STATISTICAL ANALYSIS PLAN

D8111C00010

A PHASE IV OPEN-LABEL, NON-RANDOMIZED, MULTI-COHORT, MULTICENTER STUDY IN PREVIOUSLY UNVACCINATED IMMUNOCOMPROMISED ADULTS TO DETERMINE THE IMMUNOGENICITY AND SAFETY OF AZD1222 VACCINE FOR THE PREVENTION OF COVID-19

AUTHOR: PPD

VERSION NUMBER AND DATE: V2.0, 26MAY2023

CCI

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan v2.0 (dated 26May2023) for protocol D8111C00010.

	Name	Signature	Date (DDMmmYYYY)
Author:	PPD	Refer to eSignature	
Position:	Biostatistician 1		
Company:	IQVIA		

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date (DDMmmYYYY)
Approved by:	PPD	Refer to eSignature (Due to technical difficulties, signed in CCI and not in CCI.)	
Position:	Statistical Scientist		
Company:	IQVIA		
Approved by:	PPD	Refer to eSignature	
Position:	Global Product Statistician- Delegate		
Company:	AstraZeneca		
Approved by:	PPD	Refer to eSignature	
Position:	Study Statistician		

PPD

CCI

Company:	AstraZeneca

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Version
1.0	21Jan2022	PPD	Not Applicable – First Version
2.0	26May2023	PPD	Additional secondary objective and corresponding estimand added along with additional categories in appendix 7 to bring in line with Protocol v4.0. Addendum added to limit the scope of the final analysis due to the study terminating early due to lack of enrollment. Modifications to Visit windowing, IAS analysis set inclusion criteria and GMT calculations update to clarify planned analyses

TABLE OF CONTENTS

[redacted]

CCI

[redacted]

CCI [redacted]

1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of immunogenicity and safety data for protocol D8111C00010. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This SAP is based on protocol amendment 4.0, dated 31Mar2022.

2. STUDY OBJECTIVES AND ESTIMANDS

2.1. PRIMARY OBJECTIVE

The primary immunogenicity objective is to characterize the immunogenicity of a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in SARS-CoV-2 naïve immunocompromised adults and immunocompetent adults ≥ 18 years.

2.2. SECONDARY OBJECTIVES

The secondary safety objective is to characterize the reactogenicity and safety of a 3-dose primary vaccination series with AZD1222 with a 4-week dosing interval in SARS-CoV-2 naïve immunocompromised adults ≥ 18 years.

The immunogenicity secondary objectives are:

- To characterize the immunogenicity after a 3rd-dose in a 3 dose primary vaccination series with AZD1222 in immunocompromised adults ≥ 18 years.
- To describe the immunogenicity of a 2-dose primary vaccination with AZD1222 in adults ≥ 18 years with 4-week dosing interval between SARS-CoV-2 naïve participants with the below conditions compared to immunocompetent participants:
  - Solid organ transplant
  - Hematopoietic stem cell transplant
  - Solid organ cancer patients receiving cytotoxic chemotherapy

CCI

[redacted]

- Chronic inflammatory disorders
- Primary immunodeficiency
- Any immunocompromised condition, pooled populations above

- To describe the immunogenicity after the 3rd dose in a 3-dose primary vaccination series with AZD1222 in adults ≥ 18 years between SARS-CoV-2 naïve immunocompromised participants (see above conditions) compared to immunocompetent participants after a 2-dose primary vaccination.
- To describe the immunogenicity of the AZD1222 vaccination between 28 days post 3rd-dose compared to 28 days post 2nd-dose, in adults ≥ 18 years between SARS-CoV-2 naïve immunocompromised and immunocompetent participants.
- To characterize the immunogenicity after a 3rd-dose booster vaccination of AZD1222, administered 6 months after dose 1 of a 2-dose primary vaccination with AZD1222, in immunocompetent adults ≥ 18 years.

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives are:

- To monitor the occurrence of COVID-19 in immunocompromised adults ≥ 18 years that have received 2 doses of AZD1222.
- To further describe humoral and cell mediated responses to AZD1222 following administration of AZD1222 in immunocompromised adults ≥ 18 years of age.
- To explore correlations between anti-S, pseudo-neutralization, and ChAdOx1 nAb antibody titres.

2.4. ESTIMANDS

The primary and secondary estimands to support regulatory decisions are described in the following table:

CCI [redacted]

Table A: List of Estimands

Estimand	Attributes				
	Population	**Treatment Condition of Interest**	**Variable/Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
The immunogenicity of a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in SARS-CoV-2 naïve immunocompromised adults and immunocompetent adults ≥ 18 years.	SARS-CoV-2 naïve immunocompromised adults and immunocompetent adults ≥ 18 years, who don't have exclusionary important protocol deviations (IPDs) and received at least one IM dose of AZD1222.	2 IM doses of AZD1222 with a 4-week dosing interval	a) SARS-CoV-2 specific GMTs in SARS-CoV-2 S and Neutralizing antibodies b) A binary response, whereby participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from day of baseline value to 28 days post each dose) as measured by the S and Neutralizing antibodies	For participants who withdraw from the study, or who use restricted medications judged to have the potential to interfere with the generation or interpretation of an immune response, absence of data following these participants' withdrawal or subsequent data following the IPDs will be treated as missing. Participants who (1) did not receive their second dose of AZD1222 or (2) tested positive	a) GMTs 28 days post each dose in SARS-CoV-2 S and Neutralizing antibodies b) Number and percentage of participants achieving a seroresponse (≥ 4-fold rise in titres from day of baseline value to 28 days post each dose) as measured by the S and Neutralizing antibodies

CCI [redacted]

				for SARS-CoV-2 infection (RT-PCR) will be censored at day 29/ the date of the positive test, whichever is earliest.	
The immunogenicity of a 2-dose primary vaccination with AZD1222 in adults ≥ 18 years with a 4-week dosing interval between SARS-CoV-2 naïve immunocompromised participants compared to immunocompetent participants.	SARS-CoV-2 naïve immunocompromised adults and immunocompetent adults ≥ 18 years, who don't have exclusionary important protocol deviations (IPDs) and received 2 IM doses of AZD1222.	2 IM doses of AZD1222 with a 4-week dosing interval	a) SARS-CoV-2 specific GMTs in SARS-CoV-2 S and Neutralizing antibodies b) A binary response, whereby participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from day of baseline value to 28 days post second dose) as measured by the S and Neutralizing antibodies	For participants who withdraw from the study, did not receive 2 IM doses of AZD1222, or who use restricted medications judged to have the potential to interfere with the generation or interpretation of an immune response, absence of data following these participants' withdrawal or subsequent data following the IPDs will be treated as missing. Participants who tested positive for SARS-CoV-2 infection (RT-PCR) will be censored at the date of the positive test.	a) Ratio of post-treatment GMTs from day of baseline value to 28 days post second dose in SARS-CoV-2 S and Neutralizing antibodies between each SARS-CoV-2 naïve immunocompromised cohort (including the pooled immunocompromised cohort) and the immunocompetent participants b) Difference in percentages of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from day of baseline value to 28 days post second dose) as measured by the S and

CCI [redacted]

					Neutralizing antibodies between each SARS-CoV-2 naïve immunocompromised cohort (including the pooled immunocompromised cohort) and the immunocompetent participants
The immunogenicity of a 3-dose primary vaccination with AZD1222 with a 4-week dosing interval in SARS-CoV-2 naïve immunocompromised adults ≥ 18 years.	SARS-CoV-2 naïve immunocompromised adults ≥ 18 years, who don't have exclusionary important protocol deviations (IPDs) and received at 3 IM doses of AZD1222.	3 IM doses of AZD1222 with a 4-week dosing interval	a) SARS-CoV-2 specific GMTs in SARS-CoV-2 S and Neutralizing antibodies b) A binary response, whereby participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from day of baseline value to 28 days post third dose) as measured by the S and Neutralizing antibodies	For participants who withdraw from the study, did not receive 3 IM doses of AZD1222, or who use restricted medications judged to have the potential to interfere with the generation or interpretation of an immune response, absence of data following these participants' withdrawal or subsequent data following the IPDs will be treated as missing. Participants who tested positive for SARS-CoV-2 infection	a) GMTs 28 days post third dose in SARS-CoV-2 S and Neutralizing antibodies b) Number and percentage of participants achieving a seroresponse (≥ 4-fold rise in titres from day of baseline value to 28 days post third dose) as measured by the S and Neutralizing antibodies

CCI [redacted]

