STATISTICAL ANALYSIS PLAN

D8111C00002

A PHASE I/II RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED MULTICENTRE STUDY IN PARTICIPANTS AGED 18 YEARS OR OLDER TO DETERMINED THE SAEFTY AND IMMUNOGENICITY OF AZD1222, A NON-REPLICATING CHADOX1 VECTOR VACCINE, FOR THE PREVENTION OF COVID-19

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VERSION NUMBER AND DATE: V3.0, 9DEC2021

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan v3.0 (dated 9Dec2021) for protocol D8111C00002.

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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.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Version
1.0	29Oct2020	PPD	Not Applicable – First Version
1.1	28Dec2020	PPD	Section 1 - Updated protocol version. Section 2.2 - Added the objective to assess antibody responses to AZD1222 RBD antigen. Section 3.3 - Removed previously added items, and updated this to 'There is no changes to the analyses planned in the protocol'. Section 4.3 to Section 4.5 - Updated the defintions for primary and final analyses. - Added a additional analysis. Section 7.1 - Updated this section as per latest protocl amendment update. Section 9.1 - Added new analyses of: number of participants with at least 28 days follow-up

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			post 1st dose; number of participants who received 1st dose and discontinued from study intervention and discontinued from study, or remained in study follow up or completed study. Section 16.2.1 -Updated the calculation of GMT and GMFR to be based on log base 2 transformation of titer. Section 17.1.2.3 - Added a new analysis of AESIs by relationship to study intervention. APPENDIX 4 - The lower bound of mild fever is updated from 38.0 °C to 37.9 °C.
1.2	18Jan2021	PPD	Section 3.1 - Added a brief description for timing of primary analysis. Section 3.3 - Solicited AEs to be analyzed between Day 1-7 and Day 29 – 35. Section 16.1.3 - Added a definition for *P* used in hypotheses. Section 17.1.2.4 - Updated analysis for solicited AEs to be

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			presented for 7 days. Section 17.5 - Updated section title from 'Other Safety Assessments' to 'Immunologic Responses'.
2.0	20Jan2021	PPD	Section 1 - Updated the protocol amendment date. Section 17.5.1 - Updated sub-header to 'Neutralizing Antibodies: Immunoglobulins G and M'.
2.1	4Nov2021	PPD	Section 1 - Added text to explain that updates to this latest version apply to Final Analysis. Section 7.10, Section 16.2.5, Section 16.3.4 and Section 17.1.1.3 - Added new sections to explain data handling for subjects who were inoculated with non-study COVID-19 vaccine. Section 16.3.1.1 - Added a new censor derivation for subjects who were inoculated with non-study COVID-19 vaccine. Various sections - Added a paragraph to explain whether the analysis will be included in the Final Analysis.

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2.2	9Nov2021	PPD	Section 17.1.1.3 Added new AE analyses for subjects who were inoculated with non-study COVID-19 vaccine that only include AE data that started post inoculation of non-study COVID-19 vaccination.
3.0	9Dec2021	PPD	Final version

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1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of efficacy (including immunogenicity) and safety data for protocol D8111C00002. 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 3, dated 18 January 2021.

This SAP is updated post Primary and Additional Analyses, and prior to database lock for the Final Analysis. All changes made to this version of the SAP are marked in italics.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVES

The primary objectives are:

- To assess antibody responses to AZD1222 Spike antigen following 2 intramuscular (IM) doses of AZD1222 or placebo.
- To assess the safety, tolerability, and reactogenicity profile of the candidate vaccine AZD1222.

2.2. SECONDARY OBJECTIVES

The secondary objectives are:

- To assess antibody responses to AZD1222 receptor-binding domain (RBD) antigen following 2 IM doses of AZD1222 or placebo.
- To assess time course of antibody to AZD1222 Spike and RBD antigens of AZD1222 (Meso Scale Discovery [MSD] serology assay).
- To assess the function of neutralizing antibody (nAb) against severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) spike protein.

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- To assess the safety of the candidate vaccine AZD1222.

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives are:

- To describe occurrence of symptomatic Coronavirus Disease 2019 (COVID-19) in recipients of AZD1222 and placebo.
- To describe occurrence of severe COVID-19 and seroresponse to non-Spike SARS-CoV-2 antigens.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a multicentre, randomised, double-blind, parallel-group, placebo-controlled, 52-week Phase I/II study. In this study, 256 eligible participants will be randomised in a 3:1 ratio to receive 2 IM doses of either AZD1222 with 5×10^{10} viral particles (vp) (nominal) or placebo administered 4 weeks apart.

The study has 2 cohorts with different age populations. Cohort C will include healthy participants aged 18 to 55 years. Cohort D will include healthy elderly participants aged ≥ 56 years. In Cohort D, the elderly population is further divided into 2 different age subgroups; aged 56 to 69 years (Subcohort D1) and aged ≥ 70 years (Subcohort D2). At least 30% of participants in Cohort D will be secured for participants with age ≥ 70 years. Regarding Cohorts C and D, 128 participants will be randomised in a 3:1 ratio to receive either AZD1222 or placebo within each cohort.

After completion of clinical data lock for primary analysis, 57 days after first vaccination and 28 days after second vaccination, the study will become single blind, where only participants are blinded from allocation of investigational product. All participants will be unblinded and participants on the placebo arm may be vaccinated when a licensed vaccine for COVID-19 becomes available in Japan for the general population.

Table A: Study Design

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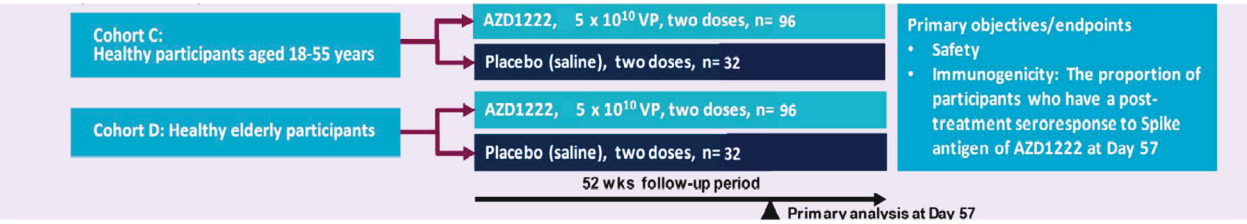

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in protocol Section 1.3.

