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
N/A	7/28/2023	Initial approved SAP	N/A	N/A
Other	9/21/2023	Updates and clarifications of data presentation following blind data review.	N/A	Following team review of blind data review outputs.
4.2.4 Exploratory Endpoint – Correlation statistics 4.6.2 Adverse Events	1/26/2024	The exploratory correlation analysis was updated to include a sensitivity analysis for repeated measures. The identification process of AESIs has been modified at a program level and the SAP section has been updated to reflect this.	N/A	Correlation sensitivity analysis was added to correctly account for repeated measures across multiple visits. SAP text updated to correctly reflect current AESI identification process.

1 INTRODUCTION

The purpose of this SAP is to give details for the statistical analysis of study D7000C00001 SUPERNOVA sub-study supporting the CSR. The reader is referred to the CSP, CRF, and SIP for details of study design and conduct, data collection, and study integrity, respectively.

The term "investigational product" or "IP" is used throughout this document to include all study interventions, namely AZD3152 1200 mg IV and AZD7442 (EVUSHELD™) 300 mg IM. AZD7442 is a combination product of two monoclonal antibodies, namely AZD1061 (cilgavimab) and AZD8895 (tixagevimab). AZD3152 and AZD7442 are specified when referring to participants who received the specified intervention.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

In sections 1.1 and 3 of the CSP, the population for the primary endpoint of predicted SARS-CoV-2 nAb responses is incorrectly named as the "SARS-CoV-2 PK analysis set." Within this SAP, the correctly named population of "PK analysis set" is used.

In section 9.3 of the CSP, the Safety analysis set definition states that the set will include all participants in the Full analysis set, which is defined as "all randomized participants who received part or all of study intervention." Because this definition does not account for participants who are dosed and were not randomized into the study, the definition for the Safety analysis set within the SAP will include all participants who received part or all of study intervention. This definition can be found in section 3.2 of this SAP.

In section 9.3 of the CSP, the PK analysis set definition includes "…or interpretation of PK parameters…" This part of the statement is erroneously included in the definition as there are no PK parameters being calculated for this study. In section 3.2 of this SAP, the definition is revised to omit this statement.

The definitions for the PK analysis set and the SARS-CoV-2 nAb analysis set have been updated within the SAP to exclude participants who did not receive the full dose per protocol.

In section 9.4.3 of the CSP it is stated that the correlation analysis of predicted nAb titers and change from baseline observed nAb titers will be performed within each treatment arm. However, the objectives and endpoints in sections 1.1 and 3 of the CSP state that this will only be performed for the AZD3152 arm. The SAP will be consistent with sections 1.1 and 3 of the CSP and only conduct this analysis for the AZD3152 arm.

The CSP states that XBB.1.5 or other circulating VOC will be used for the primary analysis. Due to the possibility of a different circulating VOC being used for regulatory

submissions, the text within this SAP has been updated so that the VOC used for a specific regulatory submission is pre-specified. Section 4.2.1 pre-specifies the circulating VOC that will be used for the primary endpoint analysis for a specific regulatory submission. The use of XBB.1.5 for correlation analysis remains the same.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

Two planned analyses will be conducted. The primary analysis will take place after all participants complete Visit 3 (Day 29) or have withdrawn from the study. The final analysis will take place after the last end-of-study visit. The Day 29 primary analysis will present available safety, PK, and predicted nAb data up to and including the Day 29 visit to evaluate the primary objectives of the study. At the time of the Day 29 primary analysis, only data through the Day 29 visit will be included in tables and figures. Any data available within the CDL that occurs after the Day 29 visit but prior to the DCO will be included in listings at the primary analysis. The final analysis will include all available data collected through the follow-up period of 15 months from Day 1.

If there is a medical need for AZD3152 to be submitted for health authority review urgently, additional analyses will be conducted. The SAP and SIP will provide details regarding analysis for emerging VOC and data readouts that may reveal treatment assignments.

The planned analyses and reporting of the sub-study results will be conducted independently from the SUPERNOVA parent study.

3.2 Analysis Populations

The analysis population definitions are presented in Table 1.

Table 1 Populations for Analysis

Analysis Set	Description
Full analysis set	All randomized participants who received part or all of study intervention. Participants will be classified according to the assigned treatment they are randomized to. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination.
Safety analysis set	The safety analysis set will include participants who received part or all of study intervention and will report participants according to the actual treatment received regardless of the assigned treatment. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination.

Table 1 Populations for Analysis

Analysis Set	Description
Pharmacokinetics analysis set	All participants in the FAS, who received a full dose of IMP per protocol, with sufficient information to estimate at least 1 postdose quantifiable serum concentration for any mAb component. Participants will be classified according to the actual mAb components received regardless of their assigned treatment. Participants with protocol deviations that may interfere with the serum concentrations may be excluded or have data collected after the protocol deviations set to missing.
ADA analysis sets	The ADA analysis sets will consist of all the Safety analysis set participants with a non-missing baseline and at least one non-missing post-baseline ADA result of the same mAb component. For example, the AZD3152 ADA analysis set consists of participants in the Safety analysis set with a non-missing baseline AZD3152 ADA result and at least one non-missing post-baseline AZD3152 ADA result. The AZD7442 ADA analysis set is defined as being ADA-evaluable for either one or both of AZD1061 and AZD8895. There are 4 ADA analysis sets: AZD3152 ADA analysis set, AZD1061 ADA analysis set, AZD8895 analysis set, and AZD7442 analysis set
SARS-CoV-2 nAb analysis set	All participants in the Safety analysis set, who received a full dose of IMP per protocol, with baseline and postdose antibody measurements with quantifiable SARS-CoV-2 serum nAb titers. Participants who test positive for SARS-CoV-2 infection at baseline will be excluded from the analysis set. Participants will be classified according to the actual mAb components received regardless of their assigned study intervention. Participants with protocol deviations that may interfere with generation or interpretation of an antibody response may be excluded depending on the details of the deviation.
PK / SARS-CoV-2 nAb analysis set	All participants who are included in both the PK analysis set and the SARS-CoV-2 nAb analysis set.

3.3 General Considerations

This sub-study is designed to evaluate the safety, PK, and neutralizing activity of AZD3152 compared with AZD7442 for pre-exposure prophylaxis of COVID-19. The primary endpoint is safety as well as predicted Day 29 nAb titers derived from serum PK and IC50 for SARS-CoV-2 variants XBB.1.5 (or other circulating VOC [see section 4.2.1.2]) following AZD3152 administration and Alpha following AZD7442 administration. To align with the PK analysis set, all treatment groups will be presented by the treatment actually received unless otherwise specified.

The first 12 participants will be enrolled as a Sentinel Safety Cohort, randomized in a 2:1 ratio to AZD3152 and AZD7442, respectively. Unless otherwise specified, summaries will include all participants and there will not be separate summaries for the Sentinel Safety Cohort. Sentinel Safety Cohort participants will be included in the same analysis sets as other participants.

Categorical variables will be summarized using frequency and percentages, where the denominator for calculation is the underlying analysis set population, unless otherwise stated. A row denoted as "Missing" will be included in the count tabulations, where necessary, to account for missing values. Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate. Descriptive statistics will include the n < LLOQ, n > ULOQ, geometric mean, geometric standard deviation, geometric coefficient of variation, median, minimum, and maximum for general concentration data. Point estimates will be presented with a 95% CI and reported p-values will correspond to a 2-sided test unless otherwise stated. Data will be provided in data listings sorted by treatment group and participant number. Tabular summaries will be presented by the actual treatment received and visit (where applicable).

All statistical analyses will be conducted using SAS®, version 9.4 or higher and entimICE AZ 4.4 – Service Pack 8.

3.3.1 General Study Level Definitions

Study days will be calculated relative to the first dose of the IP. When the date of the event is prior to date of the first dose of IP, the study day will be calculated as: (date of event - date of first dose of IP). When the date of the event is on or after the date of the first dose of IP, the study day will be calculated as: (date of event - date of first dose of IP + 1). When an event date is partial or missing, the listings will display the study day and any corresponding durations as missing; the imputed dates will not be shown in the listings.

In general, baseline is the last non-missing measurement taken before the first dose of the IP. Pre-dose measurements specified in the SoA taken on the same date as the first dose of the IP (Day 1) will be considered baseline regardless of the timing recorded. The change from baseline will be calculated as: post-baseline - baseline. The percentage change from baseline will be calculated as: 100 × (change from baseline) / baseline.

3.3.2 Visit Window

A windowing convention will be used to determine the analysis value for a given study visit for visit-based assessments, as specified in Appendix A.