				(RT-PCR) will be censored at the date of the positive test.	
Sensitivity analysis- The immunogenicity of a 3-dose primary vaccination with AZD1222 with a 4-week dosing interval in SARS-CoV-2 naïve immunocompromised adults ≥ 18 years.	SARS-CoV-2 naïve immunocompromised adults ≥ 18 years, who don't have exclusionary important protocol deviations (IPDs) and received at 3 IM doses of AZD1222.	3 IM doses of AZD1222 with a 4-week dosing interval	A binary response, whereby participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from visit 8 [pre-dose 3] to 28 days post third dose) as measured by the S and Neutralizing antibodies	For participants who withdraw from the study, did not receive 3 IM doses of AZD1222, or who use restricted medications judged to have the potential to interfere with the generation or interpretation of an immune response, absence of data following these participants' withdrawal or subsequent data following the IPDs will be treated as missing. Participants who tested positive for SARS-CoV-2 infection (RT-PCR) will be censored at the date of the positive test.	Number and percentage of participants achieving a seroresponse (≥ 4-fold rise in titres from visit 8 value [pre-dose 3] to 28 days post third dose) as measured by the S and Neutralizing antibodies
The immunogenicity of	SARS-CoV-2 naïve immunocompromised	3 IM doses of AZD1222	a) SARS-CoV-2 specific GMTs in SARS-CoV-2 S and Neutralizing	For participants who withdraw from the study, did not receive	a) Ratio of post-treatment GMTs from day of baseline value to 28

CCI

a 3-dose primary vaccination with AZD1222 in adults ≥ 18 years with a 4-week dosing interval for SARS-CoV-2 naïve immunocompromised participants compared to immunocompetent participants after 2-dose primary vaccination.	participants ≥ 18 years, who don't have exclusionary important protocol deviations (IPDs) and received 3 IM doses of AZD1222 (2 IM doses of AZD1222 for immunocompetent participants).	with a 4-week dosing interval (2 IM doses of AZD1222 for immunocompetent participants)	antibodies b) A binary response, whereby participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from day of baseline value to 28 days post third dose [28 days post second dose for immunocompetent participants]) as measured by the S and Neutralizing antibodies	3 IM doses of AZD1222 (2 IM doses of AZD1222 for immunocompetent participants), or who use restricted medications judged to have the potential to interfere with the generation or interpretation of an immune response, absence of data following these participants' withdrawal or subsequent data following the IPDs will be treated as missing. Participants who tested positive for SARS-CoV-2 infection (RT-PCR) will be censored at the date of the positive test.	days post third dose (28 days post second dose for immunocompetent participants) in SARS-CoV-2 S and Neutralizing antibodies between each SARS-CoV-2 naïve immunocompromised cohort (including the pooled immunocompromised cohort) and the immunocompetent participants b) Difference in percentages of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from day of baseline value to 28 days post third dose [28 days post second dose for immunocompetent participants]) as measured by the S and Neutralizing antibodies between each SARS-CoV-2 naïve

CCI [redacted]

					immunocompromised cohort (including the pooled immunocompromised cohort) and the immunocompetent participants
To describe the immunogenicity of the AZD1222 vaccination between 28 days post 3rd-dose compared to 28 days post 2nd-dose, in adults ≥ 18 years between SARS-CoV-2 naïve immunocompromised and immunocompetent participants.	SARS-CoV-2 naïve immunocompromised adults and immunocompetent adults ≥ 18 years, who don't have exclusionary important protocol deviations (IPDs) and received at least one IM dose of AZD1222.	3 IM doses of AZD1222 with a 4-week dosing interval	a) Ratio of SARS-CoV-2 specific GMT titres b) Difference in seroresponse rates of SARS-CoV-2 specific titres (≥ 4-fold increase in titres from 28 days post dose 2 to 28 days post dose 3)	For participants who withdraw from the study, did not receive 3 IM doses of AZD1222, or who use restricted medications judged to have the potential to interfere with the generation or interpretation of an immune response, absence of data following these participants' withdrawal or subsequent data following the IPDs will be treated as missing. Participants who tested positive for SARS-CoV-2 infection (RT-PCR) will be censored at	a) Ratio of post-treatment GMTs from 28 days post second dose to 28 days post third dose in SARS-CoV-2 S and Neutralizing antibodies for each SARS-CoV-2 naïve immunocompromised cohort (including the pooled immunocompromised cohort) and the immunocompetent participants b) Difference in percentages of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from 28 days post second dose to 28 days post third dose) as measured by the S and

CCI [redacted]

				the date of the positive test.	Neutralizing antibodies for each SARS-CoV-2 naïve immunocompromised cohort (including the pooled immunocompromised cohort) and the immunocompetent participants
The immunogenicity of a 3-dose booster vaccination with AZD1222, administered 6 months after dose 1 of a 2-dose primary vaccination in SARS-CoV-2 naïve immunocompetent adults ≥ 18 years.	SARS-CoV-2 naïve immunocompetent adults, who don't have exclusionary important protocol deviations (IPDs) and received 3 IM doses of AZD1222.	3 IM doses of AZD1222 with a 4-week dosing interval between doses 1 and 2 and a 6 month interval after dose 1.	a) SARS-CoV-2 specific GMTs in SARS-CoV-2 S and Neutralizing antibodies b) A binary response, whereby participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from day of baseline value to 28 days post third dose) as measured by the S and Neutralizing antibodies	For participants who withdraw from the study, or who use restricted medications judged to have the potential to interfere with the generation or interpretation of an immune response, absence of data following these participants' withdrawal or subsequent data following the IPDs will be treated as missing. Participants tested positive for SARS-CoV-2 infection (RT-PCR) will be censored at the	a) GMTs 28 days post third dose in SARS-CoV-2 S and Neutralizing antibodies b) Number and percentage of participants achieving a seroresponse (≥ 4-fold rise in titres from day of baseline value to 28 days post third dose) as measured by the S and Neutralizing antibodies

CCI [redacted]

				date of the positive test.	

CCI [redacted]

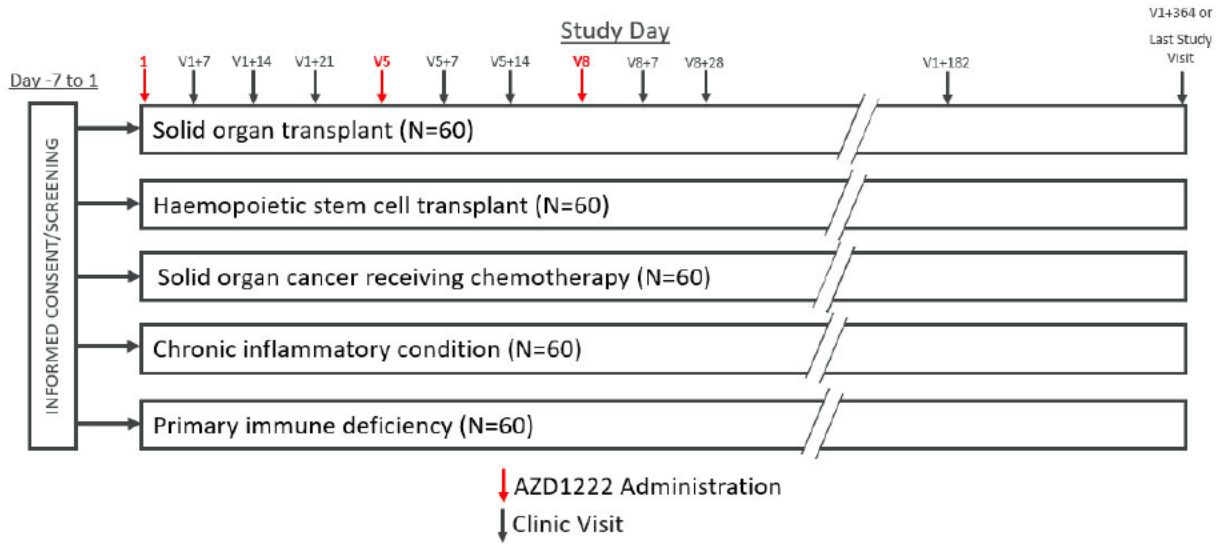
3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

D8111C00010 is a Phase IV, open-label, non-randomized, multi-cohort, multicenter study of the immunogenicity and safety of AZD1222 for the prevention of COVID-19 in previously unvaccinated immunocompromised adults ≥18 years. Immunocompromised participants will receive primary vaccination with 3 IM doses of AZD1222 separated by 4 weeks and will continue to be followed to the end of the study. Immunocompetent participants will receive a primary vaccination series with 2 IM doses of AZD1222 separated by 4 weeks followed by a third dose booster 6 months after dose 1 and will continue to be followed to the end of the study.

