STATISTICAL ANALYSIS PLAN

D8110C00001

A PHASE III RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED MULTICENTER STUDY IN ADULTS TO DETERMINE THE SAFETY, EFFICACY, AND IMMUNOGENICITY OF AZD1222, A NON-REPLICATING CHADOX1 VECTOR VACCINE, FOR THE PREVENTION OF COVID-19

AUTHOR: PPD

VERSION NUMBER AND DATE: V3.0, 28FEB2021

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan v3.0 (dated 28Feb2021) for protocol D8110C00001.

	Name	Signature	Date (DDMmmYYYY)
Author:	PPD	Refer to eSignature	
Position:	PPD		
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	
Position:	Lead Statistician		
Company:	AstraZeneca		
Approved by:	PPD	Refer to eSignature	
Position:	Global Product Statistician		
Company:	AstraZeneca		

MODIFICATION HISTORY

Date of the Document Modification / Version	Author	Significant Changes from Previous Version
06Oct2020/ Version 1.0	PPD	Initial version.
03Feb2020/ Version 2.0	PPD	Note: editorial updates are not listed. • Section 2.2: New secondary endpoint is added per PA3 to evaluate efficacy regardless of prior infection; Revised the first secondary endpoint per PA4 to permit formal statistical comparison; Identified the 4 key secondary endpoints per PA4 to indicate these are the endpoints that are multiplicity protected. • Section 2.4: Population definitions are updated to clarify that participant must be seronegative; Updates to align with Section 2.2; Added details for inclusion of unblinding/EUA vaccination as intercurrent event. • Sections 3.1-3.2: Updates to align with PA3 and PA4. • Section 4: Description of an analysis performed by OWS to evaluate immunological markers as correlates of risk among vaccinees and towards the development of surrogates of protection . • Sections 4.1-4.3: Updated to align with PA3 and PA4. Clarification added for role of DSMB, including oversight of the interim analysis. Additional details for interim and primary analyses, including new analysis planned once all participants have completed their first year of follow up. • Section 5.1: Added details for exclusion of participant enrolled at two sites and another sponsor COVID-19 vaccine trial. • Section 5.3-5.5: Definition of per protocol population is updated to use FVS

		per PA4. Updates to clarify approach for patients with dosing errors. • Section 7.3,7.4 are updated to include additional analysis performed once all participants have completed their first year of follow up. • Section 7.4: Updated to reflect multiplicity protection for key secondary endpoints per PA4. • Section 7.6, 7.7: Country is removed from the statistical models. Clarification added for possible issues of non-convergence due to sparse data for subgroup levels (see also 16.1.6). • Section 9.1: Disposition updated to include patients unblinded to treatment assignment. • Section 10: Added demographic summary based on SAF for the substudy and IAS for the substudy. • Section 11: Added summary of baseline co-morbidities for FVS. • Section 15: Added summary of the interval between dose 1 and dose 2. • Section 16: Updated to add details for handling discordance between local and central SARS-CoV-2 RT-PCR results. Includes plan to address unblinding/EUA vaccine as intercurrent events. Added summary of duration of FU time for FAS and FVS. • Section 16.1.3: Updated to use log of total number of participants for each combination of treatments and strata as offset for stratified exact poisson model. Additional details provided for handling sparse data and non-convergence issues. Clarification added for calculation of the follow up time. • Section 16.1.4: Removed multiple imputation analysis when AZD1222 imputed as having event and Placebo imputed as no event and also when AZD1222 imputed as no event and Placebo imputed as having event. • Section 16.1.5: Updated to include repeat of primary endpoint analysis

		excluding participants with out-of-window vaccination due to the clinical hold. • Section 16.1.6: Replace FAS by FVS regardless of baseline serostatus for subgroup analysis for serostatus at baseline; Clarification added for subgroup analysis methods. • Section 16.2.1.1-16.2.1.6, 16.2.3: Updated to incorporate the updates for key secondary endpoints and the new secondary endpoints per PA3 and PA4. Also added supportive analysis for severe COVID endpoint post first dose. • Section 16.2.3: Added subgroup analysis by baseline serostatus for key secondary endpoints. • Section 16.3.1.3, 16.3.1.4: Added supportive analysis for COVID-19-related hospitalization and COVID-19-related ICU post first dose. • Section 17: Details added for treating unblinding/EUA vaccine as an intercurrent event. Updated to use log base 2 for GMT calculation. Clarification added that participants who do not receive dose 2 are excluded from summaries at timepoints post-dose 2. • Section 17.1.1, Section 17.1.2: Added summaries for participants in the substudy by age group and by clinical hold status. • Section 18: Details added throughout for treating unblinding/EUA vaccine as an intercurrent event, including addition of summaries of events in the double-blind, unblinded, and overall study periods for SAEs, MAAEs and AESIs. • Section 18.1.7: AESIs were updated per PA3 and PA4. Summary of AESIs by severity grade and summary of related AESIs by severity grade were added. Added summaries of AESIs by age group, sex and race. • Section 18.1.8: Added additional summaries of adverse event. • Section 18.2: Updated to reflect solicited events are captured on days 2-8,

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		with 24 hour recall period. Added summaries by age groups. • Appendix 6: Updated to reflect symptom criteria for CDC endpoint definition. • Appendix 7: New appendix for AESI.
28Feb2020/ Version 3.0	PPD	Note: editorial updates are not listed. • Updates to align with protocol amendment 6. Exploratory endpoint (the incidence of SARS-CoV-2 RT-PCR positive symptomatic illness occurring post first dose of study intervention) promoted to a secondary endpoint. • Updated the threshold for frequent adverse events from 2% to 1%. • Clarifications added regarding the calculation of follow-up time.

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1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for protocol D8110C00001. 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 6.0, dated 19Feb2021.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVES

The primary objectives are:

- To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of COVID-19
- To assess the safety and tolerability of 2 IM doses of AZD1222 compared to saline placebo
- To assess the reactogenicity of 2 IM doses of AZD1222 compared to saline placebo (Substudy only)

2.2. SECONDARY OBJECTIVES

The secondary objectives are:

- To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of SARS-CoV-2 infection*
- To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of symptomatic COVID-19 using CDC criteria
- To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of University of Oxford-defined symptomatic COVID-19
- To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo in the prevention of COVID-19 in all study participants, regardless of evidence of prior SARS-CoV-2 infection*
- To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of severe or critical symptomatic COVID-19*
- To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of COVID-19-related Emergency Department visits*
- To assess antibody responses to AZD1222 S antigen following 2 IM doses of AZD1222 or saline placebo (Substudy and Illness Visits only)
- To determine anti-SARS-CoV-2 neutralizing antibody levels in serum following 2 IM doses of AZD1222 or saline placebo (Substudy and Illness Visits only)
- To estimate the efficacy of AZD1222 compared to saline placebo for the prevention of COVID-19 following the first dose

* Key secondary endpoints, multiplicity protected.