3.3. CHANGES TO ANALYSES FROM PROTOCOL

It is defined in protocol that the incidence of local and systemic solicited reactogenicity signs and symptoms are to be collected for 7 days following throughout vaccination from Day 1 to 8 and Day 29 to 36. This has been updated in Section 17.1.2.4 to present solicited AEs collected in eDiary for 7 days, from Day 1 to 7 and Day 29 to 35. Date of agreement of change is 15 Jan 2021, during meeting discussion between IQVIA and AstraZeneca statistical team.

4. PLANNED ANALYSES

4.1. DATA MONITORING COMMITTEE

There will be no Data Monitoring Committee for this study.

4.2. INTERIM ANALYSIS

There will be no interim analysis for this study.

4.3. PRIMARY ANALYSIS

The primary analysis will include immunogenicity data up to Day 57 from participants enrolled before the study

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interruption and safety data gathered in all participants up to Day 57.

All planned primary analyses identified in this SAP (exept for exploratory efficacy analysis, which will only be performed at final analysis) will be performed by IQVIA Biostatistics following Sponsor authorization of this SAP, Sponsor authorization of the analysis sets, clinical data lock, and general study unblinding.

4.4. Additional Analysis

The additional analysis will include immunogenicity data in all participants up to Day 57.

Immunogenicity analyses performed at primary analysis will be repeated for all participants up to Day 57. These analyses will be performed by IQVIA Biostatistics. The Sponsor authorization of the SAP, Sponsor authorization of the analysis sets, clinical data lock, and general study unblinding will be performed at primary analysis and not at the timing of additional analysis.

4.5. Final Analysis

The final analysis will include all endpoints up to Day 365 in all participants.

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 clinical data lock.

5. Analysis Sets

5.1. All Participants Analysis Set

The all participants analysis set will contain all participants screened who signed informed consent form for the study, to be used for reporting disposition and screening failures.

5.2. Total Vaccinated Analysis Set

The total vaccinated analysis set (TVS) will contain all participants who received at least one dose of study intervention. Erroneously vaccinated participants (eg, those randomised to placebo treatment but were actually given

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active vaccine treatment) are accounted for in this analysis set by assigning them to the treatment they actually received.

This analysis set will be used for the analysis of safety, exploratory efficacy and immunogenicity endpoints.

5.3. *Fully Vaccinated Analysis Set for Immunogenicity*

The fully vaccinated analysis set (FVS) for immunogenicity will include all participants in the TVS who have received two doses of study intervention and have no important protocol deviations judged to have the potential to interfere with the generation or interpretation of immune responses. Protocol deviations will be reviewed by the study team before unblinding to determine exclusion from the immunogenicity. Participants who have a post-baseline seroresponse (≥ 4 fold rise in titers from Day 1 baseline value) to nucleocapsid antibodies by MSD serology assay at post-baseline up to Day 57 will be excluded from this analysis set.

This analysis set will be used for the analysis of immunogenicity endpoints.

5.4. *Fully Vaccinated Analysis Set for Efficacy*

The fully vaccinated analysis set (FVS) for efficacy will include all participants in the TVS who have received two doses of study intervention, and who remain on-study 15 days after their second dose without having had a prior SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) positive confirmed COVID-19 infection.

This analysis set will be used for applicable exploratory endpoints.

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

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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, AND EARLY TERMINATION DATA

For by-visit summaries, data recorded at the nominal visit will be presented. That is, unscheduled, 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). An exception to this rule applies to immunogenicity analysis as stated in Section 6.4.

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

6.4. WINDOWING CONVENTIONS

A windowing convention will be used to determine the analysis value for a given study visit for immunogenicity data analyses. The window conventions are:

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1. A window of +/- 7 days from the target day is applied to the following visits: Study Days 15, 29, 43, 57 (for Day 29, the date and time of second dose of study intervention can be used as upper bound);

2. A window of +/- 30 days from the target day is applied to the following visits: Study Day 183 and Day 365;

Table B: Analysis windows for immunogenicity by visit

Dosing Period	Visit	Day Relative to Dose within the Dosing Period [b]	Visit Window (Study Day) Relative to the Dosing Period
Period 1 (Relative to Dose 1)	Baseline [a]	≤ 1	≤ 1
	Day 15	15	8 - 21
	Day 29	29	22 - 35
Period 2 (Relative to Dose 2)	Day 43	15	8 - 21
	Day 57	29	22 - 35
	Day 183	155	125 - 185
	Day 365	337	307 - 367

(a) Where time is available, the time of the collection must be prior to the first dose of study intervention. Day 1 observations taken after the first dose are considered post-baseline values.
(b) 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.

One or more results for a particular immunogenicity 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.

Beside the 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:

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

7. STATISTICAL CONSIDERATIONS

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

group and visit, when applicable.

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

7.1. SAMPLE SIZE CALCULATION

Regarding Cohort C, 128 participants will be randomised in a 3:1 ratio to receive either AZD1222 or placebo. Regarding Cohort D, in a similar way, 128 participants will be randomised in a 3:1 ratio to receive either AZD1222 or placebo, but participants will be stratified at randomisation by age group (i.e., Subcohorts D1 vs D2). At least 30% of participants in Cohort D will be secured for participants with age ≥ 70 years.