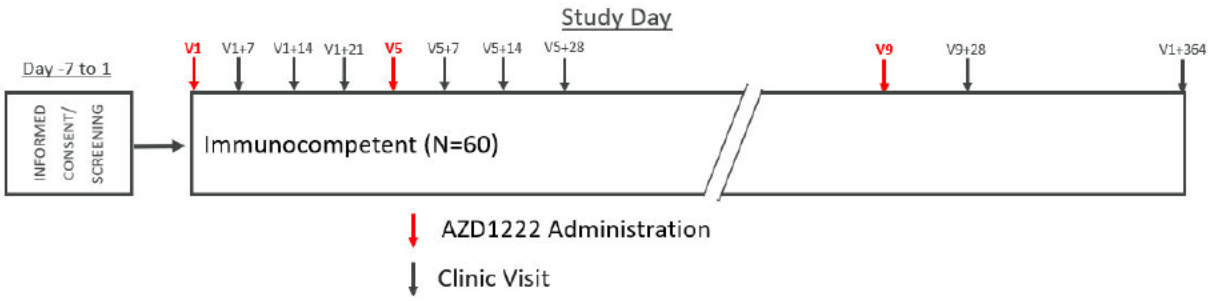
The study includes adults ≥ 18 years with stable immunocompromising conditions or on stable doses of immunocompromising therapeutics, enrolled in 5 disease cohorts of approximately 60 participants each. A sixth cohort will contain approximately 60 immunocompetent participants. Participants will be allocated to the immunocompromised according to the underlying aetiology of their immunocompromised status.

Table B: Study Design for Immunocompromised Participants



CCI

Table C: Study Design for Immunocompetent Participants



3.2. SCHEDULE OF EVENTS

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

3.3. CHANGES TO ANALYSES FROM PROTOCOL

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

4. PLANNED ANALYSES

4.1. DATA MONITORING COMMITTEE

There will be no Data Monitoring Committee (DMC) for this study.

4.2. PRIMARY ANALYSIS

A primary analysis will occur when all participants within a cohort have completed visit 8 (i.e., 28 days after the second dose). The data cut-off date will be the date the last participant reaches the trigger for the primary analysis and the corresponding data will be coded and cleaned up to the data cut-off date. Additional primary analyses and data cut-offs may occur after all participants within a given cohort have completed visit 8 depending on participant recruitment.

CCI [redacted]

4.3. SECONDARY ANALYSIS

A secondary analyses of a third dose (primary series) will occur when all participants within an immunocompromised cohort have completed visit 10 (i.e., 28 days after the third dose). The data cut-off date will be the date the last participant reaches the trigger for the secondary analysis and the corresponding data will be coded and cleaned up to the data cut-off date. Additional secondary analyses and data cut-offs may occur after all participants within a given cohort have completed visit 10 depending on participant recruitment.

4.4. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Sponsor authorization of this SAP, Sponsor authorization of the analysis sets, and database lock (DBL). All participants in the study will be assessed for immunogenicity and safety to the end of the study. The final DBL will occur when all participants have completed the study.

5. ANALYSIS SETS

5.1. ALL PARTICIPANTS ANALYSIS SET

The all participants analysis (PAS) set will contain all participants screened for the study. All participants analysis set is to be used for reporting disposition and screening failures.

All participants screened are those who provide informed consent.

5.2. FULL ANALYSIS SET

The full analysis set (FAS) will contain all enrolled participants, i.e., those participants who meet screening eligibility criteria. Participants who withdraw consent to participate in the study will be included up to the date of their study withdrawal.

5.3. SAFETY ANALYSIS SET

The safety analysis set (SAF) consists of all participants who have received at least one dose of study intervention.

A participant who has on one or several occasions received active study intervention is classified as active for all summaries, including summaries by dose.

5.4. IMMUNOGENICITY ANALYSIS SET

The immunogenicity analysis (IAS) set will include all participants in the safety analysis set who have at least one baseline and post-baseline record in immunogenicity data and no protocol deviations judged to have the potential to interfere with the generation or interpretation of an immune response.Details of exclusionary protocol deviations will be defined in a separate PD plan (See Section 9.2). Protocol deviations will be reviewed by the study team before database lock to determine exclusion from the immunogenicity analysis set.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

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

Study Day will be computed as follows:

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

In addition, day relative to vaccination will be derived for each vaccination dose. For example, day relative to the first dose will be equal to the Study Day. Day relative to the second dose will start with a value of 1 on the day of the second dose.

In the situation where the event date is partial or missing, Study Day and any corresponding durations will appear

partial or missing in the listings.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to the first dose of study intervention (including unscheduled assessments). In the case where the last non-missing measurement and the date and time of the first dose of study intervention coincide, that measurement will be considered pre-baseline, but adverse events (AEs) and medications commencing on the date of the first dose of study intervention will be considered post-baseline.

6.3. UNSCHEDULED VISITS, RETESTS, AND EARLY TERMINATION DATA

For by-visit summaries, data recorded at the nominal visit will be presented. That is, unscheduled, retest (same visit number assigned), and early termination measurements will not be included in by-visit summaries but might contribute to the baseline timepoint and/or maximum value, where required (e.g. shift table).

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

6.4. WINDOWING CONVENTIONS

A windowing convention will be used to determine the analysis value for a given study visit for immunogenicity . The window definitions as following will be used:

1. A window of + /- 7 days from the target day is applied to the V1+14, V1+28, V5+14, V5+28 and V8+28 visits for the immunocompromised participants and to the V1+14, V1+28, V5+14, V5+28 and V9+28 visits for the immunocompetent participants.

2. A window of +/- 30 days from the target day is applied to the V1+182 and V1+364 visits for the immunocompromised participants and to the V1+182 and V1+364 visits for the immunocompetent participants.

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

CCI

[redacted]

Table D: Analysis windows for Immunogenicity by Visit (Immunocompromised participants)

Dosing Period	Visit	Day Relative to Dose within the Dosing Period [a]	Visit Window (Study Day) Relative to the Dosing Period
Relative to Dose 1	Baseline (V1)	≤ 1	≤ 1
	V3	15	8 – 21
	V5	29	22 – 35
Relative to Dose 2	V7	15	8 – 21
	V8	29	22 - 35
Relative to Dose 3	V10	29	22 - 35
Relative to Dose 1	V11	183	153 - 212
	V12	365	335 - 394

(a) For each dosing period, the administration of the study intervention is designated as Study Day 1. For analyses within a period, the study day value is incremented by 1 for each date following the vaccine administration. Dates prior to the vaccine administration are decremented by 1, with the date preceding the vaccine administration designated as Study Day -1 (there is no Study Day 0).

Table E: Analysis windows for Immunogenicity by Visit (Immunocompetent Participants)

Dosing Period	Visit	Day Relative to Dose within the Dosing Period [a]	Visit Window (Study Day) Relative to the Dosing Period
Relative to Dose 1	Baseline (V1)	≤ 1	≤ 1
	V3	15	8 – 21
	V5	29	22 – 35
Relative to Dose 2	V7	15	8 – 21
	V8	29	22 - 35
Relative to Dose 1	V9	183	153 - 212
Relative to Dose 3	V10	29	22 - 35
Relative to Dose 1	V11	365	335 - 394

(a) For each dosing period, the administration of the study intervention is designated as Study Day 1. For analyses within a period, the study day value is incremented by 1 for each date following the vaccine administration. Dates prior to the vaccine administration are decremented by 1, with the date preceding the vaccine administration designated as Study Day -1 (there is no Study Day 0).

Beside immunogenicity analyses, no visit windowing will be performed for analysis of other variables in this study.

6.5. COMMON CALCULATIONS

Change from baseline will be calculated as:

CCI

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

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

7. STATISTICAL CONSIDERATIONS

For continuous data, descriptive statistics (i.e., n [number of subjects with available data], mean or geometric mean, standard deviation [SD], median, minimum, and maximum values) will be presented by cohort and visit, when applicable.

For categorical data, the number and percentages of subjects in each category will be presented by cohort and visit, when applicable.

7.1. SAMPLE SIZE CALCULATION

It is expected that approximately 360 participants will be enrolled (approximately 60 participants in each cohort). There is no statistical hypothesis testing planned for this study. Descriptive analyses will support evaluation of safety and immunogenicity.

7.2. MISSING DATA

Missing safety data will not be imputed. Partial or completely missing medication dates will be handled as described in APPENDIX 1. Partial or completely missing medical history/concomitant illness dates will be handled similarly.

Missing immunogenicity data will be handled as described in Section 16.1.5 of this analysis plan.

7.3. STATISTICAL TESTS

There is no formal statistical hypothesis testing planned for this study. Descriptive analyses will support evaluation of safety and immunogenicity and qualitative comparison between cohorts.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

No statistical testing will be performed for this study, thus there is no need to control the overall study type I error.

CCI

[redacted]

7.5. MULTICENTER STUDIES

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

7.6. EXAMINATION OF SUBGROUPS

Subgroup analyses will be conducted as stated in Sections 16.1.1.1 and 16.1.3.

The subgroups are:

- Age group at informed consent (≥ 18 to < 65 years and ≥ 65 years)
- Sex (male and female)

7.7. SOFTWARE VERSION

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

8. OUTPUT PRESENTATIONS

APPENDIX 2 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore, the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics.

9. DISPOSITION AND WITHDRAWALS

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

9.1. DISPOSITION

The number and percentage of participants by cohort and overall for the PAS will be presented for the below unless otherwise stated.