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives are:

- To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the all-cause

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mortality

- To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for COVID-19-related deaths
- To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of COVID-19-related hospitalizations
- To estimate the efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of COVID-19-related ICU admissions
- To quantify SARS-Cov-2 viral loads in infected participants treated with 2 IM doses of AZD1222 or saline placebo (Illness Visits only)
- To characterize sequence variations in SARS-CoV-2 through genotypic analyses in participants treated with 2 IM doses of AZD1222 or saline placebo (Illness Visits only)
- To quantify duration of viral shedding in symptomatic SARS-CoV-2 infected participants treated with 2 IM doses of AZD1222 or saline placebo (Illness Visits only)
- To assess the biometric profiles associated with COVID-19 using a biosensor in participants treated with 2 IM doses of AZD1222 or saline placebo (Illness Visits only)
- To assess symptoms associated with COVID-19 using an e-Diary in participants treated with 2 IM doses of AZD1222 or saline placebo (Illness Visits only)
- To assess SARS-CoV-2 specific antibodies in an ACE2 competition assay following 2 IM doses of AZD1222 or saline placebo (Substudy only)
- To assess B- and T-cell responses following 2 IM doses of AZD1222 or saline placebo (Substudy only)
- To assess SARS-CoV-2 antibodies in nasal secretions following 2 IM doses of AZD1222 or saline placebo (Substudy only)
- To assess anti-vector responses to the ChAdOx-1 adenovirus vector following 2 IM doses of AZD1222 or saline placebo (Substudy only)
- To assess additional immune responses following 2 IM doses of AZD1222 or saline placebo

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2.4. ESTIMANDS

Table A: List of Estimands

Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
The efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of COVID-19	Adults ≥ 18 years of age who are healthy or have medically-stable chronic diseases and are at increased risk for SARS-CoV-2 acquisition and COVID-19, and who are seronegative at baseline	2 IM doses of AZD1222 or Placebo	A binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs ≥ 15 days post second dose of study intervention. Otherwise, a participant is not defined as a COVID-19 case.	For participants who withdraw from the study prior to having met the criteria for the primary efficacy endpoint, absence of data following these participants' withdrawal will be treated as missing (i.e. counted as not having met the criteria); Participants who withdraw before 15 days post second dose or who have a case prior to 15 days post second dose will be excluded from primary endpoint analysis. Participants who (1) were unblinded to treatment assignment or (2) received COVID-19 licensed vaccine but were not	Vaccine Efficacy (VE), calculated as 1-relative risk. (Relative risk is the incidence in the vaccine group relative to the incidence in the control group.)

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Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
				unblinded to treatment assignment, in both cases prior to having met the criteria for the primary efficacy endpoint will be censored at the date of unblinding/ licensed COVID-19 vaccine administration, whichever is earlier.	
The safety and tolerability of 2 IM doses of AZD1222 compared to saline placebo	Adults ≥ 18 years of age who are healthy or have medically-stable chronic diseases, and are at increased risk for SARS-CoV-2 acquisition and COVID-19	2 IM doses of AZD1222 or Placebo	a) Incidence of AEs for 28 days post each dose of study intervention b) Incidence of SAEs, MAAEs, and AESIs from Day 1 post treatment through Day 730	Participants unblinded to treatment assignment or participants who received licensed COVID-19 vaccine but were not unblinded will be censored at the date of unblinding/ COVID-19 licensed vaccine administration, whichever is earlier.	Number and percentages of participants who have the incidence; Number of the events.

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Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
The reactogenicity of 2 IM doses of AZD1222 compared to saline placebo (Substudy only)	Adults ≥ 18 years of age who are healthy or have medically-stable chronic diseases and are at increased risk for SARS-CoV-2 acquisition and COVID-19	2 IM doses of AZD1222 or Placebo	Incidence of local and systemic solicited AEs for 7 days post each dose of study intervention	Participants unblinded to treatment assignment/received licensed COVID-19 vaccine but not unblinded prior to having completed 7 days of follow up post each dose will be censored at the date of unblinding/ licensed COVID-19 vaccine administration, whichever is earlier.	Number and percentages of participants who have the incidence.

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The efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of SARS-CoV-2 infection	Adults ≥ 18 years of age who are healthy or have medically-stable chronic diseases and are at increased risk for SARS-CoV-2 acquisition and COVID-19, and who are seronegative at baseline.	2 IM doses of AZD1222 or Placebo	A binary response, whereby a participant has at least one post-treatment response (negative at baseline to positive post treatment with study intervention) for SARS-CoV-2 Nucleocapsid antibodies occurring ≥ 15 days post second dose of study intervention.	For participants who withdraw from the study prior to having met the criteria for the endpoint, absence of data following these participants' withdrawal will be treated as missing (i.e. counted as not having met the criteria); Participants who withdraw before 15 days post second dose or who have a case prior to 15 days post second dose will be excluded from analysis. Participants who (1) were unblinded to treatment assignment or (2) received COVID-19 licensed vaccine but were not unblinded to treatment assignment, in both cases prior to having met the criteria for the primary efficacy endpoint will be censored at the date of unblinding/ licensed COVID-19 vaccine administration, whichever is earlier.	Vaccine Efficacy (VE), calculated as 1-relative risk. (Relative risk is the incidence in the vaccine group relative to the incidence in the control group.)
The efficacy of 2 IM doses of AZD1222	Adults ≥ 18 years of age who are healthy or have medically-stable chronic	2 IM doses of AZD1222 or Placebo	A binary response, whereby a participant has least one case of SARS-CoV-2 RT-PCR	For participants who withdraw from the study prior to having met the criteria for the endpoint, absence of data following	Vaccine Efficacy (VE), calculated as 1-relative risk. (Relative risk is the

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Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
compared to saline placebo for the prevention of symptomatic COVID-19 using CDC criteria	diseases and are at increased risk for SARS-CoV-2 acquisition and COVID-19, and who are seronegative at baseline.		positive symptomatic illness occurring ≥ 15 days post second dose of study intervention using CDC criteria.	these participants' withdrawal will be treated as missing (i.e. counted as not having met the criteria); Participants who withdraw before 15 days post second dose or who have a case prior to 15 days post second dose will be excluded from analysis. Participants who (1) were unblinded to treatment assignment or (2) received COVID-19 licensed vaccine but were not unblinded to treatment assignment, in both cases prior to having met the criteria for the primary efficacy endpoint will be censored at the date of unblinding/ licensed COVID-19 vaccine administration, whichever is earlier.	incidence in the vaccine group relative to the incidence in the control group.)