These sample sizes (96 for AZD1222 versus 32 for placebo) were determined mainly for safety evaluation and based on feasibility. With the sample size of 96 participants in the AZD1222 treatment arm in each cohort, at least 1 participant with an AE of incidence rate of 2.5% can be detected with probability of about 90%. The placebo arm is needed for securing the objectivity of the safety evaluation of the AZD1222 arm and it is also needed as a control for evaluating immunogenicity as stated below. For these purposes, the minimum sample size was given to the placebo arm (1/3 of the AZD1222 arm).

It is difficult to calculate an accurate sample size necessary for comparing the proportion of participants who have a seroresponse to SARS-CoV-2 spike protein between the AZD1222 and placebo arms because of insufficient information on immunogenicity in both arms at the moment. It is expected that the minimum number of participants per cohort will be about 36. Under a slightly conservative assumption about seroresponse rates of 10% assumed on placebo and over 75% on AZD1222, it is expected that the sample size of 36 (27 for AZD1222 vs 9 for placebo) will provide 93% power for showing the superiority of seroresponse of the AZD1222 treatment compared with placebo based on Fisher's exact test at 2-sided 5% alpha.

7.2. MISSING DATA

Missing efficacy data (including immunogenicity data) and safety data will not be imputed.

Partial or completely missing medication/medical history/concomitant illnesses/related procedures dates will be handled as described in APPENDIX 1.

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7.3. STATISTICAL TESTS

All statistical tests will be conducted at the two-sided 5% significant level, unless otherwise specified in the description of the analyses. Confidence Intervals (CIs) will be two-sided with 95% coverage.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

Given the exploratory nature of this study, no adjustment for multiple comparisons and multiplicity will be performed. That is, only nominal p-values will be provided for the immunogenicity endpoints.

No statistical testing will be performed for the safety endpoints.

7.5. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers in Japan. 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. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

No adjustments for covariates and factors are to be consiered for the analyses.

7.7. EXAMINATION OF SUBGROUPS

Subgroup analyses will be conducted as stated in Section 16.2.1, Section 16.2.2 and Section 17.1.2.1.

The subgroups are:

- Baseline Body Mass Index (BMI) group (<30 kg/m^2 and ≥ 30 kg/m^2), derivation of BMI given in Section 10.1;
- Gender (male and female).

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7.8. ANALYSIS BY COHORT

All analyses will be presented by Cohorts C and D, and Subcohorts D1 and D2, and total participants of Cohort C plus Cohort D, unless otherwise specified. Within each cohort, the analysis of AZD1222 and placebo will also be presented, unless otherwise specified.

For disposition, demographic, baseline characteristics, medical history, concomitant illnesses, related procedures, prior and concomitant medication, and exposure, the analysis summary will be presented with AZD1222, placebo and overall.

7.9. SOFTWARE VERSION

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

7.10. SUBJECTS WHO WERE INOCULATED WITH NON-STUDY COVID-19 VACCINE

It is reported that post Primary Analysis, some subjects were inoculated with licensed non-study vaccines for COVID-19 when the vaccines became available to the general public in Japan. For the Final Analysis, the data handling of these subjects' data are explained in following sections, Section 16.2.5 (immunogenicity analysis), , Section 16.3.1.1 and Section 16.3.4 (efficacy analysis) and Section 17.1.1.3 (safety analysis).

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

Cohorts C, D and Subcohorts D1, D2, and total participants of Cohort C plus Cohort D separately.

Analyses for patients dispostion and protocol deviations described in this section will be updated for the Final Analysis.

9.1. DISPOSITION

Number of participants screened will be presented for the all participants analysis set. Number and percentages of participants with screen failure and reason for screen failure will also be presented based on the all participants analysis set. A listing will present participants not meeting all eligibility criteria with the details of criteria not met.

Number of participants randomized will be presented for the all participants analysis set. Number of participants randomized but not vaccinated (including reason for withdrawal) will also be presented for the all participants analysis set.

Number of participants with at least 28 days follow-up post first dose will be presented for the all participants analysis set.

Number of participants who received first dose and discontinued from study intervention will be presented for the following:

- discontinued from study.
- remained in study follow-up.
- completed study.

Similar summaries will be provided for each dose:

- Number and percentages of participants vaccinated for first dose, in study after first dose and before second dose, discontinued the study intervention (including reason for withdrawal) after first dose and before second dose and discontinued the study (including reason for withdrawal) after first dose and before second dose will be presented.
- Number and percentages of participants vaccinated for second dose, in study (for primary analysis only) after 28 days post second dose and discontinued from study (including reason for withdrawal) before 28 days post second dose and who discontinued early from the study (including reason for withdrawal) after 28 days

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(including 28 days) post second dose will be presented.

The analysis of number of ongoing participants after first or second dose will only be presented for primary analysis and will not be included in the final analysis.

Number of participants included and excluded from each analysis set (including reason for exclusion) will be summarized based on the all participants analysis set. A listing showing inclusion and exclusion of each participant from each analysis set, including reason for exclusion, will be provided.

9.2. PROTOCOL DEVIATIONS

Number and percentages of participant with important protocol deviations, as identified by the study team in a blinded fashion before the clinical data lock, will be provided based on the TVS for each category of protocol deviations specified in the Protocol Deviations Management Plan.

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

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The following demographic and other baseline characteristics will be presented by Cohorts C, D and Subcohorts D1, D2, and total participants of Cohort C plus Cohort D separately:

- Age (years) – at the date of signed informed consent
- Age group (years), applicable only to Subcohort D1: < 65 and ≥ 65
- Sex
- Race
- Childbearing potential for female participants only
- Ethnicity
- Weight (kg)
- Height (cm)

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- BMI (kg/m^2)

Continuous demographic and other baseline characteristics will be summarized using descriptive statistics based on the TVS and FVS for efficacy. For categorical demographic and other baseline characteristics, number and percentages of participants in each category will be provided based on the TVS. No statistical testing will be carried out for demographic or other baseline characteristics.

Analysis for demographic and baseline characteristics described in this section will not be updated for the Final Analysis.