- Number of participants screened will be presented overall for the PAS.
- Participants with screen failure and reason for screen failure will be presented overall for the PAS.
- Participants enrolled and participants enrolled but not vaccinated.
- Participants who completed the study, ongoing in the study (primary and secondary analysis only), discontinued early from study and reasons for discontinuing early from study (percentages for reasons will be based on enrolled participants that discontinued early from the study).
- Participants vaccinated for first dose, discontinued from study before second dose and reasons for discontinuing early from study before second dose (percentages for reasons will be based on enrolled participants that discontinued from the study before second dose).
- Participants who discontinued study intervention and reasons for discounting study intervention (percentages for reasons will be based on enrolled participants that discontinued study intervention).
- Participants vaccinated for second dose, discontinued from study before third dose and reasons for discontinuing early from study before third dose (percentages for reasons will be based on enrolled participants that discontinued from the study before third dose).
- Participants vaccinated for third dose, discontinued from study after third dose and reasons for discontinuing early from study after third dose (percentages for reasons will be based on enrolled participants that discontinued from the study after third dose).

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

The number and percentage of participants enrolled by country and site will be provided, including the dates when the first and last participants were enrolled at each site, overall and by cohort.

9.2. PROTOCOL DEVIATIONS

The number and percentage of participants with important protocol deviations will be summarized overall and by cohort based on the all participants analysis set, overall and by protocol deviation category. The number and percentage of participants with exclusionary protocol deviations for the immunogenicity analysis set will also be provided overall and by cohort. Protocol deviation categories are defined in a separate PD plan.

A listing of important protocol deviations identified by the study team will be provided.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

- Age (years) – calculated relative to date of consent
- Age groups (refer to Section 7.6)
- Sex
- Race
- Ethnicity
- Country
- Weight (kg)
- Height (cm)
- Body Mass Index (BMI) (kg/m^2)

Continuous demographic and other baseline characteristics will be summarized using descriptive statistics overall and by cohort based on the SAF analysis set. For categorical demographic and other baseline characteristics, number and percentage of subjects in each category will be provided overall and by cohort based on the SAF analysis set. No statistical testing will be carried out for demographic or other baseline characteristics.

10.1. DERIVATIONS

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

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

11. SURGICAL AND MEDICAL HISTORY

Surgical and medical history are defined as any surgeries that happened before the first dose of study intervention and any medical conditions/diseases that started and stopped before the first dose of study intervention.

Surgical and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 23.0 or higher, and will be summarized by System Organ Class (SOC) and Preferred Term (PT) overall and by cohort based on the SAF analysis set. A subject having more than one surgery/medical condition/disease within the same SOC/PT will be counted only once for that SOC or PT.

All surgical and medical history will be listed.

Baseline co-morbidities solicited on the eCRF page will be summarized separately from medical histories overall and by cohort based on the SAF.

12. CONCOMITANT ILLNESSES

Concomitant conditions/illnesses are defined as any medical conditions/illnesses that started before the first dose of study intervention AND were ongoing at the time of the first dose of study intervention or ended on the first dose of study intervention.

Concomitant conditions/illnesses will be coded using the MedDRA, version 23.0 or higher, and will be summarized by SOC and PT overall and by cohort based on the SAF analysis set. A participant having more than one medical condition/illness within the same SOC or PT will be counted only once for that SOC or PT.

All concomitant conditions/illnesses will be listed.

13. MEDICATIONS

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

Concomitant medications are defined as:

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

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

All medications will be coded using the World Health Organization (WHO) Drug Global dictionary, version B3 March 2020 or later. The dictionary will be updated when a new dictionary version becomes available to IQVIA.

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

All prior and concomitant medications will be listed.

14. EXPOSURE TO STUDY DRUG

Due to the simplicity of dosing for this study, exposure is summarized in the Disposition table. No other summary will be reported. A listing will provide exposure information for all participants in the SAF analysis set.

Report of overdose and medication error, if any, will be listed for the SAF analysis set.

15. COMPLIANCE WITH STUDY DRUG

Compliance will not be calculated since participants are vaccinated within clinic.

A summary of the interval between doses 1 and 2, doses 2 and 3 and doses 1 and 3 of study intervention will be provided. The dosing interval between dose X and dose Y is calculated as the date of dose Y – date of dose X +1 for all participants who received dose X and Y of study intervention. This analysis will be based on the SAF. The

CCI

[redacted]

summary based on IAS for the study will also be repeated by age group (18-64 years and ≥65 years).

16. IMMUNOGENICITY ENDPOINTS

Unless otherwise indicated, all immunogenicity summaries and figures will be presented by cohort (including the pooled immunocompromised cohort) and visit, when appropriate, based on the immunogenicity analysis set.

For all immunogenicity endpoints, participants will be censored at the date of first positive PCR test for SARS-CoV-2 infection/non-study COVID-19 vaccine administration/exclusionary restricted medication, whichever occurs first, such that data from all visits after the date of first positive PCR test for SARS-CoV-2 infection/non-study COVID-19 vaccine administration/exclusionary restricted medication will be excluded from derivations and all by-visit summaries. All immunogenicity data regardless of censoring will be listed for all participants, with all censored assessments flagged.

For summaries over time, participants who do not receive dose 2 of study intervention will be excluded from all time points post dose 2. Participants who do not receive dose 3 of study intervention will be excluded from all time points post dose 3.

All participants will be assessed for serum samples for SARS-COV-2 serology testing.

The immunogenicity primary endpoints are:

- Post-treatment GMTs and GMFRs from day of dosing baseline value to 28 days post dose 1 and dose 2 in SARS-CoV-2 S antibodies.
- Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from day of dosing baseline value to 28 days post dose 1 and dose 2) for the S antibodies.
- Post-treatment GMTs and GMFRs from day of dosing baseline value to 28 days post dose 1 and dose 2 in SARS-CoV-2 neutralizing antibodies (pseudo-neutralization assay)
- Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from day of dosing baseline value to 28 days post dose 1 and dose 2) as measured by SARS-CoV-2 neutralizing antibodies (pseudo-neutralization assay)

CCI

The immunogenicity secondary endpoints are:

- Ratio of post-treatment GMTs at 28 days post second dose in SARS-CoV-2 S antibodies between each immunocompromised cohort (including the pooled immunocompromised cohort) and immunocompetent participants.
- Difference in proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from day of dosing baseline value to 28 days post second dose) to the S antibodies between each immunocompromised cohort (including the pooled immunocompromised cohort) and immunocompetent participants.
- Ratio of post-treatment GMTs at 28 days post second dose in SARS-CoV-2 neutralizing antibodies (pseudo-neutralization assay) between each immunocompromised cohort (including the pooled immunocompromised cohort) and immunocompetent participants.
- Difference in proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from day of dosing baseline value to 28 days post second dose) as measured by SARS-CoV-2 neutralizing antibodies (pseudo-neutralization assay) between each immunocompromised cohort (including the pooled immunocompromised cohort) and immunocompetent participants.
- Post-treatment GMTs and GMFRs from day of dosing baseline value to 28 days post dose 3 in SARS-CoV-2 S antibodies for each immunocompromised cohort (including the pooled immunocompromised cohort).
- Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from day of dosing baseline value to 28 days post dose 3) in the S antibodies for each immunocompromised cohort (including the pooled immunocompromised cohort).
- Post-treatment GMTs and GMFRs from day of dosing baseline value to 28 days post dose 3 in SARS-CoV-2 neutralizing antibodies (pseudo-neutralization assay) for each immunocompromised cohort (including the pooled immunocompromised cohort).
- Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from day of dosing baseline value to 28 days post dose 3) as measured by SARS-CoV-2 neutralizing antibodies (pseudo-neutralization assay) for each immunocompromised cohort (including the pooled immunocompromised cohort).
- Ratio of post-treatment GMTs at 28 days post third dose in SARS-CoV-2 S antibodies between each

CCI [redacted]

immunocompromised cohort (including the pooled immunocompromised cohort) and post-treatment GMTs at 28 days post second dose in SARS-CoV-2 S antibodies in immunocompetent participants.

- Difference in proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from day of dosing baseline value to 28 days post third dose [second dose for immunocompetent participants]) to the S antibodies between each immunocompromised cohort (including the pooled immunocompromised cohort) and immunocompetent participants.
- Ratio of post-treatment GMTs at 28 days post third dose in SARS-CoV-2 neutralizing antibodies (pseudo-neutralization assay) between each immunocompromised cohort (including the pooled immunocompromised cohort) and post-treatment GMTs at 28 days post second dose in SARS-CoV-2 neutralizing antibodies (pseudo-neutralization assay) in immunocompetent participants.
- Difference in proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from day of dosing baseline value to 28 days post third dose [second dose for immunocompetent participants]) as measured by SARS-CoV-2 neutralizing antibodies (pseudo-neutralization assay) between each immunocompromised cohort (including the pooled immunocompromised cohort) and immunocompetent participants.

The supportive analysis to immunogenicity secondary endpoints are:

- Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from day of dosing visit 8 (pre-dose 3) value to 28 days post dose 3) in the S antibodies for each immunocompromised cohort (including the pooled immunocompromised cohort).
- Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from day of dosing visit 8 (pre-dose 3) value to 28 days post dose 3) as measured by SARS-CoV-2 neutralizing antibodies (pseudo-neutralization assay) for each immunocompromised cohort (including the pooled immunocompromised cohort).