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The efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of University of Oxford-defined symptomatic COVID-19	Adults ≥ 18 years of age who are healthy or have medically-stable chronic diseases and are at increased risk for SARS-CoV-2 acquisition and COVID-19, and who are seronegative at baseline.	2 IM doses of AZD1222 or Placebo	A binary response, whereby a participant has the at least one case of SARS-CoV-2 RT-PCR positive symptomatic illness occurring ≥ 15 days post second dose of study intervention using University of Oxford-defined symptom criteria.	For participants who withdraw from the study prior to having met the criteria for the endpoint, absence of data following these participants' withdrawal will be treated as missing (i.e. counted as not having met the criteria); Participants who withdraw before 15 days post second dose or who have a case prior to 15 days post second dose will be excluded from analysis. Participants who (1) were unblinded to treatment assignment or (2) received COVID-19 licensed vaccine but were not unblinded to treatment assignment, in both cases prior to having met the criteria for the primary efficacy endpoint will be censored at the date of unblinding/ licensed COVID-19 vaccine administration, whichever is earlier.	Vaccine Efficacy (VE), calculated as 1-relative risk. (Relative risk is the incidence in the vaccine group relative to the incidence in the control group.)
The efficacy of 2 IM doses of AZD1222	Adults ≥ 18 years of age who are healthy or have medically-stable chronic	2 IM doses of AZD1222 or Placebo	A binary response, whereby a participant is defined as a COVID-19 case if their first	For participants who withdraw from the study prior to having met the criteria for the endpoint, absence of data following	Vaccine Efficacy (VE), calculated as 1-relative risk. (Relative risk is the

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Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
compared to saline placebo for the prevention of COVID-19 in all study participants, regardless of evidence of prior SARS-CoV-2 infection	diseases and are at increased risk for SARS-CoV-2 acquisition and COVID-19.		case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs ≥ 15 days post second dose of study intervention regardless of evidence of prior SARS-CoV-2 infection. Otherwise, a participant is not defined as a COVID-19 case.	these participants' withdrawal will be treated as missing (i.e. counted as not having met the criteria); Participants who withdraw before 15 days post second dose will be excluded from primary endpoint analysis. Participants who (1) were unblinded to treatment assignment or (2) received COVID-19 licensed vaccine but were not unblinded to treatment assignment, in both cases prior to having met the criteria for the primary efficacy endpoint will be censored at the date of unblinding/ licensed COVID-19 vaccine administration, whichever is earlier.	incidence in the vaccine group relative to the incidence in the control group.)

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The efficacy of 2 IM doses of AZD1222 compared to saline placebo for the prevention of severe or critical symptomatic COVID-19	Adults ≥ 18 years of age who are healthy or have medically-stable chronic diseases and are at increased risk for SARS-CoV-2 acquisition and COVID-19, and who are seronegative at baseline.	a) 2 IM doses of AZD1222 or Placebo b) At least one dose of AZD1222 or Placebo	a) A binary response, whereby a participant has at least one case of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring ≥ 15 days post second dose of study intervention. b) A binary response, whereby a participant has at least one case of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring post first dose of study intervention.	For participants who withdraw from the study prior to having met the criteria for the endpoint, absence of data following these participants' withdrawal will be treated as missing (i.e. counted as not having met the criteria); Participants who withdraw before 15 days post second dose or who have a case prior to 15 days post second dose will be excluded from analysis (endpoint a only). Participants who (1) were unblinded to treatment assignment or (2) received COVID-19 licensed vaccine but were not unblinded to treatment assignment, in both cases prior to having met the criteria for the primary efficacy endpoint will be censored at the date of unblinding/ licensed COVID-19 vaccine administration, whichever is earlier.	Vaccine Efficacy (VE), calculated as 1-relative risk. (Relative risk is the incidence in the vaccine group relative to the incidence in the control group.)
The efficacy of 2 IM doses of	Adults ≥ 18 years of age who are healthy or have	2 IM doses of AZD1222	A binary response, whereby a participant has at least one	For participants who withdraw from the study prior to having met the criteria for	Vaccine Efficacy (VE), calculated as 1-relative

Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
AZD1222 compared to saline placebo for the prevention of COVID-19-related Emergency Department visits	medically-stable chronic diseases, and are at increased risk for SARS-CoV-2 acquisition and COVID-19, and who are seronegative at baseline.	or Placebo	case of COVID-19-related Emergency Department visit occurring ≥ 15 days post second dose of study intervention.	the endpoint, absence of data following these participants' withdrawal will be treated as missing (i.e. counted as not having met the criteria); Participants who withdraw before 15 days post second dose or who have a case prior to 15 days post second dose will be excluded from analysis. Participants who (1) were unblinded to treatment assignment or (2) received COVID-19 licensed vaccine but were not unblinded to treatment assignment, in both cases prior to having met the criteria for the primary efficacy endpoint will be censored at the date of unblinding/ licensed COVID-19 vaccine administration, whichever is earlier.	risk. (Relative risk is the incidence in the vaccine group relative to the incidence in the control group.)