When one or more results are available for the same visit window, the result with the date closest to the expected visit date will be used in the analysis. If two observations are equidistant from the expected visit date, the later observation will be used in the analysis.

3.3.3 Handling of Unscheduled Visits

Scheduled, unscheduled, retest, and early discontinuation measurements will will follow the windowing conventions described in section 3.3.2. All windowed measurements will contribute to the baseline and maximum values and will be included in the listings. Windowed visits will be included in the by-visit summaries.

3.3.4 Multiplicity/Multiple Comparisons

The primary analysis of the primary endpoint will be a non-inferiority comparison using a comparability threshold as described in section 4.2.1.4. The sub-study will be considered successful if the null hypothesis of the primary analysis is rejected. The following testing strategy will be applied:

- Non-inferiority comparison of predicted nAb titers against XBB.1.5 (or other circulating VOC) variant following administration of AZD3152 vs predicted nAb titers against Alpha variant following administration of AZD7442, tested at a one-tailed $\alpha = 0.05$

If the primary comparison above rejects the null hypothesis, then:

- If the primary comparison uses the AZD3152 predicted nAb titers against XBB.1.5 variant, then the next comparison will use the AZD3152 predicted nAb titers against another circulating VOC. If the primary comparison uses the AZD3152 predicted nAb titers against another circulating VOC, then this test will not be performed:
  - Non-inferiority comparison of predicted nAb titers against another circulating VOC following administration of AZD3152 vs predicted nAb titers against Alpha variant following administration of AZD7442, tested at a one-tailed $\alpha = 0.05$
- For comparisons above where non-inferiority is established, a superiority comparison of predicted nAb titers against XBB.1.5 (or other circulating VOC) variant following administration of AZD3152 vs predicted nAb titers against Alpha variant following administration of AZD7442, tested at a one-tailed $\alpha = 0.025$ will be performed

3.3.5 Handling of Protocol Deviations in Study Analysis

The study team will identify important protocol deviations before each analysis as specified in the PDMP. Participants who are identified as having experienced an IPD will be included in the analyses, or may have their data prior to the IPD included in the analyses and their data following the IPD excluded from the analyses.

3.4 Sample Size Calculation

Rejection of the null hypothesis of inferiority of AZD3152 against AZD7442 requires that the lower bound of the two-sided 90% CI of the predicted nAb GMT ratio exceeds 0.80. This margin choice has been selected in line with bioequivalence testing for PK and is appropriate for use with predicted nAb titers.

CCI [redacted] This is consistent with PK variability observations from the PROVENT study.

With an assumed GMTR of 1.0 there is > 90% Power to detect non-inferiority using a two-sided 90% CI from an analysis of variance. With an assumed GMTR of 2.0, there is > 95% Power to detect superiority using a two-sided 95% CI from an analysis of variance.

The sample size calculations assume a 5% dropout rate prior to the Day 29 visit. If the dropout rate is higher than expected then an increase in sample size may be considered, with details provided in a separate Blinded Sample Size Re-estimation Analysis Plan.

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivations, analyses, and data presentation per domain.

4.1 Study Population

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

Unless otherwise stated, the Safety analysis set will be used for this domain.

4.1.1 Subject Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Participants will be classified as follows:

- Participants screened
- Participants randomized
- Participants who received IP
- Participants who received AZD7442 and also received the optional dose of AZD3152
- Participants who are ongoing, completed, or discontinued/withdrawn

4.1.1.2 Presentation

All participants who were screened will be included in the presentation. The number and percentage of participants within each disposition category will be tabulated by treatment arm, and screen failures will be included in the Total column for applicable categories. The number of participants randomized and dosed will serve as the denominator for percentage calculations. The number and percent of participants completing or withdrawing by the Day 29 visit will be summarized. Disposition data for discontinued subjects will be included in a listing.

The following study population characteristics will also be summarized:

- Incidence of participants' status related to global/country situations

Other key information to understand the integrity of the study will be summarized.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

The analysis population definitions are presented in section 3.2.

4.1.2.2 Presentation

The number of participants included in each analysis set will be reported per treatment and overall. In addition, for each analysis set, the number of participants excluded, including the reasons, will be reported. Subjects excluded from each analysis set will be included in a listing.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

A detailed list of possible IPDs and the process for reviewing them by the clinical study team will be outlined in the PDMP. The protocol deviation categories will be reviewed by the medical and statistical team members before the CDL and classified as important per the PDMP.

At a minimum, the following deviations categories will be included for review and classified as important for the evaluation and implementation of the study:

- Inclusion criteria
- Exclusion criteria
- Study withdrawal
- Investigational product deviation
- Concomitant use of disallowed medications
- Planned study procedures

- Possible impact on safety assessments
- Potential to interfere with PK concentrations or interpretation of PK responses
- Potential to interfere with the generation or interpretation of an antibody response

4.1.3.2 Presentation

The number and percentage of participants with IPDs will be provided per treatment and the total per protocol deviation category. Participants with important protocol deviations will be included in a listing.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Age categories will be defined as: 18 – 64 years, ≥ 65 years

4.1.4.2 Presentation

A summary of demographic characteristics will be provided. Demographics will be summarized per treatment and overall through descriptive statistics. Demographic characteristics data will be included in a listing.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

BMI, in kg/m^2, will be calculated as: weight (kg) / height $(m)^2$. BMI categories will be defined as: < 18.5, 18.5 - < 25, 25 - < 30, 30 - <40, and ≥ 40. Other BMI categories may be included.

SARS-CoV-2 infection within last 6-months will be determined if the last confirmed infection date is ≤ 183 days prior to Day 1.

COVID-19 vaccination within last 6-months will be determined if the last confirmed vaccination date is ≤ 183 days prior to Day 1.

4.1.5.2 Presentation

Baseline characteristics will be summarized similarly to demographic characteristics. Height, weight, BMI, baseline ECG interpretation, immunocompromised status (immunocompromised or immunocompetent/healthy), pre-dose SARS-CoV-2 serology (anti-nucleocapsid) serum sample results, prior SARS-CoV-2 infection, SARS-CoV-2 infection within 6 months, prior COVID-19 vaccination, and COVID-19 vaccination within 6 months will be included in the summary of baseline characteristics.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

Not applicable for this prophylaxis study.

4.1.6.2 Presentation

Not applicable for this prophylaxis study.

4.1.7 Medical History

4.1.7.1 Definitions and Derivations

Medical history will be coded using the latest MedDRA dictionary version. Medical history is defined as any medical condition or disease that started and stopped before the first dose of IP.

Clinically significant abnormal physical examination findings at screening will be recorded as medical history.

4.1.7.2 Presentation

Medical history will be categorized by SOC and PT and summarized by treatment arm and overall. A participant having more than one condition within the same SOC or PT will be counted only once for the particular SOC or PT.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

All medications will be coded using the latest WHODrug Dictionary version.

Medication is regarded as prior if stopped before the first IP dosing date. Medication is considered concomitant if the start date is on or after the first IP dosing date or if started before the IP dose and is ongoing after the IP dose. The algorithm for imputing missing or partial medication start and stop dates is provided the SUPERNOVA parent SAP.

4.1.8.2 Presentation

Prior and concomitant medications will be categorized by ATC Level 2 and preferred drug name and summarized by treatment arm and overall. A participant having more than one medication within the same ATC Level 2 or preferred drug name will be counted only once for the particular ATC Level 2 or preferred drug name. Prior and concomitant medications will be summarized separately.

Prohibited and restricted concomitant medications will be summarized separately.

Considerations for analyses through a specified visit

For the primary analysis, summaries of prior and concomitant medications will be presented through the Day 29 visit. To account for variability in actual visit times, concomitant medications collected up to and including the earlier of (1) Study Day 35 or (2) the day prior to the date of optional dose of AZD3152 at the Day 29 visit will be included in the summaries.

If analyses through the Day 91 or 181 visits are to be performed, concomitant medications collected up to and including Study Days 103 and 188, respectively, will be included in the summaries.

Considerations for crossover participants

Concomitant medications will be presented through Day 29 visit and post Day 29 visit. Summaries of concomitant medications through Day 29 visit will classify participants by the treatment received at the Day 1 visit. Summaries of concomitant medications post Day 29 visit will reclassify crossover participants. In these summaries, all participants who only received one dose at Day 1 and did not crossover will still be classified by the treatment received at Day 1. The AZD7442 immunocompromised participants who received the optional AZD3152 dose at Day 29 visit will be classified in a 3rd treatment arm separate from the non-crossover participants.