10.1. DERIVATIONS

BMI, in kg/m^2, will be calculated as follows, and presented with 2 decimal points:

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

11. MEDICAL HISTORY

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

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 23.0 or later, and will be summarized by System Organ Class (SOC) and Preferred Term (PT) based on the TVS. A participant having more than one medical condition/disease within the same SOC/PT will be counted only once for that SOC or PT.

All medical history will be listed.

Analysis of medical history described in this section will not be updated for the Final Analysis, only listing of medical history will be updated for the Final Anlaysis.

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 day of first

dose of study intervention.

Concomitant conditions/illnesses will be coded using the MedDRA, version 23.0 or later, and will be summarized by SOC and PT based on the TVS. 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.

Analysis of concomitant illnesses described in this section will not be updated for the Final Analysis, only listing of concomitant illnesses will be updated for the Final Analysis.

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 day of 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.

Prior and concomitant medications will be summarized by Anatomical Therapeutic Class (ATC) level 2 and preferred drug name based on the TVS. 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.

Analyses of prior and concomitant medications described in this section will be updated for the Final Analysis.

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14. EXPOSURE TO STUDY INTERVENTION

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 TVS.

Report of overdose and medication error, if any, will be listed for the TVS.

Listings of exposure to study invention and of overdose will not be updated for the Final Analysis.

15. COMPLIANCE WITH STUDY INTERVENTION

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

16. EFFICACY ENDPOINTS (INCLUDING IMMUNOGENICITY)

Unless otherwise specified, all summaries and figures for immunogenicity will be presented by Cohorts C, D, and Subcohorts D1 and D2, and total participants of Cohort C plus Cohort D separately, based on the TVS and FVS for immunogenicity. Exploratory efficacy analysis will be based on TVS and FVS for efficacy.

16.1. PRIMARY IMMUNOGENICITY

Primary immunogenicity analysis described in this section will not be updated for the Final Analysis.

16.1.1. PRIMARY IMMUNOGENICITY ENDPOINT

The primary immunogenicity endpoint is the proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from Day 1 baseline value) to the Spike antigens of AZD1222 (MSD serology assay) at Day 57.

16.1.2. DATA IMPUTATION METHOD FOR PRIMARY IMMUNOGENICITY ENDPOINT

A titer 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

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assay with LLoQ = 30 generally reports value below LLoQ as "<30". The data listings will present the value as "<30", while value of 15 (i.e., 30/2) is to be used in the summaries and analyses.

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

16.1.3. PRIMARY ANALYSIS OF PRIMARY IMMUNOGENICITY ENDPOINT

Seroresponse is a binary outcome where a success is when the fold rise in titers compared to baseline is ≥ 4. The fold rise in titers is calculated as the ratio of the post-vaccination titer level to the baseline titer level.

The number and proportion of participants who have a seroresponse to the Spike antigens of AZD1222 based on MSD serology assay at Day 57 will be summarized for AZD1222 and placebo. The summary will also include the 95% CI of the proportion of participants achieving seroresponse at Day 57, calculated based on the Clopper-Pearson method. This summary will be repeated for Cohorts C, D and Subcohorts D1, D2, and total participants of Cohort C plus Cohort D separately.

The proportion of participants who have a post-treatment seroresponse at Day 57 will be compared between AZD1222 and placebo using the Fisher's exact test at the 2-sided 5% alpha level for each cohort. Fisher's exact test will not be presented for Subcohorts D1 and D2.

The null hypothesis and alternative hypothesis to be tested are defined as follows:

Null hypothesis: $P_{active} = P_{placebo}$

Alternative hypothesis: $P_{active} \neq P_{placebo}$

where P is the proportion of seroresponse participants.

16.1.3.1. Subgroup analysis for immunogenicity

The analysis of seroresponse to the Spike antigens of AZD1222 at Day 57 will be repeated for the subgroups defined in Section 7.7. Fisher's exact test will not be presented for subgroup analysis.

16.1.4. SENSITIVITY ANALYSES FOR PRIMARY IMMUNOGENICITY ENDPOINT

No sensitivity analyses will be performed for the primary immunogenicity endpoint.

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16.2. SECONDARY IMMUNOGENICITY

The secondary immunogenicity endpoints are:

- Geometric mean titers (GMT) and geometric mean fold rise (GMFR) of immunogenicity against Spike and RBD antigens of AZD1222 (MSD serology assay) at each time point up to Day 365.
- Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from Day 1 baseline value) to RBD antigen of AZD1222 based on MSD serology assay at Day 57.
- Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from Day 1 baseline value) to AZD1222 as measured by SARS-CoV-2 nAb (wild-type assay or pseudoneutralisation assay) at Day 57.
- GMT and GMFR of nAb to SARS-CoV-2 at each time point up to Day 365.

For analyses described above, only the analysis of GMT and GMFR up to Day 365 will be updated for the Final Analysis.

16.2.1. GMTS AND GMFRS

GMTs and GMFRs will be calculated for AZD1222 and placebo and will be summarized at each scheduled visit (refer to protocol Section 1.3), for the following titer measurements:

- Antibodies against Spike and RBD antigens of AZD1222 based on MSD serology assay
- Antibodies against nAb to SARS-CoV-2

Descriptive statistics for GMTs and GMFRs will include number of participants, geometric mean, 95% CI, minimum and maximum and will be presented by Cohorts C, D and Subcohorts D1, D2, and total participants of Cohort C plus Cohort D separately.

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

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

Individual Spike and RDB antigens of AZD1222 based on MSD serology assay and nAb to SARS-CoV-2 at different timepoints will be presented in a plot where data for all placebo participants will be pooled and participants in AZD1222 of Cohorts C, D1 and D2, and total participants of Cohort C plus Cohort D will be presented separately.

16.2.1.1. Subgroup analysis for immunogenicity

The analysis of antibodies against Spike and RBD antigens of AZD1222 (based on MSD serology assay) and antibodies against nAb to SARS-CoV-2 will be repeated for the subgroups defined in Section 7.7.