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Antibody responses to AZD1222 S antigen following 2 IM doses of AZD1222 or saline placebo (Substudy and Illness Visits only)	Adults ≥ 18 years of age who are healthy or have medically-stable chronic diseases, and are at increased risk for SARS-CoV-2 acquisition and COVID-19, and who are seronegative at baseline and who don't have exclusionary important protocol deviations (IPDs).	2 IM doses of AZD1222 or Placebo	a) Post-treatment GMTs and GMFRs in SARS-CoV-2 S, RBD antibodies (MSD serology assay) b) A binary response, whereby participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from day of baseline value to 28 days post each dose) to the S, RBD antigens of AZD1222 (MSD serology assay)	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) were unblinded to treatment assignment or (2) received COVID-19 licensed vaccine but were not unblinded to treatment assignment, in both cases prior to having met the criteria for the primary efficacy endpoint will be censored at the date of unblinding/ licensed COVID-19 vaccine administration, whichever is earlier.	a) Post-treatment GMTs and GMFRs values from day of baseline value to 28 days post each dose in SARS-CoV-2 S, RBD antibodies b) Number and percentage of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from day of baseline value to 28 days post each dose) to the S, RBD antigens of AZD1222
Anti-SARS-CoV-2 neutralizing antibody levels	Adults ≥ 18 years of age who are healthy or have medically-stable chronic diseases, and are at	2 IM doses of AZD1222 or Placebo	a) Post-treatment GMTs and GMFRs in SARS-CoV-2 neutralizing antibodies (wild-type assay or pseudo-	For participants who withdraw from the study or use restricted medications judged to have the potential to interfere with the generation or interpretation of an immune	a) Post-treatment GMTs and GMFRs values from day of baseline value to 28 days post each dose in

Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
in serum following 2 IM doses of AZD1222 or saline placebo (Substudy and Illness Visits only)	increased risk for SARS-CoV-2 acquisition and COVID-19, and who are seronegative at baseline, and who don't have exclusionary important protocol deviations (IPDs).		neutralization assay) b) A binary response, whereby participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from day of baseline value to 28 days post each dose) to AZD1222 as measured by SARS-CoV-2 neutralizing antibodies (wild-type assay or pseudo-neutralization assay)	response, absence of data following these participants' withdrawal or subsequent data following the IPDs will be treated as missing. Participants who (1) were unblinded to treatment assignment or (2) received COVID-19 licensed vaccine but were not unblinded to treatment assignment, in both cases prior to having met the criteria for the primary efficacy endpoint will be censored at the date of unblinding/ licensed COVID-19 vaccine administration, whichever is earlier.	SARS-CoV-2 neutralizing antibodies b) Number and percentage of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from day of baseline value to 28 days post each dose) to AZD1222 as measured by SARS-CoV-2 neutralizing antibodies

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Label	Attributes				
	Definition Population	**Treatment Condition of Interest**	**Variable/Endpoint**	**Intercurrent event handling strategy**	**Population-level summary measure**
The efficacy of AZD1222 compared to saline placebo for the prevention of COVID-19 following the first dose	Adults ≥ 18 years of age who are healthy or have medically-stable chronic diseases and are at increased risk for SARS-CoV-2 acquisition and COVID-19, and who are seronegative at baseline	At least one IM dose of AZD1222 or Placebo	A binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs post first dose of study intervention. Otherwise, a participant is not defined as a COVID-19 case.	For participants who withdraw from the study prior to having met the criteria for the primary efficacy endpoint, absence of data following these participants' withdrawal will be treated as missing (i.e. counted as not having met the criteria). Participants who (1) were unblinded to treatment assignment or (2) received COVID-19 licensed vaccine but were not unblinded to treatment assignment, in both cases prior to having met the criteria for the primary efficacy endpoint will be censored at the date of unblinding/ licensed COVID-19 vaccine administration, whichever is earlier.	Vaccine Efficacy (VE), calculated as 1-relative risk. (Relative risk is the incidence in the vaccine group relative to the incidence in the control group.)

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3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

D8110C00001 is a Phase III randomized, double-blind, placebo-controlled multicenter study assessing the safety, efficacy, and immunogenicity of AZD1222 compared to placebo for the prevention of COVID-19. Approximately 300 sites globally will participate in this study.

Participants will be adults ≥ 18 years of age who are healthy or have medically-stable chronic diseases and are at increased risk for SARS-CoV-2 acquisition and COVID-19. Approximately 30 000 participants will be randomized in a 2:1 ratio to receive 2 IM doses of either 5×10^{10} vp (nominal, $\pm 1.5 \times 10^{10}$ vp) AZD1222 (n = approximately 20 000) or saline placebo (n = approximately 10 000) 4 weeks apart, on Days 1 and 29. Randomization will be stratified by age (≥ 18 to < 65 years, and ≥ 65 years), with at least 25% of participants to be enrolled in the older age stratum. Participants who received their first dose of study intervention between 28 August 2020 and 06 September 2020 will receive their second dose of study intervention outside of the study window.

All participants will be assessed for efficacy and safety. The first participants randomized in each age group in the USA, including 1 500 participants 18 to 55 years of age, 750 participants 56 to 69 years of age, and 750 participants ≥ 70 years of age, will also participate in a substudy assessing the reactogenicity and immunogenicity of AZD1222. To further investigate cell-mediated immunogenicity, in particular Th1/Th2 responses, after AZD1222 or placebo administration, an immunogenicity cohort of approximately 300 participants will be added.

Participants will remain on study for 2 years following administration of the first dose of study intervention (Day 730). If AZD1222 is proven to be safe and efficacious based on the primary endpoint analysis, following discussion at that time with the US FDA, other Regulators if appropriate, and the COVID-19 Vaccine DSMB, participants allocated to the placebo group will be offered AZD1222 when doses are available. Placebo participants treated with AZD1222 will continue to be followed in the study.

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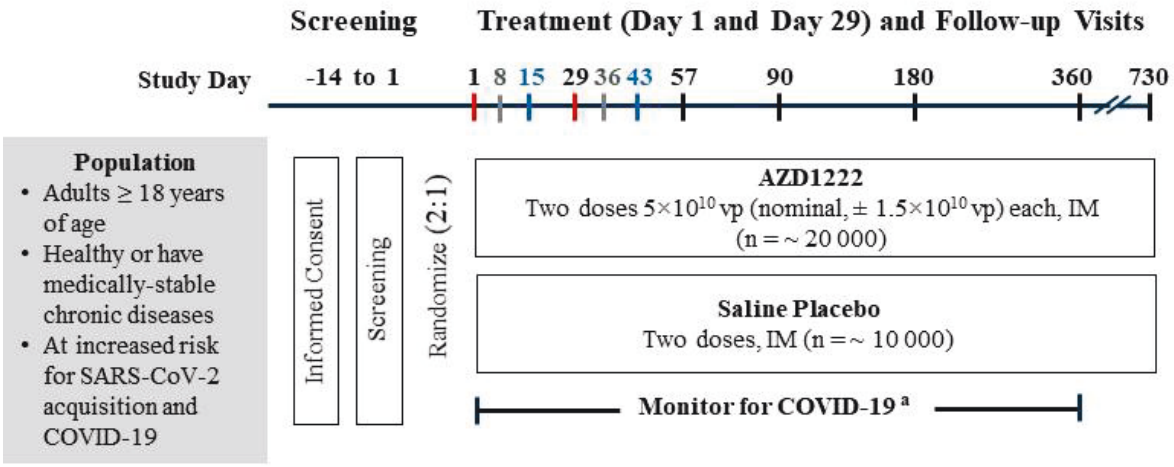
Table B: Study Design



[a] Participants who present with qualifying symptoms will be tested for SARS-CoV-2 and if positive, will complete illness visits.