4.1.9 Study Drug Compliance

4.1.9.1 Definitions and Derivations

Because IP is administered as a single dose by site staff at the study site, study drug compliance will be presented in the summary of participant disposition, as described in section 4.1.1.

4.1.9.2 Presentation

Not applicable.

4.1.10 Duration of Follow-Up

4.1.10.1 Definitions and Derivations

Duration of on-study follow-up will be calculated using the earliest of date of data cut-off, date of death, date of completion, or date of discontinuation. Duration of safety follow-up will be calculated using the earliest of date of data cut-off or date of last safety assessment. Durations of follow-up will be calculated as described in section 3.3.1.

4.1.10.2 Presentation

Duration of follow-up will be categorized by on-study follow-up and safety follow-up and summarized by treatment arm and overall. Descriptive statistics will be presented for each follow-up parameter.

4.2 Endpoint Analyses

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

Table 2 Overview of Objectives

Statistical category	Endpoint	Population	Intercurrent event strategy	Population level summary (analysis)	Details in section
Objective 1: To compare the predicted nAb responses to SARS-CoV-2 XBB.1.5 variant (or other circulating VOC) following AZD3152 administration vs predicted nAb responses to SARS-CoV-2 Alpha variant following AZD7442 administration					
Primary estimand: primary analysis of the primary endpoint	Predicted nAb titer derived from serum PK at Day 29 and IC50	PK analysis set	Treatment policy strategy	GMT ratio	4.2.1.4
Primary estimand: sensitivity analyses of the primary endpoint	Predicted nAb titer derived from serum PK at Day 29 and IC50	PK analysis set	Treatment policy strategy	GMT ratio	4.2.1.5
Supplementary estimand: supplementary analyses of the primary endpoint	Predicted nAb titer derived from serum PK at Day 29 and IC50	PK analysis set	Treatment policy strategy	Descriptive statistics	4.2.1.6
Objective 2: To characterize the PK of AZD3152 and AZD7442 in serum					
Secondary	AZD3152, AZD7442, AZD1061, and AZD8895 concentrations over time	PK analysis set	N/A	Descriptive statistics	4.4.1
Objective 3: To evaluate the ADA response to AZD3152 and AZD7442 in serum					
Secondary	Incidence of ADA to AZD3152, AZD7442, AZD1061, and AZD8895; ADA titers	ADA analysis sets	N/A	Descriptive statistics	4.5.1
Objective 4: To characterize the correlation between predicted nAb titers and the change from baseline measured serum nAb titers against the relevant SARS-CoV-2 variants with the 1200 mg IV AZD3152 dose					
Exploratory	Predicted nAb titers and change from baseline observed serum nAb titers against XBB.1.5 SARS-CoV-2 variant	PK / SARS-CoV-2 nAb analysis set	Treatment policy	Descriptive correlation statistics	4.2.4

4.2.1 Primary Endpoint – Predicted nAb titer derived from serum PK and IC50 at Day 29 visit

The primary endpoint is the predicted nAb titer derived from the observed serum PK concentration at Day 29 and the IC50 for SARS-CoV-2 variants XBB.1.5 (or other circulating VOC) following AZD3152 administration and Alpha following AZD7442 administration. The analysis of this endpoint will be included in the primary analysis.

4.2.1.1 Definition

The primary endpoint is defined in Table 3 within the estimand framework.

Table 3 Primary Estimand

Attribute	Details
Treatment condition of interest	AZD3152
Alternative treatment condition	AZD7442
Population	PK analysis set
Variable/endpoint	Predicted nAb titer derived from serum PK at Day 29 visit and IC50 for SARS-CoV-2 variants XBB.1.5 (or other circulating VOC) following AZD3152 administration and Alpha following AZD7442 administration
Intercurrent event strategy	The intercurrent events are: • Concomitant medications taken on or after Day 1 which interfere with PK Endpoint results with a date on or after the occurrence of an intercurrent event will not be included in the analysis.
Population-level summary	Geometric Mean Titer ratio

4.2.1.2 Derivations

The primary endpoint variable is the predicted Day 29 nAb titer from serum PK at the Day 29 visit and in-vitro pseudovirus IC50 for SARS-CoV-2 variants XBB.1.5 (or other circulating VOC) following AZD3152 administration and Alpha following AZD7442 administration. The predicted Day 29 nAb titer is derived by dividing the observed serum PK concentration at the Day 29 visit in ng/mL by the in-vitro IC50 in ng/mL for each variant. For all participants in the PK analysis set, the observed serum PK concentration result must be collected within +/- 4 days of Day 29. Any PK samples outside this window will not be included in the analysis. The AZD7442 Alpha IC50 of CCI and the AZD3152 XBB.1.5 IC50 of CCI will be used, as assessed by Monogram Biosciences (South San Francisco, CA). The endpoint value for each arm will be calculated as follows:

$$\text{AZD7442 Day 29 predicted nAb titer} = \frac{\text{AZD7442 serum PK conc. (ng/mL)}}{\text{CCI}}$$

$$AZD3152\ \text{Day 29 predicted nAb titer} = \frac{\text{AZD3152 serum PK conc. (ng/mL)}}{\text{CCI}}$$

Data collected for the predicted nAb titer endpoint will only be included in the analysis prior to the occurrence of an intercurrent event. Data collected for each endpoint that has a date on or after the occurrence of an intercurrent event will not contribute to the analysis.

If a different circulating VOC is used for the AZD3152 arm, the endpoint will be derived by dividing the AZD3152 serum PK concentration by the IC50 for that circulating VOC.

4.2.1.3 Handling of Dropouts and Missing Data

The process for handling of dropouts and missing data is described here for the various analyses.

Primary Analysis

Participants who are missing the Day 29 PK serum concentration result will not be included in the PK analysis set at the time of the primary analysis, and thus would not be included in the primary analysis model.

Any PK serum concentration measurement that is below the LLOQ will have their value imputed as half of the LLOQ value. Any PK serum concentration measurement that is reported as "above the ULOQ" will be imputed as the ULOQ value.

Predicted nAb titer values will be calculated from the observed serum PK concentration values (if available) and the imputed serum PK concentration values (if imputed).

Sensitivity Analyses

The handling rules for sensitivity analyses will be the same as that described for the Primary Analysis within this section.

Supplementary Analyses

The handling rules for supplementary analyses will be the same as that described for the Primary Analysis within this section.

4.2.1.4 Primary Analysis of Primary Endpoint

The primary analysis of the primary endpoint will target the primary estimand described in section 4.2.1.1. The analysis will be performed on the PK analysis set.

A non-inferiority comparison will be performed using the ratio of predicted nAb GMT (GMTR) at Visit 3 (Day 29) of the XBB.1.5 variant (or other circulating VOC) for participants receiving AZD3152 versus the Alpha variant for participants receiving AZD7442 with a comparability threshold of 0.8. The one-tailed Type I error rate is 0.05. Non-inferiority will be concluded if the lower bound of the two-sided 90% CI for the

GMTR is > 0.8. Demonstration of non-inferiority provides 95% confidence that participants treated with AZD3152 will have nAb titers associated with protection against symptomatic COVID-19 observed in the PROVENT trial.

Statistical Hypotheses

If the null hypothesis is rejected in favor of the alternative hypothesis at a one-tailed Type I error rate of α = 0.05, the data provide evidence that AZD3152 is not inferior to AZD7442 with respect to predicted nAb titers against the specified variant. The hypotheses are:

$$\text{Null hyopthesis } (H_0): \quad \frac{Predicted\ GMT_{AZD3152}}{Predicted\ GMT_{AZD7442}} \leq 0.80$$

$$\text{Alternative hypothesis } (H_A): \quad \frac{Predicted\ GMT_{AZD3152}}{Predicted\ GMT_{AZD7442}} > 0.80$$

If the null hypothesis for the non-inferiority comparison is rejected, a superiority test will be conducted at a one-tailed Type I error rate of α = 0.025, with the following hypotheses:

$$\text{Null hyopthesis } (H_0): \quad \frac{Predicted\ GMT_{AZD3152}}{Predicted\ GMT_{AZD7442}} \leq 1.00$$

$$\text{Alternative hypothesis } (H_A): \quad \frac{Predicted\ GMT_{AZD3152}}{Predicted\ GMT_{AZD7442}} > 1.00$$

If the primary non-inferiority comparison uses the predicted nAb titers of a different circulating VOC, no further testing will be performed after the superiority test. If the primary non-inferiority comparison uses the predicted nAb titers of XBB.1.5, a second non-inferiority test will be conducted at a one-tailed Type I error rate of α = 0.05. This third comparison will compare the predicted nAb titers against a different circulating VOC for AZD3152 versus the predicted nAb titers against Alpha for AZD7442. The hypotheses are:

$$\text{Null hyopthesis } (H_0): \quad \frac{Predicted\ GMT_{AZD3152}}{Predicted\ GMT_{AZD7442}} \leq 0.80$$

$$\text{Alternative hypothesis } (H_A): \quad \frac{Predicted\ GMT_{AZD3152}}{Predicted\ GMT_{AZD7442}} > 0.80$$

Analysis Method

The analysis method for the primary analysis of the primary endpoint will be to fit an ANOVA model to the data. The $\log_{10}$-transformed values of the predicted nAb titers at the Day 29 visit (as calculated in 4.2.1.2) will be the response variable in the ANOVA model. The model will include treatment arm as the primary explanatory variable. The factor effects ANOVA model is specified as:

$$\log_{10}\left(Predicted\ nAb\ titer_{ij}\right) = \mu. + \tau_i + \varepsilon_{ij},$$

where $\mu.$ is the constant component common to all observations, τ_i is the effect of the ith treatment arm, and ε_{ij} are independent identically distributed $N(0, \sigma^2)$.