The exploratory immunogenicity endpoints are:

- Post-treatment GMTs and GMFRs from day of dosing baseline value to 28 days post dose 3 in SARS-CoV-2 S antibodies in immunocompetent participants.
- Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from day of dosing baseline value to 28 days post dose 3) in the S antibodies in immunocompetent participants.

CCI

- Post-treatment GMTs and GMFRs from day of dosing baseline value to 28 days post dose 3 in SARS-CoV-2 neutralizing antibodies (pseudo-neutralization assay) in immunocompetent participants.
- Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from day of dosing baseline value to 28 days post dose 3) as measured by SARS-CoV-2 neutralizing antibodies (pseudo-neutralization assay) in immunocompetent participants.
- Post-treatment GMTs and GMFRs from baseline value to 28 days post each dose in ChAdOx1 neutralizing antibodies
- Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from Day 1 baseline value to 28 days post each dose) as measured by ChAdOx1 neutralizing antibodies
- Post-treatment GMTs and GMFRs from day of dosing baseline value to 28 days post each dose in SARS-CoV-2 RBD antibodies
- Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from day of dosing baseline value to 28 days post each dose) to the RBD antibodies

The exploratory cell-mediated immune (CMI) response endpoint is:

- Intracellular cytokine staining and flow cytometry for B- and T-cell responses from day of dosing baseline to 14 days post each dose

Other exploratory assays for humoral and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data and will be described in a separate document.

Pairwise correlations between anti-S, pseudo-neutralization, and ChAdOx1 nAb antibody titres, 28 days after Dose 1 and 28 days after Dose 2 will be explored.

16.1. ANALYSIS OF IMMUNOGENICITY ENDPOINTS

Individual titre values for each endpoint, seroresponse and fold rise compared to baseline will be presented in a data listing.

CCI

16.1.1. QUANTIFICATION OF ANTIBODY LEVELS

SARS-CoV-2 S, RBD and nucleocapsid antibodies will be assessed quantitatively using a validated multiplexed MSD immunoassay at each scheduled visit as per protocol section 1.3. SARS-CoV-2 NAb will be measured using validated pseudoneutralization assays.

The antibody titre measurements will be summarized at each scheduled visit using geometric mean titre (GMT) and geometric mean fold rise (GMFR).

Descriptive statistics for GMTs and GMFRs will include number of participants, GMT, 95% confidence interval (CI), median, minimum and maximum.

The ratio of post-treatment GMTs values between each immunocompromised cohort and immunocompetent group will be presented with corresponding 95% confidence limits.

The GMT will be calculated as the antilogarithm of Σ (base 2 log transformed titre/n), i.e. as the antilogarithm transformation of the mean of the log-transformed titre, where n is the number of participants with titre information. The 95% CI will be calculated as the anti-logarithm transformation of the upper and lower limits for a two-sided CI for the mean of the log-transformed titres.

The fold rise is calculated as the ratio of the post-vaccination titre level to the pre-vaccination titre level, i.e., the baseline level (See Section 6.2). GMFR will be calculated as anti-logarithm of Σ (base 2 log transformed (post-vaccination titre/ pre-vaccination titre)/n). The 95% CIs for GMFR will be calculated similarly to those for GMT.

The antibody titre measurements will be presented in a data listing.

16.1.1.1. SUBGROUP ANALYSIS FOR QUANTIFICATION OF ANTIBODY LEVELS

The analysis of quantification of antibody levels will be repeated for the subgroups defined in Section 7.6.

16.1.2. SERORESPONSE RATE

Seroresponse is a binary outcome where a success is when the fold rise in titres compared to baseline is ≥4.

Seroresponse will be calculated for the immunocompromised cohort (including the pooled immunocompromised cohort) and immunocompetent cohort and will be summarized at each scheduled visit as per protocol section 1.3.

CCI

The number and percentage of participants with post-vaccination seroresponse, and 95% CIs will be provided and the 95% CI of seroresponse rate will be calculated using the Clopper-Pearson exact method. For 0% or 100% seroreponse, a 97.5% CI will be provided.

The difference in the seroresponse rate between each of the immunocompromised cohort and immunocompetent patients will be presented with corresponding 95% confidence limits using the Newcombe score without continuity correction.

16.1.3. Subgroup Analysis for Seroresponse Rate

The analysis of seroresponse will be repeated for the subgroups defined in Section 7.6.

16.1.4. Cell-mediated Immune Response

CMI responses (i.e., B-cell and T-cell responses) will be assessed as per the schedule of events (refer to protocol, Section 1.3).

CMI data will be reported separately from the CSR.

16.1.5. Missing Data Imputation Method for Immunogenicity Endpoints

A titre value measured below the lower limit of quantification (LLoQ) will be imputed to a value that is half of the LLoQ in summaries and analyses, but will be listed as reported in the raw serology data. For example, a serologic assay with LLoQ = 30 generally reports values below LLoQ as "<30". The data listings will present the values as "<30", while values of 15 (i.e., 30/2) are to be used in the summaries and analyses.

Titre values measured as above upper limit of quantification (ULoQ) will be imputed at the ULoQ value.

16.1.6. Model Adjustment

The GMT endpoint will be analysed using an analysis of variance (ANOVA) model separately for each cohort (including the pooled immunocompromised cohort), and includes the log base 2-transformed value of titre as the dependent variable and visit, sex, and age group as fixed effects and participant as a random effect. On the log scale, the models will be used to estimate least square means for each cohort by visit. The model-adjusted titre levels will be derived as the LS means for each cohort and visit combination, plus the residual from the model fit. These values

will then be back-transformed.

All analysis detailed in Section 16 will be repeated on model adjusted titre levels.

17. SAFETY ENDPOINTS

All safety summaries will be presented by cohort based on the SAF analysis set. There will be no statistical comparisons between the cohorts for safety data.

The secondary safety endpoints are:

- Reactogenicity: Incidence of local and systemic solicited AEs for 7 days after each dose of AZD1222 by eDiary.
- Incidence of unsolicited AEs for 28 days post dose after each vaccination.
- Incidence of Serious adverse events (SAEs), Medically attended adverse events (MAAEs) and AEs of special interest (AESIs) from Day 1 post treatment to last study visit.
- Absolute and change from baseline for safety laboratory measures

There are also other safety endpoints such as vital signs.

17.1. ADVERSE EVENTS

All AEs are considered to be unsolicited AEs (collected by 'open question' at study visits) unless categorized as solicited AEs recorded in an eDiary (see Section 17.2).

Non-serious AEs will be recorded for 28 days post each dose of study intervention. SAEs will be recorded from the time of signature of the informed consent form through the last participant contact. MAAEs and AESIs will be recorded from Day 1 through the last participant contact.

AEs will be coded using the MedDRA dictionary, version 23.0 or higher.

Overall summaries of number and percentage of participants, and number of events with following AE categories will be provided by cohort based on the SAF:

- All AEs

CCI [redacted]

- All SAEs
- Related AEs by severity
- Related SAEs
- AEs leading to discontinuation from study intervention
- Related AEs leading to discontinuation from study intervention
- AEs leading to study discontinuation
- Related AEs leading to study discontinuation
- COVID-19 related AEs
- MAAEs
- AEs with outcome of death
- AESIs
- Related AESIs

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

An overall summary of number and percentage of participants, and number of events within each of the categories described above will be provided for the period from 1-28 days post any dose by cohort based on the SAF.

Adverse events post the first study intervention occurring within 28 days of each dose will be summarized by SOC and PT by cohort, including exposure adjusted rates. Specific AEs will be counted once for each participant for calculating percentages. Exposure adjusted rate is calculated as number of participants with AEs in categories above/total patient-year exposure to investigational study intervention. Patient years is determined by summing the total number of follow-up days of each participant, and then dividing by 365.25. The exposure period is calculated from time of first intervention to end of study.

Summary of AEs occurring within 28 days post each intervention will be broken down further by post each dose, maximum severity and events related to study intervention. If the same AE occurs multiple times within a particular participant, the highest severity observed will be reported.

CCI

[redacted]

Non-serious AEs, including exposure adjusted rates, will be summarized by PT. AEs within 28 days of each study intervention will also be summarized by PT.

All AEs will be listed.

17.1.1. Severity Grading for AEs

Severity will be classified as mild, moderate, severe, potentially life-threatening and fatal (increasing severity) by using the FDA Grading for AEs. Should a participant experience multiple events within a SOC or PT, only the participants' worst FDA grade will be counted for that SOC or PT.

17.1.2. Relationship to Study Intervention/Non-Study Intervention/Procedure

Relationship to study intervention/procedure, as indicated by the Investigator, will be classified as not related, related.

17.1.3. Adverse Events with an Outcome of Death

AEs with an outcome of death are those events which are recorded as "Fatal" on the AE page of the eCRF. A summary of AEs with an outcome of death by SOC and PT will be prepared.