Red bars (Day 1 and Day 29): Administration of study intervention.
Gray bars (Day 8 and Day 36): Visits will be telephone contacts, not study site visits.
Blue bars (Day 15 and Day 43): Visits will only be for participants in the substudy. The first participants randomized in each age group in the USA, including 1 500 participants 18 to 55 years of age, 750 participants 56 to 69 years of age, and 750 participants ≥ 70 years of age, will also participate in a substudy assessing the reactogenicity and immunogenicity of AZD1222.
COVID-19 = coronavirus disease 2019; IM = intramuscular; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; USA = United States of America; vp = viral particles.

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.

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4. PLANNED ANALYSES

In addition to the planned analyses described below, an analysis to evaluate immunological markers as correlates of risk among vaccinees and towards the development of surrogates of protection will be performed by Operation Warp Speed (OWS). This analysis and corresponding sampling plan will be described in a separate stand-alone statistical analysis plan.

4.1. DATA MONITORING COMMITTEE

An independent COVID-19 Vaccine DSMB will provide oversight, to ensure safe and ethical conduct of the study. Full details of the COVID-19 Vaccine DSMB can be found in the COVID-19 Vaccine DSMB Charter. An independent Neurological AESI Expert Committee will be available to review and provide advice to the Protocol Safety Review Team (PSRT) and the COVID-19 Vaccine DSMB on request about the diagnosis and causality assessment of selected neurological AESIs occurring in the AZD1222 clinical development program.

The COVID19 Vaccine DSMB will facilitate the interim analysis for safety and efficacy and have the responsibility of evaluating cumulative safety and other clinical study data at regular intervals and making appropriate recommendations based on the available data. During the study, the benefit/risk assessment will be continuously monitored by the COVID-19 Vaccine DSMB to ensure that the balance remains favorable. For example, events of potential vaccine associated enhanced respiratory disease will be evaluated by periodic reviews of COVID-19 cases by the DSMB. Harm for severe COVID-19 cases is any vaccine efficacy (VE) ≤0 for which Fisher's exact test (1-sided) is statistically significant at the 5% level. This assessment will begin after 8 cases of severe COVID-19 have accrued in the study and will be performed in real time as events occur. Harm monitoring will include all COVID-19 cases and all severe COVID-19 cases from day 1 for participants in the full analysis set. Harm monitoring for overall COVID-19 cases will use the same boundary as severe COVID-19 cases (ie, VE ≤0 for which Fisher's exact test (1-sided) is statistically significant at the 5% level) but will be performed on a weekly basis.

Based on the output of harm monitoring reviews by the DSMB, the study could be paused for further evaluation of the potential signal. Full details of the COVID-19 Vaccine DSMB composition and operations can be found in the COVID-19 Vaccine DSMB Charter.

4.2. INTERIM ANALYSIS (IA)

All planned analyses for the interim efficacy analysis will be conducted by an independent statistics group providing

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support to the DSMB and IA when approximately 75 events meet the primary endpoint definition (i.e., when approximately 50% of the total amount of statistical information is available) have been reported across the active and control groups within the population of participants who are seronegative at baseline. The interim analysis will be used to support early assessment of efficacy and cumulative safety based on the available data. Detail of this interim analysis will be described in the DSMB plan, but methodology will be consistent with that described in this document.

In the event that the DSMB determines that the efficacy and safety have been definitively established based on review of the interim efficacy analysis and the cumulative safety data, a decision may be made by the Oversight Group and Unblinded Review Committee (URC) to proceed with regulatory submission based on the IA data cut (details are provided in the URC charter). Personnel from the Sponsor and its representatives (including IQVIA) associated with the analyses and regulatory submission of interim results will be unblinded and the full set of analyses described in this SAP will be performed.

4.3. PRIMARY ANALYSIS

All planned analyses for the primary analysis are detailed in this SAP and will be performed by IQVIA Biostatistics following Sponsor authorization of this SAP, Sponsor authorization of the analysis sets, database lock (DBL), and general study unblinding.

The primary DBL will occur after approximately 150 events that meet the primary endpoint definition have been observed across the active and control groups within the population of participants who are seronegative at baseline. All personnel involved in the analyses of the study will remain blinded until the primary DBL and protocol deviations are identified, unless early evidence of efficacy is demonstrated during interim analysis (refer to Section 4.2 for details).

In the event that the results of the interim or primary analysis are statistically significant for the primary efficacy endpoint, an additional analysis will be performed once all participants have completed their first year of follow up.

4.4. FINAL ANALYSIS

All planned analyses for the final analysis are detailed in this SAP and will be performed by IQVIA Biostatistics following Sponsor authorization of this SAP, Sponsor authorization of the analysis sets, and DBL. All participants in the study will be assessed for efficacy, immunogenicity and safety for 2 years following the first dose of study

intervention (Day 730). 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.

One participant was discovered through monitoring activities to have enrolled into the study at two separate clinical sites under two subject identification numbers (20053000001 & 20052760009). This participant was randomized at both sites and received both doses of study intervention, for a total of four doses. This participant is also believed to have received at least one dose of study intervention for a separate sponsor study of a COVID-19 vaccine candidate. Details related to this issue are under investigation at the time of approval for this analysis plan. This participant will be included in the PAS but will be excluded from all other analysis sets, and thus excluded from all analyses. A separate listing of this participant's data will be prepared.

5.2. FULL ANALYSIS SET

The full analysis set (FAS) will contain all randomized participants who received at least one dose of study intervention, irrespective of their protocol adherence and continued participation in the study. Participants will be analyzed according to their randomized treatment irrespective of whether or not they have prematurely discontinued, according to the intent-to-treat principle. Participants who withdraw consent to participate in the study will be included up to the date of their study withdrawal.

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

5.3. FULLY VACCINATED ANALYSIS SET

The fully vaccinated analysis set (FVS) will include all participants in the FAS who are seronegative at baseline, receive two doses of study intervention, and who remain on-study 15 days after their second dose without having

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had a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection.

The FVS will be used for the primary endpoint analysis as well as for applicable secondary and exploratory endpoints.