16.2.2. SERORESPONSE RATE

Seroresponse is defined in Section 16.1.3. The number and proportion of participants who have a seroresponse to the RBD antigen (as measured by MSD serology) and seroresponse to AZD1222 (as measured by nAb) at Day 57 will be summarized separately for AZD1222 and placebo. The summary will also include the 95% CI of the proportion of participants achieving seroresponse at Day 57, calculated based on the Clopper-Pearson method. This summary will be repeated for Cohorts C, D and Subcohorts D1, D2, and total participants of Cohort C plus Cohort D separately. A similar analysis for RDB antigens of AZD1222 will also be performed.

Seroresponse rate will be compared between AZD1222 and placebo using the Fisher's exact test at the 2-sided 5% alpha level for each cohort, Cohorts C, D, and total participants of Cohort C plus Cohort D separately.

16.2.2.1. Subgroup analysis for seroresponse rate

The analysis of seroresponse rate will be repeated for the subgroups defined in Section 7.7.

16.2.3. DATA IMPUTATION METHOD FOR SECONDARY IMMUNOGENICITY ENDPOINTS

Data imputation rules as described in Section 16.1.2 will be applicable to the secondary immunogenicity endpoints.

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16.2.4. SENSITIVITY ANALYSES FOR SECONDARY IMMUNOGENICITY ENDPOINT

No sensitivity analyses will be performed for the secondary immunogenicity endpoint.

16.2.5. DATA HANDLING FOR SUBJECTS INOCULATED WITH NON-STUDY COVID-19 VACCINE

For subjects who were inoculated with non-study COVID-19 vaccine, their immunogenicity data from the time of the non-study COVID-19 vaccination will not be included in the analysis, ie, any immunogenicity data collected after the date of non-study COVID-19 vaccination will be removed, however this data will be provided in listings. The date of non-study COVID-19 vaccination can be obtained from the Concomitant Medication eCRF page.

16.3. EXPLORATORY EFFICACY

The exploratory efficacy endpoints are:

- Virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19.
- Hospital admissions associated with COVID-19.
- Intensive care unit admissions associated with COVID-19.
- Deaths associated with COVID-19.
- Seroresponse against non-Spike (nucleocapsid) SARS-CoV-2 antigens (MSD serology assay).

Exploratory efficacy analyses were not performed for the Primary Analysis and will be presented for the Final Analysis.

16.3.1. EXPLORATORY EFFICACY ENDPOINTS

16.3.1.1. Virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19

The incidence of the first virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19 will be summarized for the TVS and the incidence of the first virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19 occurring ≥ 15 days post second dose of study intervention will be summarized for the FVS for efficacy and presented for AZD1222 and placebo by Cohorts C and D and Subcohorts D1 and D2, and total

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participants of Cohort C plus Cohort D separately.

A participant who is found to be positive to COVID-19 based on the SARS-CoV-2 RT-PCR test is considered as having symptomatic case of COVID-19. This is because, according to current medical practice in Japan, only participants with symptomatic symptoms of COVID-19 are likely to be prescribed the SARS-CoV-2 RT-PCR test.

A participant could have multiple assessments of SARS-CoV-2 RT-PCR test throughout the study duration, but only the first positive SARS-CoV-2 RT-PCR test, occurring post first dose of study intervention for the analysis based on TVS and occurring ≥ 15 days post second dose of study intervention for the analysis based on FVS for efficacy, will be counted.

Kaplan-Meier curves will be presented for AZD1222 and placebo in the TVS and FVS for efficacy, showing the cumulative incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic COVID-19 post first dose of study intervention or occurring ≥ 15 days post second dose of study intervention, respectively. The time to event is calculated as follows:

- For analysis based on TVS:

  (Date of Onset of Symptomatic SARS-CoV-2 RT-PCR Positive Event) – (Date of First Dosing) + 1.

- For analysis based on FVS for efficacy:

  (Date of Onset of Symptomatic SARS-CoV-2 RT-PCR Positive Event) – (Date of Second Dosing + 15) + 1.

For participants who were inoculated with non-study COVID-19 vaccine and did not meet the virologically confirmed (RT-PCR) symptomatic cases of COVID-19 post first dose of study intervention and up to the time of non-study COVID-19 vaccine inoculation for TVS or ≥ 15 days post second dose of study intervention and up to the time of non-study COVID-19 vaccine inoculation for FVS for efficacy, time to event is censored and calculated as follows.

- *For analysis based on TVS:*

  (Date of non-study COVID-19 vaccination) – (Date of First Dosing) + 1.

- *For analysis based on FVS for efficacy:*

  (Date of non-study COVID-19 vaccination) – (Date of Second Dosing + 15) + 1.

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For *other* participants who do not meet the virologically confirmed (RT-PCR) symptomatic cases of COVID-19 post first dose of study intervention for TVS or ≥ 15 days post second dose of study intervention for FVS for efficacy, time to event is calculated as follows:

(a) Participants who completed the study or discontinued the study early without a virologically confirmed (RT-PCR) positive test.

For these participants, the time to event will be censored and calculated as,

- For analysis based on TVS:

(Date of End of Study or Date of Last RT-PCR Assessment, whichever is later) – (Date of First Dosing) + 1.

- For analysis based on FVS for efficacy:

(Date of End of Study or Date of Last RT-PCR Assessment, whichever is later) – (Date of Second Dosing + 15) + 1.

(b) For participants who are not tested positive SARS-CoV-2 as confirmed by RT-PCR and remained in the study at the time of primary analysis.

These participants will be censored and the data cut-off date will be used in the time to event calculation as follow,

- For analysis based on TVS:

(Date of Data Cut-Off) – (Date of First Dosing) + 1.

- For analysis based on FVS for efficacy:

(Date of Data Cut-Off) – (Date of Second Dosing + 15) + 1.