The ANOVA model will provide an estimate of the mean titer difference of the $\log_{10}$-transformed predicted nAb titers between AZD3152 and AZD7442 and the two-sided CI of the mean titer difference on the $\log_{10}$-scale. The GMT ratio and two-sided CI of the GMT ratio will be calculated as the anti-logarithm transformation of these values, respectively. For non-inferiority comparisons, the CI will be a two-sided 90% CI; for the superiority comparison, the CI will be a two-sided 95% CI.

4.2.1.5 Sensitivity Analyses of the Primary Endpoint

The first sensitivity analysis will target the primary estimand using ANOVA and ANCOVA models with the $\log_{10}$-transformed values of the predicted nAb titers at Day 29 as the response variable, treatment arm as the primary explanatory variable, and will explore the following:

- model adjustment using age as a continuous covariate, adjusting to the mean age across all participants in the primary analysis
- model adjustment including BMI as a continuous covariate, adjusting to the mean BMI across all participants in the primary analysis
- model adjustment including sex as a categorical covariate
- model adjustment including various combinations of the above covariates

This first sensitivity analysis will be included in the primary analysis.

The second sensitivity analysis will repeat the primary analysis and target the primary estimand, but will use the observed nAb titers at Day 29 for the endpoint variable. The $\log_{10}$-transformed value of the observed nAb titer will be used as the response variable in the ANOVA model. No other changes to the population or the model will be made. A consistent GMT ratio of this model compared to the GMT ratio of the primary analysis model may indicate the robustness of the prediction method used in the primary analysis model. This sensitivity analysis will be included in the final analysis.

The third sensitivity analysis, if conducted, will repeat the primary analysis and target the primary estimand, but will derive the predicted nAb titer endpoint using alternative IC50 values. No other changes to the population or the model will be made for this analysis. A consistent GMT ratio of this model compared to the GMT ratio of the primary analysis model may indicate a robustness against the choice of IC50 value. This sensitivity analysis may be included in the final analysis.

The sensitivity analyses are listed in Table 4:

Table 4 Sensitivity Analyses of the Primary Endpoint

Model Short Name	Sensitivity Model
Model 1	Sensitivity analysis 1: ANCOVA adjusting for age as continuous covariate
Model 2	Sensitivity analysis 1: ANCOVA adjusting for BMI as continuous covariate
Model 3	Sensitivity analysis 1: ANOVA adjusting for sex as categorical covariate
Model 4	Sensitivity analysis 1: ANCOVA adjusting for continuous age and continuous BMI
Model 5	Sensitivity analysis 1: ANCOVA adjusting for continuous age and categorical sex
Model 6	Sensitivity analysis 1: ANCOVA adjusting for continuous BMI and categorical sex
Model 7	Sensitivity analysis 1: ANCOVA adjusting for continuous age, continuous BMI, and categorical sex
Model 8	Sensitivity analysis 2: ANOVA using observed nAb titers at Day 29 as response variable
Model 9	Sensitivity analysis 3: ANOVA using predicted nAb titers at Day 29 calculated using alternative IC50 values

4.2.1.6 Supplementary Analyses of the Primary Endpoint

Descriptive statistics of predicted nAb titers will be presented as a supplementary analysis. Tables will include descriptive statistics for GMT. The GMT statistics will include n, geometric mean, gSD, 95% CI, minimum, maximum, n (%) < LLOQ, and n (%) > ULOQ.

The following tables and figures will be presented:

- Table summarizing GMT over time by arm/variant
- Box and whisker plots of GMT over time by arm/variant

The supplementary analysis will be performed at the primary analysis and repeated at subsequent analyses for all available timepoints.

4.2.1.7 Subgroup Analyses

The primary analysis model may be repeated for the following subgroups if sufficient sample size:

- Immunocompromised vs immunocompetent/healthy
- Age group (≥ 65 years, < 65 years)

4.2.2 Secondary Endpoint – Serum concentrations

The secondary endpoint of serum concentrations is described in section 4.4.1.

4.2.3 Secondary Endpoint – Incidence of ADA

The secondary endpoint of incidence of ADA is described in section 4.5.1.

4.2.4 Exploratory Endpoint – Correlation statistics

The exploratory endpoint is the association between predicted nAb titers and the change from baseline measured serum nAb titers against the relevant SARS-CoV-2 variants. The analysis of this endpoint may be included in the primary analysis, if data are available.

4.2.4.1 Definition

The exploratory endpoint is defined in Table 5 within the estimand framework.

Table 5 Exploratory Estimand

Attribute	Details
Treatment condition of interest	AZD3152
Alternative treatment condition	N/A
Population	PK / SARS-CoV-2 nAb analysis set
Variable/endpoint[a]	Association between predicted nAb titers and the change from baseline measured serum nAb titers against the XBB.1.5 SARS-CoV-2 variant.
Intercurrent event strategy	The intercurrent events are: • Serum nAb titers: Infection with SARS-CoV-2 on or after Day 1 • Serum nAb titers: COVID-19 treatment, vaccination, or other prophylactic received on or after Day 1 • Predicted and serum nAb titers: Concomitant medications taken on or after Day 1 which interfere with PK Endpoint results with a date on or after the occurrence of an intercurrent event will not be included in the analysis.
Population-level summary	Pearson or Spearman correlation coefficient

[a] Data from multiple studies and timepoints may be pooled to give a more complete picture of the association between predicted and observed nAb titers. If performed, these pooled analyses will be presented separate from this study.

4.2.4.2 Derivations

There are two variables of interest for this exploratory endpoint. The first variable is the primary endpoint variable of predicted nAb titer defined in section 4.2.1.2. The second variable is the change from baseline measured serum nAb titer. This will be calculated as described in section 3.3.1. Both variables will be calculated for all post baseline timepoints using available observed values. For a given participant, results will be included in the analysis if the predicted nAb titer and the change from baseline measured serum nAb titer come from samples collected on the same calendar day.

Infection with SARS-CoV-2 may be identified through AEs, lab data, or other relevant data collected within the study. In Table 5, intercurrent events are identified specifically for each endpoint variable contributing to this analysis. Data collected for each endpoint will only be included in the analysis prior to the occurrence of an intercurrent event. Data collected for each endpoint that has a date on or after the occurrence of an intercurrent event will not contribute to the analysis.

These derivations will be calculated for participants who are in the PK/SARS-CoV-2 nAb analysis set.

4.2.4.3 Handling of Dropouts and Missing Data

There will be no handling rules for dropouts.

All available data from participants who are in the PK/SARS-CoV-2 nAb analysis set will be included. The handling rules for missing data are as follows:

- Baseline SARS-CoV-2 nAb titer measurements that are reported as below the LLOQ will have their value imputed as half the LLOQ value. See section 4.5.2.1
- Baseline SARS-CoV-2 nAb titer measurements that are reported as above the ULOQ will have their value imputed as the ULOQ value
- Post-baseline SARS-CoV-2 nAb titer measurements or serum PK concentration measurements reported as either (1) below the LLOQ or (2) above the ULOQ will have this measurement excluded from the analysis

4.2.4.4 Primary Analysis of Exploratory Endpoint

The $\log_{10}$-transformed change from baseline in observed nAb titers will be compared visually to the $\log_{10}$-transformed predicted nAb titers for the variant XBB.1.5 to identify if a linear trend exists. If not, then the Spearman correlation between these two variables is calculated. If a linear trend exists, then the Shapiro-Wilk test for normality is performed on both endpoints. If either one of these leads to a rejection of the null hypothesis at the α= 0.05 Type I error level, then the Spearman correlation between the two variables is calculated. Otherwise, the Pearson correlation coefficient is calculated. The number of participants, correlation coefficient, and the corresponding Fisher Z-transformed two-sided 95% CI will be presented in a scatter plot, along with a regression line fit to the data.