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

5.4. PER-PROTOCOL ANALYSIS SET

The per-protocol analysis set (PPS) will include participants in the FVS who receive the correct dose of randomized study intervention and who do not have a serious protocol deviation.

Erroneously-treated participants who receive one dose of active study intervention and one dose of placebo, regardless of the sequence, will be excluded from this analysis set.

Exclusionary serious protocol deviations are those judged to potentially interfere with the generation of an immune response. Details will be defined in a separate protocol deviation (PD) plan (See Section 9.2).

5.5. SAFETY ANALYSIS SET

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

Erroneously-treated participants (e.g., participants who are given treatment different to their randomized treatment) are accounted for in this analysis set by assigning them to the treatment they actually received.

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

5.6. IMMUNOGENICITY ANALYSIS SET

The immunogenicity analysis set (IAS) will include all participants in the SAF who have 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).

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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 be displayed as missing in the listings.

6.2. BASELINE

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 to be baseline, but adverse events (AEs) and medications commencing on the date of the first dose of study intervention will be considered post-baseline.

Illness visit baseline is defined as the first non-missing measurement taken on illness visit day 1. If there is no non-missing measurement available on illness visit day 1, illness visit baseline is considered as missing.

6.3. UNSCHEDULED VISITS, RETESTS, AND EARLY TERMINATION DATA

For by-visit summaries, except for immunogenicity, 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. Visits for immunogenicity data will follow a windowing convention as described in Section 6.4.

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

6.4. WINDOWING CONVENTIONS

A windowing convention will be used to determine the analysis value for a given study visit for immunogenicity data analyses. The window definitions as following will be used for the immunogenicity (serology and cell-mediated immunity (CMI)). The window conventions are:

1. A window of + /- 7 days from the target day is applied to the following visits: Study Days 15, 29, 43 and 57;

2. A window of +/- 28 days from the target day is applied to the following visits: Study Days 180, 360 and 730;

3. For illness visits, a window of + /- 7 days is applied to the following visits: illness visit Days 14 and 28.

Table C: Analysis windows for Immunogenicity by Visit (Main Study and Substudy)

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 180	152	124 - 180
	Day 360	332	304 - 360
	Day 730	702	674 - 730

(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.

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(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. 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 D: Analysis windows for Immunogenicity by Illness Visit

Visit	Scheduled Illness Visit	Visit Window (Illness Day)
Baseline	1	1
Illness Day 14	14	8 - 21
Illness Day 28	28	22 - 35

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.

6.5. COMMON CALCULATIONS

Change from baseline will be calculated as:

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

Percent change from baseline will be calculated as:

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

Change from illness visit baseline will be calculated as:

- Change from illness visit baseline = Test value at post baseline illness visit – Illness visit baseline value

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

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7. STATISTICAL CONSIDERATIONS

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

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

The 2-sided p-value testing null hypothesis that the VE is equal to 30% will be presented for primary analysis of primary endpoint as well as supportive analysis of primary endpoint on PPS. All other tests regarding VE will present p-value testing null hypothesis that the VE is equal 0.

7.1. SAMPLE SIZE CALCULATION

Approximately 33 000 participants will be screened such that approximately 30 000 participants will be randomized in a 2:1 ratio to receive 2 IM doses of either 5×10^{10} vp (nominal, $\pm 1.5 \times 10^{10}$ vp) AZD1222 (the active group, n = approximately 20 000) or saline placebo (the control group, n = approximately 10 000) 4 weeks apart.

Note: 'Enrolled' means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not randomly assigned in the study, are considered 'screen failures,' unless otherwise specified.

The sample size calculations are based on the primary efficacy endpoint and were derived following a modified Poisson regression approach (Zou, 2004). The calculations account for an interim and primary analysis, and the timing of primary analysis will be driven by the number of events observed in the study. The interim analysis will be carried out when approximately 50% of the total amount of statistical information is available. A Lan-DeMets alpha-spending function has been used to account for multiplicity, with 0.31% alpha at the interim analysis and 4.9% at the primary analysis such that the overall Type I error is controlled at 5%. The calculations assume minimal loss to follow-up as it is anticipated that participants will remain engaged in the study. All participants will be followed for the entire duration of the study.

For the primary efficacy analysis, approximately 150 events meeting the primary efficacy endpoint definition are

required across the active and control groups within the population of participants who are seronegative at baseline to detect a VE of 60% with > 90% power. These calculations assume an observed attack rate of approximately 0.8% and are based on a 2-sided test, where the lower bound of the 2-sided 95.10% CI for VE is required to be greater than 30% with an observed point estimate of at least 50%.

An interim efficacy analysis will be conducted when approximately 75 events meeting the primary efficacy endpoint definition have been reported across the active and control groups within the population of participants who are seronegative at baseline, which will give > 70% power to detect a VE of 70% and > 90% power to detect a VE of 75%. These calculations assume an observed attack rate of approximately 0.4% and are based on a 2-sided test, where the lower bound of the 2-sided 99.69% CI for VE is required to be greater than 30% and an observed point estimate of at least 50%. A statistically significant finding at the interim analysis will not be considered a reason to stop the study, but instead will be interpreted as early assessment of efficacy.

7.2. MISSING DATA

Missing efficacy data will be handled as described in Sections 16.1.2, 16.2.2 of this analysis plan.

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

7.3. STATISTICAL TESTS

The null hypothesis for the primary endpoint is: VE is equal to 30%. Whereas, the alternative hypothesis is: VE is not equal to 30%. That is:

- Null hypothesis: VE = 30%
- Alternative hypothesis: VE ≠ 30%

The primary efficacy endpoint will be formally assessed at 2 time points during the study, giving an interim analysis and a primary analysis. A Lan-DeMets alpha-spending function has been used to control the overall type I error at 5% with 0.31% alpha at the interim and 4.9% at the primary analysis. At the interim analysis the VE will be presented with a 2-sided 99.69% CI, and statistical significance will be achieved if the 2-sided 99.69% CI is > 30%. The success criterion for the interim analysis will be statistical significance with an observed VE point estimate of at least 50%. At the primary analysis VE will be presented with a 2-sided 95.10% CI, and statistical significance will be achieved if the 2-sided 95.10% CI is > 30%. The success criterion for the primary analysis of the study will be

statistical significance with an observed VE point estimate of at least 50%.

In the event that the results of the interim or primary analysis are statistically significant for the primary efficacy endpoint, an additional analysis will be performed once all participants have completed their first year of follow up. For this analysis, VE will be presented with a 2-sided 95% CI, and statistical significance will be achieved if the 2-sided 95% CI is > 0%.