16.3.1.2. Hospital admission associated with COVID-19

The number and proportion of participants with COVID-19 related hospital admission will be summarized for the TVS and the FVS for efficacy and presented by treatment group.

In the analysis based on the FVS for efficacy, only COVID-19 related hospital admission occurring ≥ 15 days post second dose of study intervention will be counted.

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COVID-19 related hospital admissions are captured in the Serious Adverse Events electronic Case Report Form (eCRF) page.

16.3.1.3. Intensive care unit admissions associated with COVID-19

The number and proportion of participants with COVID-19 related ICU/HDU will be summarized for the TVS and the FVS for efficacy and presented by treatment group.

In the analysis based on the FVS for efficacy, only COVID-19 related ICU/HDU occurring ≥ 15 days post second dose of study intervention will be counted.

Participants who have the ICU admission date (captured in the Hospitalization eCRF page) anytime between COVID-19 related hospital admission date and discharge date (captured in the Serious Adverse Events eCRF page) will be considered as having an incidence of COVID-19 related ICU admission.

16.3.1.4. Deaths associated with COVID-19

If any participants die during the study, death is recorded as 'Death' on the "Serious Adverse Events" page of the eCRF. The number and proportion of participants who died due to COVID-19 will be summarized for the TVS and the FVS for efficacy by treatment group. All deaths, regardless of the timing, will be listed.

In the the analysis based on FVS for efficacy, only participants who died due to COVID-19 ≥ 15 days post second dose of study intervention will be counted.

16.3.1.5. Seroresponse against non-Spike (nucleocapsid) SARS-CoV-2 antigens (MSD serology assay)

Seroresponse is defined in Section 16.1.3. The number and proportion of participants who have seroresponse to the non-Spike (nucleocapsid) SARS-CoV-2 antigens based on MSD serology assay will be summarized for the TVS and the FVS for efficacy by treatment group.

In the the analysis based on FVS for efficacy, only participants achieving seroresponse ≥ 15 days post second dose of study intervention will be counted in this analysis.

The summary will also include the 95% CI of the proportion of participants achieving seroresponse calculated based on the Clopper-Pearson method.

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[redacted]

16.3.2. Data Imputation Method for Exploratory Efficacy Endpoints

Data imputation rules as described in Section 16.1.2 will be applicable to analysis of seroresponse to the non-Spike (nucleocapsid) SARS-CoV-2 antigens endpoint. Otherwise, no data imputation method will be applied to the exploratory efficacy analysis.

Participants who withdraw consent or have an early termination will have data analyzed up to the day of their study termination.

16.3.3. Sensitivity Analyses for Exploratory Efficacy Endpoints

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

16.3.4. Data Handling for Subjects Inoculated with Non-Study COVID-19 Vaccine

For subjects who were inoculated with non-study COVID-19 vaccine, their efficacy data from the time of the non-study COVID-19 vaccination will not be included in the analysis, ie, any efficacy data collected after the date of non-study COVID-19 vaccination will be removed, however this data will be provided in listings. The date of non-study COVID-19 vaccination can be obtained from the Concomitant Medication eCRF page.

17. Safety Endpoints

All safety summaries will be presented by Cohorts C, D and Subcohorts D1, D2, and total participants of Cohort C plus Cohort D separately, based on the TVS There will be no statistical comparisons between the treatment groups for safety data.

The primary safety endpoints are:

- Occurrence of solicited local reactogenicity signs and symptoms for 7 days following throughout vaccination
- Occurrence of solicited systemic reactogenicity signs and symptoms for 7 days following throughout vaccination.
- Occurrence of AEs, serious adverse events (SAEs) and adverse events of special interest (AESIs) for 28 days following throughout vaccination.

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- Change from baseline for safety laboratory measures.

The secondary safety enpoint is the occurrence of SAEs and AESIs throughout the study duration up to Day 365.

For safety analysis, only the analysis of unsolicited AEs, physical examination listing and vital sign listing will be updated for the Final Analysis.

17.1. ADVERSE EVENTS

Adverse events will be coded using the MedDRA dictionary, version 23.0 or later.

17.1.1. ALL ADVERSE EVENTS

An overall summary of number and percentages of participants within each of the categories described in the sub-sections below will be provided based on the TVS. Should a participant experience multiple event within a category, the participant will be counted only once for that category.

All AEs will be listed.

17.1.1.1. Severity grading for AEs

Severity will be classified as Food and Drug Administration (FDA) Grading for AEs, according to Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (FDA 2007). FDA Gradings for AEs will be collected on AE form of eCRF. Should a participant experience multiple events within a SOC or PT, only the participant's worst FDA grade will be counted for that SOC or PT.

17.1.1.2. Relationship to study intervention

Relationship to study intervention, as indicated by the Investigator as "Relationship to study treatment" in eCRF, will be classified as not related, or related (increasing severity of relationship).

Should a participant experience multiple events within a SOC or PT, only the participant's worst relationship will be counted for that SOC or PT.

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[redacted]

17.1.1.3. Data Handling for Subjects Inoculated with Non-study COVID-19 Vaccine

The analysis of AEs will be presented with all data including safety data of subjects who were inoculated with a non-study COVID-19 vaccine. The same analysis will be provided for 1) after removing all safety data that started post non-study COVID-19 vaccination and 2) only safety data that started post non-study COVID-19 vaccination for subjects who were inoculated with a non-study COVID-19 vaccine. The date of non-study COVID-19 vaccination can be obtained from the Concomitant Medication eCRF page. For subjects who were inoculated with a non-study COVID-19 vaccine, AEs that started post non-study COVID-19 vaccination will be included in the overall AE listings.

17.1.2. PRIMARY SAFETY ENDPOINTS

17.1.2.1. Occurrence of unsolicited AEs for 28 days following throughout vaccination

All AEs are considered to be unsolicited AEs unless categorized as solicited AEs recorded in an eDiary. All unsolicited AEs will be recorded from the start of each dose for 28 days post each dose of study intervention.