A listing of all AEs with an outcome of death will be provided.

17.1.4. Serious Adverse Events

SAEs are those events recorded as "Yes" for the question "Serious Event?" on the AE page of the eCRF.

SAEs post the first study intervention, including exposure adjusted rates, will be summarized by SOC and PT by cohort. Specific SAEs will be counted once for each participant for calculating percentages. If the same SAE occurs multiple times within a particular participant, the highest severity observed will be reported. A summary of related SAEs post the first study intervention, including exposure adjusted rates, will be presented by SOC and PT by cohort as well.

A listing of all SAEs will be provided. For SAEs with partial dates, if the known part of the date indicates that SAE stopped before the first study intervention, it will be considered as SAE prior to the first study intervention. Otherwise, it will be considered as SAE post the first study intervention.

CCI

[redacted]

17.1.5. AEs Leading to Discontinuation of Study Intervention

AEs leading to discontinuation of study intervention are those events recorded as "Drug Withdrawal" for the question "Action Taken with study treatment" on the AE pages of the eCRF. A summary of AEs leading to discontinuation of study intervention by SOC and PT will be prepared.

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

17.1.6. AEs Leading to Discontinuation of Study

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

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

17.1.7. COVID-19 Related AEs

A summary of AEs related to COVID-19 by SOC and PT by cohort will be prepared, including exposure adjusted rates.

A listing of all AEs related to COVID-19 will be provided.

17.1.8. Adverse Events of Special Interest

AESIs are events of scientific and medical interest specific to the further understanding of study intervention safety profile and require close monitoring and rapid communication by the investigators to the Sponsor. AESIs for AZD1222 are based on Brighton Collaboration case definitions (SPEAC 2020), clinical experience, and scientific interest. See APPENDIX 7 for a listing and description of AZD1222 AESIs.

AESIs will be recorded from Day 1, post first study intervention, through the last participant's contact. A summary of AESIs by categories and sub-categories listed in APPENDIX 7 and PT and by cohort will be prepared, including exposure adjusted rates. The summary will also include the number and percentage of participants with any neurologic and/or neuroinflammatory AESIs. Should a participant experience multiple events within a category or PT, the participant will be counted only once for that category or PT. A summary of related AESIs by category and PT will also be prepared, including exposure adjusted rates. A summary of AESIs by severity grade (Grade 1, Grade 2 and Grade >=3) and a summary of related AESIs by severity grade will be prepared.

CCI

[redacted]

A listing of all AESIs including those prior to the first vaccination will be provided.

17.1.9. Medically Attended Adverse Events

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

A summary of MAAEs by SOC and PT by cohort will be prepared, including exposure adjusted rates. Should a participant experience multiple events within a SOC or PT, the participant will be counted only once for that SOC or PT.

A listing of all MAAEs will be provided.

17.1.10. Vascular Disorders of Embolism and Thrombosis

A summary of Vascular Disorders of Embolism and Thrombosis events by PT by cohort will be prepared, including exposure adjusted rates.

17.2. Solicited Adverse Events

Solicited AEs are local or systemic predefined AEs for reactogenicity assessment. Solicited AEs will be collected in a Solicited AE eDiary for 7 days following each dose of AZD1222. The set of solicited AEs associated with reactogenicity are presented below:

Local	Systemic
Pain at the site of injection	Fever (> 100°F [> 37.8°C])[a]
Erythema/redness at the site of injection[b]	Chills
Tenderness	Muscle pains
Induration/swelling at the site of injection[b]	Fatigue
	Headache
	Malaise
	Nausea
	Vomiting

[a]Fever measured by any route. Investigators who consider a temperature lower than this cut-off as a fever or a 'fever' reported by participants

CCI

[redacted]

without documentation by a thermometer should record the event as 'elevated body temperature'.
[b]Swelling and redness must be ≥ 0.6 centimetres in diameter.

Severity will be assessed for solicited AEs by the participant according to toxicity grading scales modified and abridged from the FDA grading guidance (FDA, 2007). The measurements of the longest part of redness and swelling of injection sites will also be collected. These measurements will be used to derive severity grades based on the criteria presented in APPENDIX 3. Severity grading for systemic solicited AE, i.e., fever are derived based on criteria presented in APPENDIX 4. Because solicited AEs are expected to occur after vaccination, they will not be assessed for relationship to study intervention.

Solicited AEs for 7 days following each dose of study intervention will be summarized for each dose and overall. Each solicited AE will be summarized at the following time intervals: Days 1-8, and daily during the intervals Day 1 to Day 8. For each time interval, the count and percentage of participants will be determined for each of the following categories: participants evaluated, participants without any events, participants with any event, mild events, moderate events, severe events, and potentially life-threatening events. Participants should not be double counted; therefore, the event of greatest severity will be used for participants with more than 1 episode of the same event. Similar counts and percentages will be presented for solicited local AEs and solicited systemic AEs.

Quantitative and categorical summary of the day of first onset of each event and the number of days participants reported experiencing each event will be presented. The number of days a participant reported experiencing an event is calculated as the total of all days the participant reported the event, regardless of whether the symptom was reported on consecutive days (e.g., a headache reported on Day 1, Day 3, and Day 4 would be included with a duration of 3 days).

A listing of all solicited AEs will be provided.

17.3. DEATHS

If any participants die during the study as recorded on the "Death Details" page of the eCRF, a listing of all deaths due to all causes will be provided.

17.4. LABORATORY EVALUATIONS

For women participants of childbearing potential, a urine sample for pregnancy testing will be collected at screening and before each vaccination. Chemistry, hematology and coagulation tests will be performed as per the schedule of

events (refer to protocol, Section 1.3). A list of laboratory parameters to be included in the outputs is included in APPENDIX 8.

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

The following summaries will be provided by cohort based on the SAF analysis set for each of chemistry, hematology and coagulation laboratory parameters:

- Observed and change from baseline in Standard International (SI) units by visit;
- Shift from baseline to the worst post-baseline observed value according to the FDA toxicity grades (for quantitative parameters with available FDA toxicity grades; refer to Section 17.4.1)
- Listing of subjects with at least one laboratory observed value meeting a FDA toxicity grade ≥ 3 (for quantitative parameters with available FDA toxicity grades; refer to Section 17.4.1)
- Shifts from baseline to the maximum/minimum post-baseline observed value according to normal range criteria (for quantitative parameters without FDA toxicity grades; refer to Section 17.4.2);
- Listing of subjects with at least one abnormal laboratory observed value outside the normal range criteria (for quantitative parameters without FDA toxicity grades; refer to Section 17.4.2);
- Maximum post-baseline ALT/AST observed value categorized as < 3 x upper limit of normal (ULN), ≥ 3 to < 5 x ULN, ≥ 5 to < 10 x ULN or ≥ 10 ULN by maximum post-baseline total bilirubin observed value categorized as < 2 x ULN or ≥ 2 x ULN;
- Scatter plots of the maximum post-baseline observed value in ALT value by the maximum post-baseline observed value in TBL value, both expressed as multiple of ULN;
- Scatter plots of the maximum post-baseline observed value in AST value by the maximum post-baseline observed value in TBL value, both expressed as multiple of ULN;
- A listing of subjects with at least one observed value in ALT value > 3 x ULN, AST value > 3 x ULN or TBL value ≥ 2 x ULN will be provided.

All laboratory data will be listed.

CCI

17.4.1. FDA Toxicity Grades

Quantitative laboratory parameters with available FDA toxicity grades (FDA, 2007) will be categorized as follows where higher grades representing a more severe toxicity (refer to APPENDIX 9 for each parameter toxicity grade criteria):

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

Although not defined in the FDA toxicity grading system, 2007, non-missing laboratory parameter results not meeting any of the 4 grades defined in the FDA toxicity grading system will be categorized as 'No Event' for the purpose of the shift from baseline summaries.

17.4.2. Laboratory Normal Ranges

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

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

17.5. Vital Signs

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

- Systolic blood pressure (SBP) (mmHg)
- Diastolic blood pressure (DBP) (mmHg)

CCI [redacted]

- Heart rate (beats per minute [bpm])
- Oxygen saturation (%)
- Body temperature (^{0} C)

The severity grade of abnormal Vital Signs can be referred to APPENDIX 4.

The following summaries will be provided by cohort based on the SAF analysis set for each vital sign parameter:

- Observed and change from baseline by visit
- Number and percentages of subjects with at least one abnormal post-baseline observed value (refer to APPENDIX 4)
- Listing of subjects with at least one abnormal observed value (refer to APPENDIX 4)

All vital sign data will be listed.

17.6. PHYSICAL EXAMINATION

17.6.1. GENERAL PHYSICAL EXAMINATION

Physical examinations will be conducted as per the schedule of events (refer to protocol Section 1.3. Clinically significant findings at screening will be recorded on the Surgical and Medical History page of the eCRF while clinically significant changes from screening will be recorded on the AEs page of the eCRF for the post-screening visits. Hence, clinically significant findings/changes will be summarized though the Surgical and Medical history summary (refer to Section 11), concomitant illnesses (refer to Section 12) or AE summaries (refer to Section 17.1), as appropriate. That is, no summaries will be specifically provided for the general physical examination.