For the final analysis, a nominal type I error of 5% will be used for all analyses.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

The primary efficacy endpoint and 4 key secondary endpoints will be assessed at 2 time points during the study, giving an interim analysis and a primary analysis. A Lan-DeMets alpha-spending function has been used to account for multiplicity of the primary endpoint across the 2 time points, with 0.31% alpha at the interim analysis and 4.9% at the primary analysis. Thus, the interim and primary analyses will present estimates with 2 sided 99.69 and 95.10% CIs, respectively, and statistical significance will be achieved if the 2-sided CIs are > 30%. At the interim or primary analysis, the success criterion for the study will be statistically significant with an observed VE point estimate of at least 50%. If the primary endpoint achieves statistical significance at the 0.31% level at the interim (or at the 4.9% level at the primary), a hierarchical approach will be used to control for multiplicity of the primary and key secondary efficacy endpoints. That is, the null hypotheses for these efficacy endpoints will be tested in a hierarchical order, and the subsequent null hypothesis will be tested at a significance level of 0.31% or 4.9% (2-sided), at the interim and primary analysis, respectively, only if the prior null hypothesis is rejected..

A formal assessment of the key secondary efficacy endpoints at the interim or primary analysis will only be conducted if the statistical significance of the primary efficacy endpoint is demonstrated at 2-sided alpha of 0.31% at the interim or 4.9% at the primary analysis. With that, the overall Type I error is controlled at 0.05. Therefore, no further multiplicity adjustment is necessary.

The testing strategy at the interim analysis or primary analysis will be as follows:

- Step 1

    1. Interim analysis: Perform the test of primary endpoint with 0.31% alpha level. If the two-sided 99.69% CI is > 30% with VE point estimate ≥ 50%, then proceed to step 2. Otherwise no null hypothesis is rejected for the interim analysis.

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2. Primary analysis: Perform the test of primary endpoint with 4.9% alpha level. If the two-sided 95.10% CI is > 30% with VE point estimate ≥ 50%, then proceed to step 2. Otherwise no null hypothesis is rejected for the primary analysis.

- Step 2:

1. Interim analysis: Test the 4 key secondary endpoint at the significance level of 0.31% using hierarchical fixed-sequence testing in the order below. If the two-sided 99.69% CI is > 0%, then proceed to the next endpoint.

2. Primary analysis: Test the 4 key secondary endpoint at the significance level of 4.9% using hierarchical fixed-sequence testing in the order below. If the two-sided 95.10% CI is > 0%, then proceed to the next endpoint.

    - Key Secondary Endpoint 1: Incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention regardless of evidence of prior SARS-CoV-2 infection.

    - Key Secondary Endpoint 2: Incidence of the first case of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic COVID-19 occurring ≥ 15 days post second dose of study intervention.

    - Key Secondary Endpoint 3: Incidence of COVID-19-related emergency department visits occurring ≥ 15 days post second dose of study intervention.

    - Key Secondary Endpoint 4: Incidence of the first post-treatment response (negative at baseline to positive post treatment with study intervention) for SARS-CoV-2 Nucleocapsid antibodies occurring ≥ 15 days post second dose of study intervention.

In the event that the results of the interim or primary analysis are statistically significant for the primary efficacy endpoint based on the above testing strategy, an additional analysis will be performed once all participants have completed their first year of follow up. This analysis will use the same testing strategy described above for primary and key secondary endpoints, with a 5% alpha level. Non-key secondary and exploratory endpoints will not be controlled for multiplicity. Thus, nominal 2-sided p-values will be presented to compare the vaccine against the control, alongside 2-sided 95% CIs.

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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. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The analyses will be adjusted for the following covariates and factors. For details of their inclusion in the models, refer the Sections 16.1.3, 16.2.3, and 16.3.1.

- Age group at informed consent (≥ 18 to < 65 years and ≥ 65 years) derived based on date of birth recorded in the interactive response technology (IRT) system.

7.7. EXAMINATION OF SUBGROUPS

Subgroup analyses will be conducted as stated in Sections 16.1.6.

The subgroups are:

- Age group at informed consent (≥ 18 to < 65 years and ≥ 65 years);
- Gender (male and female);
- Serostatus at baseline (negative and positive), where seropositive is defined by a positive Nucleocapsid antibody level as measured by Roche Elecsys Anti-SARS-CoV-2 serology test;
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islanders, White);
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Country
- COVID-19 Co-morbidities at baseline (at least one co-morbidity, no co-morbidity)

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If models of subgroup analysis do not converge due to sparse data, changes to planned subgroup analysis, including omission of the analysis for a subgroup or subgroup level where appropriate, will be described in the CSR.

7.8. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4.

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.

9.1. DISPOSITION

Number of participants screened will be presented overall for the PAS. Number and percentage of participants with screen failure and reason for screen failure will also be presented overall based on the PAS. Number of participants randomized will be presented overall and by study arm for the PAS. Number of participants randomized but not vaccinated will be presented overall and by study arm for the PAS as well.

Number and percentages of participants vaccinated for first dose, ongoing in study (for interim and/or primary analysis only) after first dose, who discontinued early from the study (including reason for withdrawal) before second dose and who discontinued study intervention (including reason for withdrawal) will be provided overall and by study arm based on the all randomized participants. Number and percentages of participants vaccinated for second dose, ongoing in study (for interim and/or primary analysis only) after second dose, remained in study for at least 15 days post second dose, and remained in study for at least 28 days post second dose will be provided overall and by study arm based on the all randomized participants. Additionally, the number of participants unblinded to treatment at the given timepoints and number of participants who received licensed COVID-19 vaccine but were not

unblinded will be provided.

Additionally, the disposition summary table will be repeated respectively for participants who are seronegative at baseline and participants who are seropositive at baseline.

The number of participants included and excluded from each analysis set (including reason for exclusion) will be summarized overall and by study arm based on the all randomized participants. Number of participants included in the sub-study will be presented overall and by study arm.

A listing showing inclusion and exclusion of each participant 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 study arm.

9.2. PROTOCOL DEVIATIONS

All important and exclusionary protocol deviations (separately for the per protocol and immunogenicity analysis sets) will be identified prior to study unblinding from review of study monitoring deviation logs and through programmatic review of blinded data, based on pre-specified criteria. Clinical judgment from the Sponsor will be necessary to classify each deviation as important or exclusionary; reviews will be performed on an ongoing basis throughout the study. Complete details of the pre-defined criteria and clinical review frequency will be documented in a separate PD plan.