At the primary analysis this exploratory analysis will be performed using data from the Day 29 visit. This analysis may be reproduced for other circulating VOC at the Day 29 visit as data are available.

4.2.4.5 Sensitivity Analyses of the Exploratory Endpoint

This exploratory analysis will be repeated at subsequent analyses using data from all available timepoints to produce the correlation statistic.

Hamelett's mixed model [1] is to be fit using data from participants i, at actual time points j using available post-baseline measurements, with response k for either the $\log_{10}$-transformed predicted nAb titer (R_1) or $\log_{10}$-transformed change from baseline in observed serum nAb titer (R_2). Covariates include an intercept and the type of response (depicted below as <type>), where a value of 0 and 1 is assigned if the response variable is either R_1 or R_2. A random effect for type of response is to be fit at the participant level with unstructured covariance. A repeated effect is also to be fit for the type of response for visits nested within participant level with an unstructured covariance to model the residual errors. Kenward-Roger degrees of freedom is to be used and maximum likelihood estimation is performed.

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

The variance of the random effect has the form

$$G = \begin{bmatrix} Cov_i(R_1, R_1) & Cov_i(R_1, R_2) \\ Cov_i(R_2, R_1) & Cov_i(R_2, R_2) \end{bmatrix}$$

And the residual variance has the form

$$R = I_{m_i} \otimes \begin{bmatrix} Cov_{j(i)}(R_1, R_1) & Cov_{j(i)}(R_1, R_2) \\ Cov_{j(i)}(R_2, R_1) & Cov_{j(i)}(R_2, R_2) \end{bmatrix}$$

where m_i is the number of observations for participant i.

The repeated measures correlation ($\hat{\rho}$) is derived as follows and reported

$$\hat{\rho} = \frac{Cov(R_1, R_1)}{\sqrt{Var(R_1) \times Var(R_2)}}$$

$$= \frac{Cov_i(R_1, R_2) + Cov_{j(i)}(R_1, R_2)}{\sqrt{\left(Cov_i(R_1, R_1) + Cov_{j(i)}(R_1, R_1)\right) \times \left(Cov_i(R_2, R_2) + Cov_{j(i)}(R_2, R_2)\right)}}$$

$$= \frac{b + h}{\sqrt{(a + g) \times (c + i)}}$$

Applying the delta method, the partial derivative vector of $\hat{\rho}$ is defined as follows

$$\frac{\partial \boldsymbol{f}}{\partial} = \left(\frac{\partial f}{\partial a} \;\; \frac{\partial f}{\partial b} \;\; \frac{\partial f}{\partial c} \;\; \frac{\partial f}{\partial g} \;\; \frac{\partial f}{\partial h} \;\; \frac{\partial f}{\partial i}\right)$$

where

$$\frac{\partial f}{\partial a} = \frac{\partial f}{\partial g} = -\frac{1}{2}\frac{(b+h)(c+i)}{\sqrt{[(a+g)\times(c+i)]^3}}$$

$$\frac{\partial f}{\partial b} = \frac{\partial f}{\partial h} = \frac{1}{\sqrt{(a+g)\times(c+i)}}$$

$$\frac{\partial f}{\partial c} = \frac{\partial f}{\partial i} = -\frac{1}{2}\frac{(b+h)(a+g)}{\sqrt{[(a+g)\times(c+i)]^3}}$$

The 95% confidence interval is derived as follows and reported

$$\left(\hat{\rho} - 1.96 \times \sqrt{\frac{\partial f}{\partial}\boldsymbol{\Sigma}\frac{\partial f^T}{\partial}}, \hat{\rho} + 1.96 \times \sqrt{\frac{\partial f}{\partial}\boldsymbol{\Sigma}\frac{\partial f^T}{\partial}}\right)$$

where $\boldsymbol{\Sigma}$ is the asymptomatic covariance from the mixed model.

4.2.4.6 Supplementary Analyses of the Exploratory Endpoint

Additional analyses may be conducted to characterize the correlation and differences.

4.2.4.7 Subgroup Analyses

The correlation summaries may be repeated for the following subgroups if sufficient sample size:

- Immunocompromised vs immunocompetent/healthy

4.3 Pharmacodynamic Endpoints

Not applicable.

4.4 Pharmacokinetics

This section covers details related to pharmacokinetics endpoints and analyses. The PK analysis set will be used for the analyses of endpoints in this section.

4.4.1 Serum concentrations

The analysis for this endpoint will be included in the primary analysis.

4.4.1.1 Analysis

Serum concentrations for AZD7442 will be reported as the individual component concentrations AZD1061 and AZD8895, as well as the sum of the two individual component concentrations, labelled as AZD7442. Serum concentrations for AZD3152 will only be reported as AZD3152.

The analysis of serum concentrations for both treatment arms will comprise of descriptive statistics.

4.4.1.2 Definitions and Derivations

Sampling time deviations will be derived as: actual collection time - scheduled collection time.

4.4.1.3 Presentation

Descriptive statistics of serum concentrations will be tabulated by treatment arm over time.

Combined individual serum concentrations versus actual times will be plotted on both the linear and semi-logarithmic scales. Figures for the arithmetic mean (± SD) serum concentration-time data will be presented on both linear and semi-logarithmic scales. Figures for the geometric mean (+ gSD) serum concentration-time data will be presented on both linear and semi-logarithmic scales.

A listing of all serum concentration-time data, ie, individual concentrations in serum, PK scheduled times, actual sample collection times, sample actual relative times (ie, relative to time of administration of IP), as well as derived sampling time deviations (ie, difference between actual and scheduled time), will be presented for all randomized participants.

Considerations for crossover participants

For the primary analysis, summaries of PK serum concentration data through the Day 29 visit will summarize participants by the treatment arm received at the Day 1 visit. For the final analysis, summaries of PK serum concentration data after the Day 29 visit will reclassify crossover participants. In these summaries, all participants who only received one dose at Day 1 and did not crossover will still be classified by the treatment received at Day 1. The AZD7442 immunocompromised participants who received the optional AZD3152 dose at Day 29 visit will be classified in a 3rd treatment arm separate from the non-crossover participants.

4.4.1.4 Handling of Missing Data

Individual concentrations below the LLOQ of the bioanalytical assay will be reported as Not Quantifiable (NQ) in the listings with the LLOQ defined in the footnotes of the relevant TLFs. Individual serum concentrations that are Not Reportable (NR) will be

reported as NR and those that are missing will be reported as No Sample (NS) in the listings.

Serum concentrations for individual component mAbs (AZD3152, AZD1061, and AZD8895) 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.
- Any values reported as > ULOQ will be set to the ULOQ.
- At a time point where less than or equal to 50% of the concentration values are NQ, all NQ values will be set to half 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, gSD, and gCV% will be set to Not Computed (NC). The maximum value will be reported from the individual data, and the minimum and median will be set to NQ.
- If all concentrations are NQ at a time point, no descriptive statistics will be calculated for that time point. The geometric mean, minimum, median, and maximum will be reported as NQ and the gCV% and geometric mean ± gSD as NC.
- The number of values below LLOQ (n < LLOQ) will be reported for each time point together with the total number of collected values (n).

Three observations > LLOQ are required as a minimum for a serum concentration to be summarized. Two observations > LLOQ are presented as minimum and maximum with the other summary statistics as NC.