All physical examination data will be listed.

18. OTHER ANALYSIS

18.1. PREGNANCY TEST AND REPORT

Pregnancy tests and pregnancy report, if any, will be presented in the listings for the PAS.

18.2. TEST FOR ANTIBODY AGAINST SARS-COV-2 (LATERAL FLOW TEST)

Data collected for lateral flow tests performed at screening and any unscheduled visits will be presented in a listing for the PAS.

18.3. HOSPITALIZATION

Data collected for hospitalization will be presented in a listing for the SAF analysis set.

18.4. VIROLOGICALLY CONFIRMED (RT-PCR POSITIVE) SYMPTOMATIC CASES OF COVID-19

Data collected for COVID Symptom Assessments will be presented in a listing for the SAF analysis set.

18.5. THROMBOSIS IN COMBINATION WITH THROMBOCYTOPENIA

Data collected relating to thrombosis in combination with thrombocytopenia may be listed based on emerging data.

19. DATA NOT SUMMARIZED OR PRESENTED

Data that will not be summarized or listed are:

- Comments

CCI [redacted]

These data will not be summarized or listed but will be available in the Study Data Tabulation Model (SDTM) and/or Analysis Dataset Modelling (ADaM) datasets.

20. REFERENCES

US Food and Drug Administration. "Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials." Food and Drug Administration, US Department of Health and Human Services (2007).

APPENDIX 1. PARTIAL DATE CONVENTIONS

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS

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

CCI

START DATE	STOP DATE	ACTION
Partial	Known or ongoing	If medication stop date < study intervention start date, assign as prior; If (known components of medication start date show that medication started before study intervention start date) and (medication stop date ≥ study intervention start date or medication is ongoing at study intervention start date), assign as concomitant; If known components of medication start date show that medication started on or after study intervention start date, assign as concomitant.
	Partial	If known components of medication stop date show that medication stopped before study intervention start date, assign as prior; If (known components of medication start date show that medication started before study intervention start date) and (known components of medication stop date show that medication stopped on or after study intervention start date), assign as concomitant; If known components of medication start date show that medication started on or after study intervention start date b, assign as concomitant.
	Missing, not ongoing	Cannot be assigned as prior; If known components of medication start date show that medication started before study intervention start date, assign as concomitant; If known components of medication start date show that medication started on or after study intervention start date, assign as concomitant.
Missing	Known or ongoing	If medication stop date < study intervention start date, assign as prior; If medication stop date >= study intervention start date or medication is ongoing at study intervention start date, assign as concomitant.

CCI

[redacted]

START DATE	STOP DATE	ACTION
	Partial	If known components of medication stop date show that medication stopped before study intervention start date, assign as prior; If known components of medication stop date show that medication stopped on or after study intervention start date, assign as concomitant.
	Missing, not ongoing	Assign as concomitant.

APPENDIX 2. PROGRAMMING CONVENTIONS FOR OUTPUTS

DATES & TIMES

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

SPELLING FORMAT

English US.

PAPER SIZE, ORIENTATION, AND MARGINS

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

FONTS

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

PRESENTATION OF COHORTS

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

CCI

[redacted]

Cohort	Tables and Graphs	Listings
Solid organ transplant	1	1
Hematological stem cell transplant	2	2
Solid organ cancer patients receiving cytotoxic chemotherapy	3	3
Chronic inflammatory disorders	4	4
Primary immunodeficiency	5	5
Immunocompetent	6	6
Total [1]	7	n/a
Randomized, Not Vaccinated	n/a	7
Screen Failure	n/a	8

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

PRESENTATION OF NOMINAL VISITS

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

Long Name (default)	Short Name
Screening	Scrn
Baseline	Base
Visit 1	V1
Visit 1 + 7 days	V1+7
Visit 1 + 14 days	V1+14
Visit 1 + 21 days	V1+21

CCI

Long Name (default)	Short Name
Visit 1 + 28 days	V1+28
Visit 5 + 7 days	V5+7
Visit 5 + 14 days	V5+14
Visit 5 + 28 days	V5+28
Visit 8 + 7 days[a]	V8+7[a]
Visit 8 + 28 days[a]	V8+28[a]
Visit 1 + 182 days	V1+182
Visit 9 + 28 days[b]	V9+28[b]
Visit 1 + 364 days	V1+364

a Only applicable for immunocompromised cohorts
b Only applicable for immunocompetent participants

DESCRIPTIVE STATISTICS

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

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

PERCENTAGES

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

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

CCI [redacted]

LISTINGS

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

- Cohort
- Participant ID;
- Parameter, when applicable;
- Date/Time, when applicable.
- Timepoint, when applicable

APPENDIX 3. CLINICAL ABNORMALITIES: LOCAL REACTIONS TO INJECTABLE PRODUCT

Local Reaction to Injectable Product	Reaction Grade			
	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/redness [a, b]	1-2 inches (2.5–5 cm)	> 2-4 inches (5.1–10 cm)	> 4 inches (> 10 cm)	Necrosis or exfoliative dermatitis
Induration/swelling [a, b]	1-2 inches (2.5–5 cm)	> 2-4 inches (5.1–10 cm)	> 4 inches (> 10 cm)	Necrosis

a. In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable. Reactions < 0.25 inches (< 0.6 centimetres) in diameter will not be recorded.

b. Grade 4 erythema or induration is determined by study site with participant input rather than being recorded directly in Solicited AE eDiary.

ER: emergency room.

APPENDIX 4. CLINICAL ABNORMALITIES: VITAL SIGNS

Vital Sign	Vital Signs Grade			
	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)a
Fever (°C/°F)	37.9-38.4 100.1-101.1	38.5-38.9 101.2-102.0	39.0-40 102.1-104	> 40 > 104
Tachycardia (beats/minute)	101-115	116- 130	> 130	Emergency room visit or hospitalization for arrhythmia
Bradycardia (beats/minute)	50-54	45-49	< 45	Emergency room visit or hospitalization for arrhythmia

CCI

Hypertension; systolic (mm Hg)	141-150	151-155	> 155	Emergency room visit or hospitalization for malignant hypertension
Hypertension; diastolic (mm Hg)	91-95	96-100	> 100	Emergency room visit or hospitalization for malignant hypertension
Hypotension; systolic (mm Hg)	85-89	80-84	< 80	Emergency room visit or hospitalization for hypotensive shock
Respiratory rate (breaths/minute)	17-20	21-25	> 25	Intubation

Grade 4 vital signs other than fever are reported as adverse events. Use clinical judgment when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.

APPENDIX 5. CLINICAL ABNORMALITIES: SYSTEMIC (GENERAL OR ILLNESS)

Systemic (General)	Systemic Grade [a]			
	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Nausea/ vomiting	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, required outpatient intravenous hydration	Emergency room visit or hospitalization for hypotensive shock
Chills	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalization
Systemic Illness				

CCI

[redacted]

Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring intervention	Prevents daily activity and required medical intervention	Emergency room visit or hospitalization

APPENDIX 6. COVID-19 QUALIFYING SYMPTOMS

Participant must present with at least one of the following symptoms to qualify for clinical COVID-19 testing	
Duration	**Symptom**
No minimum duration	Fever
	Shortness of breath
	Difficulty breathing
Must be present for ≥ 2 consecutive days	Chills
	Cough
	Fatigue
	Muscle aches
	Body aches
	Headache
	New loss of taste
	New loss of smell
	Sore throat
	Congestion
	Runny nose
	Nausea
	Vomiting
	Diarrhoea

Adapted from (CDC 2020)

CCI

[redacted]

APPENDIX 7. ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest for this study are based on Brighton Collaboration case definitions (SPEAC 2020), clinical experience, and scientific interest. There is no current evidence to suggest that AZD1222 is associated with these AEs of special interest.