Number and percentages of participants with at least one unsolicited AE will be presented by SOC and PT. Should a participant experience multiple events within a SOC or PT, the participant will be counted only once for that SOC or PT.

Number and percentage of participants with at least one unsolicited AE will be presented by PT. Should a participant experience multiple events within a PT, the participant will be counted only once for that PT.

Number and percentage of participants with at least one unsolicited AE will be broken down further by 28 days interval post each dose (based on the start date of the event), maximum severity (refer to Section 17.1.1.1), relationship to study intervention (refer to Section 17.1.1.2).

Number and percentage of participants with at least one unsolicited AE with Grade 3 or higher will be presented by relationship to study intervention (refer to Section 17.1.1.2), SOC and PT.

Subgroup analysis will be performed for the overview summary of unsolicited AEs and the occurrence of unsolicited AEs by SOC and PT using subgroups specified in Section 7.7.

A listing of all unsolicited AEs will be provided.

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[redacted]

17.1.2.2. Occurrence of serious AEs for 28 days following throughout vaccination

Serious adverse events are those events recorded as "Serious" on the AE page of the eCRF. Only SAEs that started or worsened in severity on or after the first dose of study intervention will be presented in the summary.

Should a participant experience multiple events within a SOC or PT, the participant will be counted only once for that SOC or PT. Number and percentage of participants with at least one SAE will be broken down further by 28 days interval post each dose (based on the start date of the event) and relationship to study intervention (refer to Section 17.1.1.2).

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

17.1.2.3. Occurrence of Adverse Events of Special Interest for 28 days following throughout vaccination

Adverse events of special interest are defined in the protocol Section 8.3.8. AESIs will be recorded as "Yes" for "Was the event an AE of Special Interest?" on the AE page of the eCRF.

A summary of AESIs by SOC and PT will be presented. Should a participant experience multiple events within a SOC or PT during an interval, the participant will be counted only once for that SOC or PT during that particular interval. The summary of AESI will be broken down further by 28 days interval post each dose (based on the start date of the event).

Number and percentage of participants with at least one AESIs will be presented by relationship to study intervention (refer to Section 17.1.1.2), SOC and PT.

A listing of all AESIs will be provided.

17.1.2.4. Occurrence of solicited AEs for 7 days following throughout vaccination

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:

Table C: List of Predefined Solicited Adverse Events for Reactogenicity Assessment

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

a Fever measured by any route. Investigators who consider a temperature lower than this cutoff as a fever or a 'fever' reported by participants without documentation by a thermometer should record the event as 'elevated body temperature.'
b Swelling, redness, and induration 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, and chills, fatigue, headache and nausea/vomit are derived based on criteria presented in APPENDIX 5. 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 1-7, and Day 1 to Day 7 individually. For each interval, the count and percentages 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 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 count and percentages of participants 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.

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17.1.3. SECONDARY SAFETY ENDPOINTS

17.1.3.1. Occurrence of serious AEs throughout the study duration up to Day 365

A summary of SAEs started on and after first dose of study intervention will be presented by SOC and PT throughout the study duration up to Day 365. 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 SAEs (including SAE started prior to the start of first dose of study intervention) will be provided.

17.1.3.2. Occurrence of AESIs throughout the study duration up to Day 365

A summary of AESIs by SOC and PT throughout the study duration up to Day 365 will be presented. Should a participant experience multiple events within a SOC or PT, the participant will be counted only once for that SOC or PT.

17.1.4. OTHER ADVERSE EVENT SAFETY ENDPOINTS

17.1.4.1. 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 presented.

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

17.1.4.2. AEs Leading to Discontinuation of Study Intervention

AEs leading to discontinuation of study intervention are 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 presented.

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

17.2. LABORATORY EVALUATIONS

The analysis of change from baseline is also one of the primary safety endpoints.

Clinical chemistry and hematology 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 6.

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 based on the TVS for each of chemistry and hematology laboratory parameter:

- Observed and change from baseline in Standard International (SI) units by visit;
- Categorical value according to FDA grading guidance (FDA 2007) toxicity grades (for quantitative parameters with available FDA toxicity grades; refer to Section 17.2.1) by visit;
- A listing of participants with at least one observed value in alanine aminotransferase (ALT) value ≥ 3 x upper limit of normal (ULN) or aspartate aminotransferase (AST) value ≥ 3 x ULN together with total bilirubin value ≥ 2 x ULN will be provided.

All laboratory data will be listed.

A urine pregnancy test will be performed at scheduled visits (refer to protocol Section 1.3). Listings of pregnancy test and pregnancy report, if any, will also be presented.

17.2.1. LABORATORY TOXICITY GRADES

Quantitative laboratory parameters with available FDA toxicity grades will be categorized as follows where higher grades representing a more severe toxicity (refer to APPENDIX 7 for each parameter toxicity grade criteria). FDA grading will be categorized for laboratory parameters listed in APPENDIX 6:

- Grade 1 (i.e., mild);
- Grade 2 (i.e., moderate);

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- Grade 3 (i.e., severe)
- Grade 4 (i.e., potentially life-threatening)

Although not defined in the FDA toxicity grading system, non-missing laboratory parameter results not meeting any of the 4 grades defined in the FDA toxicity grading system will be categorized as 'No Toxicity'.

17.3. 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)
- Pulse rate (beats per minute [bpm])
- Body temperature (ºC)

Observed values of vital sign parameters will be summarized descriptively based on the TVS for all scheduled visits.

A listing of all vital sign data will also be provided.

The analysis of vital sign lisitng will be updated for the Final Analysis.

17.4. PHYSICAL EXAMINATION

Physical examinations will be conducted as per the schedule of events (refer to protocol Section 1.3). Clinically significant findings at screening will be recorded on the Medical History 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 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.

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Only the listing of physical examination containing tests assessed up till the end of study will be updated for the Final Analysis.