Serum concentrations for AZD7442 will be handled as follows:

Table 6 AZD7442 Serum Concentration Reporting and Imputation Rules

AZD1061 Concentration	AZD8895 Concentration	AZD7442 Concentration Reporting for Listings	AZD7442 Concentration Imputation for Summary Statistics
XX.xx	YY.yy	XX.xx + YY.yy	XX.xx + YY.yy
< LLOQ	< LLOQ	< LLOQ	Treat as NQ: • Set to half the LLOQ when ≤ 50% of concentration values are NQ • Set as missing when > 50% of concentration values are NQ
< LLOQ	YY.yy	YY.yy	YY.yy
XX.xx	< LLOQ	XX.xx	XX.xx
> ULOQ	> ULOQ	> 2 × ULOQ	2 × ULOQ

Table 6 AZD7442 Serum Concentration Reporting and Imputation Rules

AZD1061 Concentration	AZD8895 Concentration	AZD7442 Concentration Reporting for Listings	AZD7442 Concentration Imputation for Summary Statistics
> ULOQ	YY.yy	> ULOQ	ULOQ + YY.yy
XX.xx	> ULOQ	> ULOQ	ULOQ + XX.xx
< LLOQ	> ULOQ	> ULOQ	ULOQ
> ULOQ	< LLOQ	> ULOQ	ULOQ
NQ	YY.yy	YY.yy	YY.yy
XX.xx	NQ	XX.xx	XX.xx
NQ	< LLOQ	< LLOQ	Treat as NQ: • Set to half the LLOQ when ≤ 50% of concentration values are NQ • Set as missing when > 50% of concentration values are NQ
< LLOQ	NQ	< LLOQ	Treat as NQ: • Set to half the LLOQ when ≤ 50% of concentration values are NQ • Set as missing when > 50% of concentration values are NQ
NQ	> ULOQ	> ULOQ	ULOQ
> ULOQ	NQ	> ULOQ	ULOQ
NQ	NQ	NQ	Set as missing

4.5 Immunogenicity

This section covers details related to immunogenicity endpoints and analyses.

4.5.1 Incidence of ADA

The analysis of this endpoint will be included in the final analysis.

4.5.1.1 Analysis

The ADA analysis sets will be used for the analysis of this endpoint. The incidence of ADA to AZD3152 and AZD7442 in serum will be assessed and summarized. The ADA for AZD3152 and AZD7442 will be assessed for both Ips and separately for the AZD7442 individual component mAbs AZD1061 and AZD8895.

The number and percentage of ADA-evaluable positive participants will be determined. For ADA categories defined in section 4.5.1.2, frequencies and percentages will be presented. For ADA titers, descriptive statistics will include minimum, median, and maximum of the maximum ADA titer per participant per time point.

4.5.1.2 Definitions and Derivations

In the below subsections, the term "IP" will be used to refer to either AZD3152 or AZD7442, and "component mAbs" will be used to refer to the AZD7442 component mAbs AZD1061 and AZD8895 or AZD3152 itself (as it is a single component). All definitions below apply to both IPs.

ADA titer

ADA titer of IP is defined as the maximum of the component mAb titers at each time point.

ADA positive and ADA negative

Serum ADA assessments will be conducted utilizing a tiered approach (screen, confirm, titer [see CSP]). The ADA results from each sample will be reported as either positive or negative. If the sample is positive in the confirmatory assay, the ADA titer will be reported as well.

A participant is defined as being ADA-positive if ADA is evaluable and a positive ADA result in the confirmatory assay is available at any time, including baseline and all post-baseline measurements; otherwise the participant is defined as ADA negative if ADA evaluable.

Specifically for presentation of IP, ADA-positive to IP is having a positive ADA result to either or both component mAbs at any time, including baseline and all post-baseline measurements. ADA-negative is having negative ADA results to all evaluable component mAbs results at all times, including baseline and all post-baseline measurements. Summaries will include only ADA evaluable participants for the respective agent.

In the evaluation of ADA results to IP, if a component mAb is not ADA evaluable, all results from the component would be treated as missing.

ADA sample positive or negative status

- For a sample of a particular visit, AZD3152 is positive for that visit if the result is positive
- For a sample of a particular visit, AZD7442 is positive for that visit if either or both component mAb is/are positive

ADA participant positive or negative status

- For a participant, AZD3152 is positive if the result is positive at any visit and if the participant is ADA evaluable for AZD3152
- For a participant, AZD7442 is positive if either or both component mAbs is/are positive at any visit and if the participant is ADA evaluable for the component mAb having the positive result

Treatment-induced ADA positive

- For AZD3152, ADA negative at baseline and ADA positive at ≥ 1 post-baseline assessments with ADA titer ≥ 200
- For AZD1061, ADA negative at baseline and ADA positive at ≥ 1 post-baseline assessments with ADA titer ≥ 80
- For AZD8895, ADA negative at baseline and ADA positive at ≥ 1 post-baseline assessments with ADA titer ≥ 160
- AZD7442 is treatment-induced ADA positive if either component mAb is treatment-induced ADA positive

Treatment-boosted ADA positive

- For AZD3152, AZD1061, and AZD8895, baseline positive ADA titer that was boosted to ≥ 4-fold during the study period
- AZD7442 is treatment-boosted ADA positive if either component mAb is treatment-boosted ADA positive

Treatment-emergent ADA positive

- For AZD3152, AZD1061, and AZD8895, either treatment-induced ADA positive or treatment-bosted ADA positive
- AZD7442 is treatment-emergent ADA positive if either component mAb is treatment-emergent ADA positive

Non-treatment-emergent ADA positive

- For AZD3152, AZD1061, and AZD8895, being ADA-positive but not fulfilling the criteria of treatment-emergent ADA positive
- AZD7442 is non-treatment-emergent ADA positive if ADA-positive but not fulfilling the criteria of treatment-emergent ADA positive

Persistently ADA positive

- For AZD3152, participants who are treatment-emergent ADA positive, and having ADA post-baseline positive with ADA titer ≥ 200 at ≥ 2 post-baseline assessments (with ≥ 16 weeks between first and last positive)
- For AZD1061, participants who are treatment-emergent ADA positive, and having ADA post-baseline positive with ADA titer ≥ 80 at ≥ 2 post-baseline assessments (with ≥ 16 weeks between first and last positive)
- For AZD8895, participants who are treatment-emergent ADA positive, and having ADA post-baseline positive with ADA titer ≥ 160 at ≥ 2 post-baseline assessments (with ≥ 16 weeks between first and last positive)
- AZD7442 is persistently ADA positive if either component mAb is persistently ADA positive

Transiently ADA positive

- For AZD3152, participants who are treatment-emergent ADA positive, and having at least one post-baseline ADA positive assessment with titer ≥ 200 and not fulfilling the conditions of persistently positive
- For AZD1061, participants who are treatment-emergent ADA positive, and having at least one post-baseline ADA positive assessment with titer ≥ 80 and not fulfilling the conditions of persistently positive
- For AZD8895, participants who are treatment-emergent ADA positive, and having at least one post-baseline ADA positive assessment with titer ≥ 160 and not fulfilling the conditions of persistently positive
- AZD7442 is transiently ADA positive if treatment-emergent ADA positive and not fulfilling the conditions of persistently positive

4.5.1.3 Presentation

The following data will be tabulated:

- The number and percentage of participants in each ADA category defined in section 4.5.1.2, by treatment arm. The median, minimum, and maximum of the maximum titer for participants in the category will also be summarized.
- The number and percentage of participants with positive results at each time point will be tabulated by component mAbs and IP. The titers at these time points for these participants identified as ADA positive will be summarized by descriptive statistics; this tabulation will include a summary of the titer across all time points for each participant.
- First post-baseline positive ADA result and titer summary by time point and treatment arm. The number of participants with first ADA positive result observed at each time point will be presented, along with summary statistics of the titers.
- Serum concentrations over time by ADA status. The summary statistics presented in this table will be the same as discussed as those presented for the PK serum concentrations endpoint. ADA status will be treatment emergent ADA positive, non-treatment emergent ADA positive, and ADA negative. The PK analysis set will be used.
- Aes by ADA status. The Safety analysis set will be used.

The following figures will be presented:

- A line plot of ADA titers by treatment arm over time
- A line plot of percentage of participants with positive ADA results by visit
- A spaghetti plot of individual serum concentrations versus time profile by participant ADA status (treatment emergent ADA positive, non-treatment emergent ADA positive,

and ADA negative) on the semi-logarithmic scale. IP and component mAb data will be presented separately

The following data will be listed:

- The date and time of the blood samples collected for assessment of ADAs (samples to confirm the presence or absence of ADA from pre-dose Day 1 to last visit, including the titer for samples confirmed positive for ADA) will be listed
- The results of the ADA assessments will be listed for each participant and time point. This will include the classification of the response (positive/negative) and the measured titers, where appropriate. Serum drug concentration of the appropriate IP/mAb will also be included
- Adverse events by ADA response categories for participants who are ADA positive to IP/mAb

Considerations for crossover participants

For the primary analysis, summaries of ADA data through the Day 29 visit will summarize participants by the treatment arm received at the Day 1 visit. For the final analysis, summaries of ADA data after the Day 29 visit will reclassify crossover participants. In these summaries, all participants who only received one dose at Day 1 and did not crossover will still be classified by the treatment received at Day 1. The AZD7442 immunocompromised participants who received the optional AZD3152 dose at Day 29 visit will be classified in a 3rd treatment arm separate from the non-crossover participants.