Category	Medical Concept
Neurologic	Generalized convulsion: episodes of neuronal hyperactivity most commonly resulting in sudden, involuntary muscular contractions. They may also manifest as sensory disturbances, autonomic dysfunction and behavioural abnormalities, and impairment or loss of consciousness.
	Guillain-Barré syndrome: a peripheral nerve demyelinating disease, which can present as temporary ascending paralysis.
	Acute disseminated encephalomyelitis: defined as a uniphasic syndrome of brain inflammation and demyelination occurring in temporal association with an antecedent immunologic challenge, such as infection or an immunization. ADEM most commonly occurs in the paediatric population.
	Other neurologic events: include new onset event (acute or subacute) motor and sensory disturbances (e.g. weakness, numbness, paraesthesia, hypoesthesia, hyperesthesia, dysesthesias), bowel/bladder dysfunction, gait impairment, or visual disturbance, or any event of myelitis, encephalomyelitis, myelitis transverse, or other sudden neurological deficit.
Vascular	Thrombotic, thromboembolic, and neurovascular events: events that can manifest as transient or permanent vision problems, dizziness, trouble understanding, facial droop, slurred speech, unilateral weakness, deep vein thrombosis with swollen, warm or painful leg, pulmonary embolism with shortness of breath, chest pain or irregular heart rate.
Hematologic	Thrombocytopenia: a disorder in which there is an abnormally low platelet count; a normal platelet count ranges from 150 000 to 450 000 platelets per µL.
Immunologic	Vasculitides: a group of related disorders characterized by inflammation of blood vessels (vasculitis) leading to tissue or end-organ injury.
	Anaphylaxis: an acute hypersensitivity reaction with multi-organ-system involvement that can present as, or rapidly progress to, a severe life-threatening reaction requiring immediate medical attention.
	Vaccine-associated enhanced respiratory disease: pathogenicity has been linked to a vaccine immune response characterized by induction of non- neutralizing antibodies, and a T-cell response of the Th2 type with hypereosinophilia. VAERD may manifest as a severe form of respiratory disease with prolonged fever, and diverse clinical manifestations of disease severity and pathological changes marked by increased areas of lung consolidation, broncho-interstitial pneumonia, and necrotizing bronchiolitis.
	Potential immune-mediated conditions: a group of autoimmune inflammatory disorders characterized by an alteration in cellular homeostasis, which may or may not have an autoimmune aetiology.

CCI

[redacted]

Cardiovascular system	Myocarditis and pericarditis. Other forms of acute cardiac injury including arrhythmias, heart failure, coronary artery disease, myocardial infarction, stress cardiomyopathy.
Renal	Acute kidney injury.
Gastrointestinal	Acute liver injury. Acute pancreatitis.
Musculoskeletal system	Aseptic arthritis. Rhabdomyolysis.
Skin	Erythema multiforme. Chilblain-like lesions.
Other system	Anosmia, ageusia.

ADEM = acute disseminated encephalomyelitis; GBS = Guillain-Barré syndrome; VAERD = vaccineassociated enhanced respiratory disease.

APPENDIX 8. LABORATORY ASSESSMENTS

Chemistry (SI unit)

- Alkaline phosphatase (ALP) (U/L)
- Alanine transaminase (ALT) (U/L)
- Aspartate transaminase (AST) (U/L)
- Creatinine (µmol/L)
- Total bilirubin (µmol/L)

Hematology (SI unit)

- Hemoglobin (g/L)
- Leukocyte differential count (absolute count)
- Leukocyte count
- Platelet count (x10E9/L)

Coagulation (SI unit)

- Prothrombin time (PT) (s)
- Fibrinogen (g/L)

CCI [redacted]

- Activated partial thromboplastin time (s)
- D-dimer (µg/L DDU)

CCI

[redacted]

APPENDIX 9. FDA LABORATORY ABNORMALITY SEVERITY GRADE CRITERIA (2007)

Variable	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Haemoglobin Absolute Decreased (male)	g/L	125-135	105-124	85-104	<85
Haemoglobin Absolute Decreased (female)	g/L	110-120	95-109	80-94	<80
Haemoglobin Decrease from Baseline	g/L	1-15	16-20	21-50	>50
White Blood Cells-Elevated	cells x 10^9/L	10.8-15	>15-20	>20-25	>25
White Blood Cells-Decreased	cells x 10^9/L	2.5-3.5	1.5-2.49	1.0-1.49	<1.0
Platelets-Decreased	cells x 10^9/L	125-140	100-124	25-99	<25
Neutrophils-Decreased	cells x 10^9/L	1.5-2.00	1.0-1.49	0.5- 0.99	<0.50
Lymphocytes-Decreased	cells x 10^9/L	0.750-1.000	0.500-0.749	0.250-0.499	<0.250
Eosinophils-Elevated	cells x 10^9/L	0.650-1.500	1.501-5.000	>5.000	Hypereosinophilic
Creatinine-Elevated (converted from mg/dL)	mg/dL (µmol/L)	1.5-1.7 (133-154)	1.8-2.0 (155-181)	2.1-2.5 (182-221)	>2.5 (>221) or requires dialysis
Bilirubin-Elevated (with normal ALT/ALP)	µmol/L	1.1-1.5 × ULN	1.6-2.0 x ULN	2.0-3.0 × ULN	>3.0 × ULN

CCI

[redacted]

Bilirubin-Elevated (with abnormal ALT/ALP)	µmol/L	1.1-1.25 × ULN	1.26-1.5 × ULN	1.51-1.75 × ULN	>1.75 × ULN
Alanine Transaminase-Elevated	U/L	1.1-2.5 x ULN	2.6-5 × ULN	5.1-10 × ULN	>10 × ULN
Alkaline Phosphate-Elevated	µmol/L	1.1-2.0 × ULN	2.1-3.0 × ULN	3.1-10 × ULN	>10 × ULN
Aspartate Transaminase-Elevated	U/L	1.1-2.5 x ULN	2.6-5 × ULN	5.1-10 × ULN	>10 × ULN
Prothrombin Time	seconds	1.0-1.10 x ULN	1.11-1.20 x ULN	1.21-1.25 x ULN	>1.25 ULN
Activated Partial Thromboplastin Time	seconds	1.0-1.2 x ULN	1.21-1.4 x ULN	1.41-1.5 x ULN	>1.5 x ULN
Fibrinogen Increase	mg/dL	400-500	501-600	>600	-
Fibrinogen Decrease	mg/dL	150-200	125-149	100-124	<100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

CCI

[redacted]

STATISTICAL ANALYSIS PLAN ADDENDUM

D8111C00010

A PHASE IV OPEN-LABEL, NON-RANDOMIZED, MULTI-COHORT, MULTICENTER STUDY IN PREVIOUSLY UNVACCINATED IMMUNOCOMPROMISED ADULTS TO DETERMINE THE IMMUNOGENICITY AND SAFETY OF AZD1222 VACCINE FOR THE PREVENTION OF COVID-19

AUTHOR: PPD

VERSION NUMBER AND DATE: V1.0, 26MAY2023

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Version
1.0	26MAY2023	PPD	N/A

CCI

ADDENDUM

This statistical analysis plan (SAP) addendum describes the changes to planned analyses following the early termination for protocol D8111C00010. It describes the reduced set of analyses and data that will no longer be summarized, and specifics of further changes made to analyses. This SAP addendum is based on protocol version 4.0, dated 31Mar2022 and SAP version 2.0, dated 26May2023.

Due to early termination of the study, the sample size is much lower than planned, especially in the immunocompromised cohorts, limiting the interpretability of analyses both within and between individual cohorts.

The following changes will be made to analyses as a result of the early termination of the study:

- Only final analysis will be performed
- Immunocompromised cohorts will be pooled for summaries
- The following analyses will not be performed:
    - Model-adjusted immunogenicity analyses
    - Subgroup analyses or between arm comparisons
    - All by-visit summary tables
    - Participant enrollment by country and site summaries
    - Important protocol deviation summaries
    - Surgical and medical history outputs
    - Concomitant illnesses and medications outputs
    - Report of overdose and medication error listing
    - Compliance with study drug summary
    - Immunogenicity figures, pairwise correlations between assays and other selected outputs
    - Cell-mediated immune response outputs

- All adverse event outputs except an overall summary, unsolicited AE summary by system organ class and preferred term, solicited adverse event summary, and associated listings
- Vascular disorders of embolism and thrombosis summary
- Laboratory evaluations outputs excluding the listing of lab results
- Vital signs outputs
- Physical examinations listing
- Pregnancy tests and reports
- Lateral flow tests
- Hospitalizations
- COVID symptom assessments
- Thrombosis in combination with thrombocytopenia summaries

For all other information please refer to the main study SAP.

PPD

In Person Signer Events	Signature	Timestamp
Editor Delivery Events	**Status**	**Timestamp**
Agent Delivery Events	**Status**	**Timestamp**
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**
Envelope Summary Events	**Status**	**Timestamps**
Envelope Sent	Hashed/Encrypted	5/26/2023 7:53:51 AM
Certified Delivered	Security Checked	5/26/2023 7:54:03 AM
Signing Complete	Security Checked	5/26/2023 7:54:27 AM

Envelope Summary Events	Status	Timestamps
Completed	Security Checked	5/26/2023 7:54:27 AM

Payment Events	Status	Timestamps

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: AZD1222_D8111C00010_SAP_26May2023		
Document Title:	D8111C00010 Statistical Analysis Plan Edition 2	
Document ID:	CCI [redacted]	
Version Label:	1.0 CURRENT LATEST APPROVED	
Server Date (dd-MMM-yyyy HH:mm 'UTC'Z)	**Signed by**	**Meaning of Signature**
26-May-2023 17:01 UTC	PPD [redacted]	Content Approval
26-May-2023 17:29 UTC	PPD [redacted] CYTEL	Author Approval
26-May-2023 15:59 UTC	PPD [redacted] (IQVIA)	Author Approval

CCI [redacted]