17.5. IMMUNOLOGIC RESPONSES

17.5.1. NEUTRALIZING ANTIBODIES: IMMUNOGLOBULIN G AND M ANTIBODIES

Immunoglobulin G (IgG) and immunoglobulin M (IgM) will be tested as per the schedule of events (refer to protocol Section 1.3).

All IgG and IgM antibodies data will be listed.

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[redacted]

18. REFERENCES

FDA, (Food and Drug Administration). 2007. *Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.* Accessed August 25, 2020. https://www.fda.gov/media/73679/download.

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 only; If medication start date < study intervention start date, assign as concomitant; If study intervention start date ≤ medication start date, assign as concomitant.

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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, assign as concomitant.
	Missing, not ongoing	Cannot be assigned as prior only; If known components of medication start date show that medication started before study 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.

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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 TREATMENT GROUPS

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

Treatment Group	Tables and Graphs	Listings
AZD1222	1	1
Placebo	2	2
Total [1]	3	3
Randomized, Not Vaccinated	n/a	5

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Treatment Group	Tables and Graphs	Listings
Screen Failure	n/a	6

[1] Not applicable for efficacy 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
Day 1	D1
Day 4	D4
Day 8	D8
Day 15	D15
Day 29	D29
Day 32	D32
Day 36	D36
Day 43	D43
Day 57	D57
Day 183	D183
Day 365	D365

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DESCRIPTIVE STATISTICS

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

- Minimum and maximum, lower and upper bounds of two-sided 95% CI for percentages and Kaplan-Meier estimates: N;
- Mean (including GMT and GMFR), median, lower and upper bounds of two-sided 95% CI* for GMT/GMFR: N + 1;
- SD: N + 2

* when values are less than 0.00, 95% CI are presented to N + 2 decimal places to enable the display of meaningful values.

PERCENTAGES

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

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

P-VALUES

p-values will be reported to three decimal places. Rounding will be applied, except for the p-values < 0.001 which will be presented as '< 0.001' and p-values < 1.000 but > 0.999 which will be presented as '> 0.999'.

LISTINGS

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

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

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- Timepoint, when applicable

APPENDIX 3. TABLES FOR 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 hospitalisation
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalisation
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 < ¼ inch (< 0.6 cm) in diameter will not be recorded.

[b] Grade 4 erythema or induration is determined by site with participant input rather than being recorded directly in e-Diary.

ER = emergency room.

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APPENDIX 4. TABLES FOR CLINICAL ABNORMALITIES: VITAL SIGNS

Vital Signs [a]	Vital Signs Grade			
	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) [b] (°F) [b]	37.9-38.4 100.1-101.1	38.5-38.9 101.2-102.0	39.0-40 102.1-104	> 40 > 104
Tachycardia (beats/minute)	101-115	116- 130	> 130	ER visit or hospitalisation for arrhythmia
Bradycardia (beats/minute) [c]	50-54	45-49	< 45	ER visit or hospitalisation for arrhythmia
Hypertension; systolic (mm Hg)	141-150	151-155	> 155	ER visit or hospitalisation for malignant hypertension
Hypertension; diastolic (mm Hg)	91-95	96-100	> 100	ER visit or hospitalisation for malignant hypertension
Hypotension; systolic (mm Hg)	85-89	80-84	< 80	ER visit or hospitalisation for hypotensive shock
Respiratory rate (breaths/minute)	17-20	21-25	> 25	Intubation

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

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

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

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

ER = emergency room; Hg = mercury.

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

Systemic (General)	Systemic Grade			
	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 hrs	Some interference with activity or > 2 episodes/24 hrs	Prevents daily activity, required outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Chills	No interference with activity	Some interference with activity	Significant, prevents daily activity	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hrs or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Systemic Illness				
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	ER visit or hospitalization

ER = emergency room; hrs = hours; IV = intravenous.

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APPENDIX 6. LABORATORY ASSESSMENTS

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count)	S/P-Alkaline phosphatise (ALP)
B-Platelet count	S/P-Aspartate aminotransferase (AST)
	S/P-Alanine aminotransferase (ALT)
	S/P-Albumin
	S/P-Potassium
	S/P-Calcium, total
	S/P-Sodium
	S/P-Creatine kinase (CK)

B = blood; P = plasma; S = serum

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APPENDIX 7. TABLES FOR LABORATORY ABNORMALITIES

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***ULN" is the upper limit of the normal range.

Note: To evaluate Grade 4 Creatinine, only test result > 2.5 is required, the assessment of dialysis is not required.

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Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	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)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** "ULN" is the upper limit of the normal range.

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APPENDIX 8. ABBREVIATIONS

Abbreviation or special term	Explanation
ADaM	Analysis Dataset Modelling
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Class
BLQ	lower limit of quantification
BMI	body mass index
bpm	beats per minute
CI	confidence interval
COVID-19	Coronavirus Disease 2019
CRM	comments resolution meeting
DBP	diastolic blood pressure
eCRF	electronic Case Report Form
FVS	fully vaccinated analysis set
GMFR	geometric mean fold rise
GMT	geometric mean titer
HDU	High dependency unit

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Abbreviation or special term	Explanation
ICU	intensive care unit
IgG	immunoglobulin G
IgM	immunoglobulin M
IM	intramuscular
LLoQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MSD	Meso Scale Discovery
n	number of participants with available data
nAb	neutralising antibody
PT	preferred term
RBD	receptor-binding domain
RT-PCR	reverse transcriptase-polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome-coronavirus 2
SBP	systolic blood pressure
SD	standard deviation
SDTM	Study Data Tabulation Model
SI	Standard International

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Abbreviation or special term	Explanation
SOC	system organ class
TVS	total vaccinated analysis set
ULN	upper limit of normal
ULoQ	upper limit of quantification
ULQ	upper limit of quantification
US FDA	United States Food and Drug Administration
vp	viral particles
WHO	World Health Organization

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