4.5.2 Baseline and post-treatment nAb titers

The analysis of this endpoint may be included in the primary analysis, if data are available.

4.5.2.1 Analysis

The SARS-CoV-2 nAb analysis set will be used for the analysis of this endpoint.

A titer value that is measured as below the LLOQ will be imputed to a value that is half of the LLOQ. Titer values that are measured as above the ULOQ will be imputed to the ULOQ.

The LLOQ value for specific variants is presented in Table 7 and will be used for imputation of measured nAb results that are below the LLOQ. CCI [redacted] CCI [redacted]

Table 7 SARS-CoV-2 Variant LLOQ values

Variant	Validation Report	LLOQ (Titer, 1/Dilution)
Alpha/B.1.1.7	mg-sf-valdvr1096-001-validation-report	CCI [redacted]

Table 7 SARS-CoV-2 Variant LLOQ values

Variant	Validation Report	LLOQ (Titer, 1/Dilution)
BA.2	mg-sf-vald-vr1177-001-validation-report	CCI
BA.4/5	mg-sf-vald-vr1177-002-validation-report	
XBB.1.5	mg-sf-vald-vr1283-000-validation-report	

The GMT and GMFR of observed baseline and post-treatment nAb titers will be summarized by variant, timepoint and treatment arm.

Intercurrent events for this endpoint include:

- Infection with SARS-CoV-2 on or after Day 1
- COVID-19 treatment, vaccination, or other prophylactic received on or after Day 1

Infection with SARS-CoV-2 may be identified through AEs, lab data, or other relevant data collected within the study. Data collected for the serum nAb titer endpoint will only be included in the analysis prior to the occurrence of an intercurrent event. Data collected for the serum nAb titer endpoint that has a date on or after the occurrence of an intercurrent event will not contribute to the analysis; these data will be included in a listing.

4.5.2.2 Definitions and Derivations

The following derivations will be performed:

- The GMT is calculated as the antilog of the arithmetic mean calculated using the $\log_{10}$ transformed titer.
- The fold rise is calculated as the ratio of the post-baseline titer to the baseline result. The GMFR is the antilog of the arithmetic mean calculated using the $\log_{10}$ transformed fold rise.
- The gSD is calculatd as the antilog of the arithmetic standard deviation using the $\log_{10}$ transformed data.
- The 95% CI is calculated as the antilog of the 95% CI of the lower and upper limits for a two-sided 95% CI of the GMT or GMFR.

4.5.2.3 Presentation

Tables will include descriptive statistics for GMT and GMFR. The GMT statistics will include n, geometric mean, gSD, 95% CI, minimum, maximum, n (%) < LLOQ, and n (%) > ULOQ. The GMFR statistics will include n, geometric mean, gSD, 95% CI, minimum, and maximum.

The following tables and figures will be presented:

- Table summarizing GMT and GMFR over time by variant
- Box and whisker plots by treatment arm over time by variant

All serum nAb titer data will be included in a listing.

Considerations for crossover participants

For the primary analysis, summaries of SARS-CoV-2 nAb data through the Day 29 visit will summarize participants by the treatment arm received at the Day 1 visit. For the final analysis, summaries of SARS-CoV-2 nAb data after the Day 29 visit will reclassify crossover participants. In these summaries, all participants who only received one dose at Day 1 and did not crossover will still be classified by the treatment received at Day 1. The AZD7442 immunocompromised participants who received the optional AZD3152 dose at Day 29 visit will be classified in a 3rd treatment arm separate from the non-crossover participants.

4.5.3 SARS-CoV-2 serology (anti-nucleocapsid) serum sample

The analysis of this endpoint will be included in the final analysis.

4.5.3.1 Analysis

The Safety analysis set will be used for the analysis of this sample.

The analysis of this binary result will use descriptive statistics. The number and percentage of participants' result status will be determined.

4.5.3.2 Definitions and Derivations

Participants will be classified as having either a positive, negative, or missing result.

4.5.3.3 Presentation

Tables by treatment arm and timepoint will be presented, summarizing the number and percentage of participants who have either a positive, negative, or missing result.

Considerations for crossover participants

A table will summarize the data through Day 29, in which participants are classified by the treatment received at the Day 1 visit. A separate table summarizing the data after the Day 29 visit will reclassify crossover participants. In this table, all participants who only received one dose at Day 1 and did not crossover will still be classified by the treatment received at Day 1. The AZD7442 immunocompromised participants who received the optional AZD3152 dose at Day 29 visit will be classified in a 3rd treatment arm separate from the non-crossover participants.

4.5.4 Other exploratory assays

Other exploratory assays for humoral and immune responses that may be performed based upon emerging safety, efficacy, immunobridging, and immunogenicity data are not covered in this SAP.

4.6 Safety Analyses

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

Unless otherwise stated, the Safety analysis set will be used for this domain.

4.6.1 Exposure

4.6.1.1 Definitions and Derivations

Because IP is administered by site staff at the study site, study drug exposure will be presented in the summary of participant disposition, as described in section 4.1.1.

4.6.1.2 Presentation

Not applicable.

4.6.2 Adverse Events

4.6.2.1 Definitions and Derivations

AEs will be coded using the latest version of the MedDRA dictionary.

Adverse Events and SAEs

The definition of AEs and SAEs can be found in the CSP. The time period and frequency for collecting AE and SAE information is described in the CSP.

Imputation rules for missing AE dates are provided in Appendix B.

Immediate AEs

Immediate AEs are defined in the CSP, and will be identified as recorded by the investigator.

Injection Site Reactions and Infusion-related Reactions

Injection site reactions and infusion-related reactions are defined in the CSP, and will be identified as recorded by the investigator.

Severity ratings

Severity is graded using severity ratings adapted from CTCAE v5.0 and is described in the CSP. Severity will be categorized by rating.

Causality

The causality of AEs to IP, as indicated by the investigator, will be classified as not related or related. Should a participant experience multiple AEs within an SOC or PT, the AE will be counted as related to the particular SOC or PT if one of those is related.

Adverse Events of Special Interest

AESIs categories and duration of assessment are defined in the CSP. AESIs are events of scientific and medical interest specific to further understanding the IP safety profile. These events will be assessed from the time of study intervention administration until the study's last visit, unless otherwise specified.

AESIs will be programmatically identified through review of the reported preferred terms and classified in categories for serious hypersensitivity reactions including anaphylaxis, immune complex disease, infusion-related reactions, and cardiovascular and thrombotic events. For serious hypersensitivity reactions including anaphylaxis, these will additionally have to be classified as either an SAE or have CTCAE grade ≥ 3, and start within 30 days of dosing, to meet the criteria for an AESI. For infusion related reactions these will have to occur on the same calendar day as IP administration to meet the criteria for an AESI. For cardiovascular and thrombotic events, additionally these will have to be classified as an SAE to meet the criteria for AESI.

The list of preferred terms to identify AESIs based on MedDRA terms are not included in this SAP to facilitate their maintenance (e.g. management of MedDRA version changes), and for convenience in using them directly in SAS programming. Listings used to identify AESIs will be stored with the Biostatistics team. Terms and versions used for each CDL will be reported.

AESIs for this study include, but are not limited to:

- Anaphylaxis and other serious hypersensitivity reactions, including immune complex disease (see Appendix E)
- Infusion-related reactions (for IV administration)
- Cardiovascular and thrombotic events

Participant Exposure-Adjusted Rate

The participant time-adjusted rate is calculated as the number of participants with AEs per category divided by the total participant years. The participant years are determined by summing each participant’s total number of follow-up days divided by 365.25. The period is calculated from the time of the dose to the end of the study or the data cutoff date. The participant exposure-adjusted rate is calculated separately for each treatment arm.

4.6.2.2 Presentation

Summaries of AEs per SOC and PT will include the number and percentage of participants reporting at least one event, the number of events, and the participant time-adjusted rates, as applicable. Summaries will be presented by treatment arm. Summaries will include but may not be limited to the following:

- AEs
- Related AEs
- AEs ≥ CTCAE grade 3
- Non-serious AEs
- Immediate AEs
- SAEs
- Deaths
- AEs leading to discontinuation of IP
- AEs leading to study discontinuation
- MAAEs
- AESIs

A participant who experiences multiple events within any AE category, SOC, or PT will be counted only once within that category.

An overview table of AEs will be presented for the AE categories. In addition, the overview table and the SOC/PT AE tables will present the 95% (or one-sided 97.5% for proportions of 0% or 100%) exact Clopper-Pearson CI for the percentage of AEs.

All AE data will be provided in listings.

Summaries of AEs by subgroup (immunocompromised vs immunocompetent/healthy) may be produced.

Considerations for analyses through a specified visit

For the primary analysis, summaries of AEs will be presented through the Day 29 visit. To account for variability in actual visit times, AEs with start dates up to and including the earlier of (1) Study Day 35 or (2) the day prior to the date of optional dose of AZD3152 at the Day 29 visit will be included in the summaries.

If analyses through the Day 91 or 181 visits are to be performed, AEs with start dates up to and including Study Days 103 and 188, respectively, will be included in the summaries.

Considerations for crossover participants

Immediate AEs

Immediate AEs will be presented separately for each dose. For the first dose, summaries of immediate AEs will classify participants by the treatment arm received at the Day 1 visit. For the second dose, summaries of immediate AEs will reclassify crossover participants. In these summaries, the AZD7442 immunocompromised participants who received the optional AZD3152 dose at Day 29 visit will be classified in a 3rd treatment arm separate from the non-crossover participants. Only crossover participants will be included in summaries of immediate AEs following the second dose.

SAEs, MAAEs, and AESIs

Serious AEs, MAAEs, and AESIs will be presented through Day 29 visit and post Day 29 visit. Summaries of SAEs, MAAEs, and AESIs through Day 29 visit will classify participants by the treatment arm received at the Day 1 visit. Summaries of SAEs, MAAEs, and AESIs post Day 29 visit will reclassify crossover participants. In these summaries, all participants who only received one dose at Day 1 and did not crossover will still be classified by the treatment received at Day 1. The AZD7442 immunocompromised participants who received the optional AZD3152 dose at Day 29 visit will be classified in a 3rd treatment arm separate from the non-crossover participants.

AEs

AEs that fall into this category will be presented separately for each dose and 29-day follow-up period. For the first dose period, summaries of these AEs will classify participants by the treatment arm received at the Day 1 visit and summarize all applicable AEs through Day 29. For the second dose period, summaries of these AEs will reclassify crossover participants. In these summaries, the AZD7442 immunocompromised participants who received the optional AZD3152 dose at Day 29 visit will be classified in a 3rd treatment arm separate from the non-crossover participants. Only crossover participants will be included in summaries of immediate AEs following the second dose.

4.6.3 Clinical Laboratory, Blood Sample

4.6.3.1 Definitions and Derivations

Serum chemistry (including Troponin T or I), hematology, and coagulation sample collections will be performed per the CSP's SoA.

Quantitative laboratory parameters will be compared with the relevant local laboratory normal ranges and categorized as Low, Normal, or High. Minimum and maximum on-treatment values will be determined by considering any post-dose value, included results from Unscheduled visits.

4.6.3.2 Presentations

Descriptive statistics of quantitative clinical laboratory parameters will be summarized by treatment arm. Lab parameters will be presented by lab category. The following summaries of clinical laboratory parameters will be produced:

- Observed and change from baseline values by visit
- Shift from baseline to minimum on-treatment value
- Shift from baseline to maximum on-treatment value

Considerations for analyses through a specified visit

For the primary analysis, summaries of clinical laboratory samples will be presented through the Day 29 visit. To account for variability in actual visit times, clinical laboratory samples collected up to and including the earlier of (1) Study Day 35 or (2) the day prior to the date of optional dose of AZD3152 at the Day 29 visit will be included in the summaries.

Considerations for crossover participants

For the primary analysis, summaries of clinical laboratory data through the Day 29 visit will summarize participants by the treatment arm received at the Day 1 visit. There are no scheduled collection timepoints for clinical laboratory samples after the optional Day 29 dose, thus no separate summaries of clinical laboratory data are needed for the crossover participants.

4.6.4 Clinical Laboratory, Urinalysis

4.6.4.1 Definitions and Derivations

4.6.4.2 Presentations

Not applicable.

4.6.5 Other Laboratory Evaluations

4.6.5.1 Definitions and Derivations

Not applicable.

4.6.5.2 Presentations

Not applicable.

4.6.6 Vital Signs

4.6.6.1 Definitions and Derivations

Vital signs assessments will be performed per the CSP's SoA.

Minimum and maximum on-treatment values will be determined by considering any post-dose value, including results from Unscheduled visits.

4.6.6.2 Presentations

Descriptive statistics of vital signs results will be summarized by treatment arm. The following summaries of vital signs parameters will be produced:

- Observed and change from baseline values by visit
- Shift from baseline to minimum on-treatment value
- Shift from baseline to maximum on-treatment value

Considerations for analyses through a specified visit

For the primary analysis, summaries of vital signs will be presented through the Day 8 visit. To account for variability in actual visit times, vital signs measurements collected up to and including the earlier of (1) Study Day 14 or (2) the day prior to the date of optional dose of AZD3152 at the Day 29 visit will be included in the summaries.

Considerations for crossover participants

For the primary analysis, summaries of vital signs through the Day 8 visit will summarize participants by the treatment arm received at the Day 1 visit. For the final analysis, a separate table will be presented for participants who received AZD7442 at the Day 1 visit, are immunocompromised, and choose to receive the optional dose of AZD3152 at the Day 29 visit. This table will only include these crossover participants and will summarize vital signs data at the Day 29 visit and the Day 36 visit.

4.6.7 Electrocardiogram

4.6.7.1 Definitions and Derivations

Not applicable.

4.6.7.2 Presentations

12-lead ECG will be performed at the Screening visit. The ECG results will be summarized as part of the baseline characteristics summaries.

4.6.8 Physical Examinations

4.6.8.1 Definitions and Derivations

Not applicable.

4.6.8.2 Presentations

Findings during the physical examination at the Screening visit will be recorded as medical history and will be summarized accordingly. Findings during the physical examination at follow-up visits will be recorded as AEs and will be summarized accordingly.

4.6.9 Medication Error, Drug Abuse, and Drug Misuse

4.6.9.1 Definitions and Derivations

Not applicable.

4.6.9.2 Presentations

Not applicable.

5 INTERIM ANALYSIS

Additional interim analyses may be conducted to support regulatory requirements or at the discretion of the Sponsor.

6 REFERENCES

1. Irimata, Katherine et al. *Estimation of correlation coefficient in data with repeated measures*. SAS Institute Inc. 2018. *Proceedings of the SAS® Global Forum 2018 Conference*. Cary, NC: SAS Institute Inc. https://support.sas.com/resources/papers/proceedings18/2424-2018.pdf

7 APPENDIX

LIST OF APPENDICES

Appendix A Visit Windows

A 1 All participants

Any assessments or samples that are performed or collected only at Screening will have a visit window of ≤ -1.

Table 8 Serum chemistry, hematology, coagulation

Visit	Visit Window
Visit 1 Day 1	1
Visit 2 Day 8	2 – 19
Visit 3 Day 29	≥ 20

Table 9 SARS-CoV-2 serology, PK, ADA and antidrug nAb assessment, SARS-CoV-2 nAb, and exploratory analysis serum samples

Visit	Visit Window
Visit 1 Day 1	1
Visit 3 Day 29	2 – 60
Visit 4 Day 91	61 – 136
Visit 5 Day 181	≥ 137

A 2 Participants who received only AZD3152 or AZD7442

Table 10 Vital signs

Visit	Visit Window
Screening	≤ -1
Visit 1 Day 1	1
Visit 2 Day 8	≥ 2

A 3 Participants who received AZD7442 and the optional dose of AZD3152

Table 11 Vital signs

Visit	Visit Window
Screening	≤ -1
Visit 1 Day 1	1
Visit 2 Day 8	2 – 19
Visit 3 Day 29	20 – 33

Table 11 Vital signs

Visit	Visit Window
Visit 3a Day 36	≥ 34

Appendix B Imputation Rules for Missing Dates of AEs

Imputation rules for missing or partial start dates and stop dates of AEs are defined below:

- Missing or partial start date:
  - If only Day is missing, use the first day of the month, unless:
    - The AE end date is on/after the date of first dose or is missing/partial AND the start month and year of the AE coincide with the start month and year of the first dose. In this case, use the date and time of first dose
  - If Day and Month are both missing, use the first day of the year, unless:
    - The AE end date is on/after the date of first dose or is missing/partial AND the start year of the AE coincides with the start year of the first dose. In this case, use the date and time of first dose
  - If Day, Month, and Year are all missing, the date will not be imputed. However, if the AE end date is prior to the date of first dose, then the AE will be considered a pre-dose AE. Otherwise, the AE will be considered treatment-emergent
- Missing or partial end dates will not be imputed

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