The number and percentage of participants with important protocol deviations will be summarized overall and by study arm 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 per-protocol and immunogenicity analysis sets will also be provided overall and by study arm. Protocol deviation categories are defined in the PD plan. A listing of important protocol deviations will also be provided. Non-important protocol deviations are documented in the clinical trial management system and will be filed in the study trial master file. However, they will not be included in summaries and listings within the scope of this analysis plan.

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 7.7)
- Sex
- Race
- Ethnicity
- Weight (kg)
- Height (cm)
- Body Mass Index (BMI) (kg/m^2)
- Country
- Subgroups specified in Section 7.7

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

Additionally, the demographic and other baseline characteristics summary will be repeated by baseline serostatus.

The demographic and other baseline characteristics summary will also be repeated on the FVS, IAS, SAF for the substudy and IAS for the substudy.

10.1. DERIVATIONS

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

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

11. MEDICAL HISTORY

Medical histories are defined as any medical conditions that happened before the first dose of study intervention and

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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 higher, and will be summarized by System Organ Class (SOC) and Preferred Term (PT) overall and by study arm based on the SAF. A participant having more than one surgery/medical condition/disease within the same SOC/PT will be counted only once for that SOC or PT. All medical history will be listed.

Baseline co-morbidities solicited on the eCRF page will be summarized separately from medical histories above overall and by study arm based on the SAF and repeated for the FVS. It will also be summarized by serostatus at baseline.

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 day 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 study arm based on the SAF. 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

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March 2020 or more recent version.

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

All collected prior, concomitant medications will be listed.

14. EXPOSURE TO STUDY INTERVENTION

Due to the simplicity of dosing for this study, exposure is summarized in the participant disposition table. No other summary will be reported.

15. COMPLIANCE WITH STUDY INTERVENTION

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

A summary of the interval between dose 1 and dose 2 of study intervention will be provided overall, and separated for participants randomized prior to the clinical hold and participants randomized after the clinical hold. The dosing interval is calculated as the date of dose 2 – date of dose 1 +1 for all participants who received two doses of study intervention. This analysis will be based on the SAF as well as the IAS for the substudy. The summary based on IAS for the study will also be repeated by age group (18-55 years, 56-69 years, and ≥70 years).

16. EFFICACY ENDPOINTS

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

All data from participants with SARS-CoV-2 RT-PCR-positive results will be assessed by a blinded independent efficacy endpoint adjudication committee, to classify each participant for inclusion in the primary and secondary COVID-19-related outcomes. Additional details are provided in the Efficacy Adjudication Committee Charter.

The central laboratory test result will be used for the determination of a SARS-CoV-2 RT-PCR-positive result. In case the central laboratory result is not available, then the local laboratory test result will be used. In the event that the results of the local and central laboratory are discordant (i.e. local result is positive and central result is negative

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or unknown due to insufficient quantity), the result of the saliva SARS-CoV-2 RT-PCR collected from the illness visit day 1 will be considered.

For all efficacy endpoints which are derived as incidences from binary outcomes, participants who (1) were unblinded to treatment assignment and (2) received licensed COVID-19 vaccine but were not unblinded to treatment assignment, in both cases prior to having met the criteria for the efficacy endpoint will not be counted as having the event. Their follow up time will be censored at the date of unblinding or licensed COVID-19 vaccine administration, whichever is earlier. For all secondary and exploratory endpoints summarized by visit, participants will be excluded for all visits after the date of unblinding/licensed COVID-19 vaccine administration. All data regardless of unblinding/licensed COVID-19 vaccine administration will be listed for all participants, with unblinded/post licensed COVID-19 vaccine administration assessments flagged.

An overall summary of number and percentage of participants who are SARS-CoV-2 RT-PCR-positive, number and percentage of participants who had illness visits overall and by SARS-CoV-2 RT-PCR status, as well as the number of illness visits will be provided by study arm for the FAS and FVS. Number and percentage of participants with secondary and exploratory endpoints for Covid-19 illness will also be included.

Summary statistics for the duration of follow up time from first dose, and from second dose, as well as the duration of follow up time from 15 days post second dose by study arm will be provided for the FAS and FVS.

An overall summary of the primary and key secondary endpoints analysis will be provided on FVS regardless of baseline serostatus. Number and percentage of events, Vaccine Efficacy and corresponding CIs as well as p-value from the model will be presented.

16.1. Primary Efficacy

16.1.1. Primary Efficacy Endpoint

The primary endpoint is the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention, in a participant with negative serostatus at baseline. Participants will be included in the primary endpoint if they have RT-PCR-confirmed SARS-CoV-2 and meet the following criteria at any point from their initial illness visit at the site (Day 1) through their second illness visit (Day 14):

1. One or more Category A findings

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2. Two or more Category B findings

Category A:

- Pneumonia diagnosed by chest x-ray, or computed tomography scan
- Oxygen saturation of ≤ 94% on room air or requiring either new initiation or escalation in supplemental O_2
- New or worsening dyspnea/shortness of breath

Category B:

- Fever > 100 ˚F (> 37.8 ˚C) or feverishness
- New or worsening cough
- Myalgia/muscle pain
- Fatigue that interferes with activities of daily living
- Vomiting and/or diarrhea (only one finding to be counted toward endpoint definition)
- Anosmia and/or ageusia (only one finding to be counted toward endpoint definition)

For participants with negative serostatus at baseline who died ≥ 15 days after second dose, if there was a SARS-CoV-2 RT-PCR-positive result from central lab before death, the participant would be considered as having met the primary endpoint; if there was not a SARS-CoV-2 RT-PCR-positive result from central lab before death, but COVID19 symptoms identified and the participant had a SARS-CoV-2 RT-PCR-positive result from any lab, the participant would be considered as having met the primary endpoint as well.

16.1.2. Missing Data Imputation Method for Primary Efficacy Endpoint

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

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16.1.3. Primary Analysis of Primary Efficacy Endpoint

The primary efficacy analysis of the primary endpoint will be performed on the FVS population. For participants who withdraw from the study prior to having met the criteria for the primary efficacy endpoint, absence of data following these participants' withdrawal (or lost to follow-up, death not caused by SARS-CoV-2) will be treated as missing.

A Poisson regression model with robust variance (Zou, 2004) adjusting for follow-up time, will be used as the primary efficacy analysis model to estimate the relative risk (RR) on the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention between the AZD1222 and the placebo groups. The model contains the term of study arm and age group at the time of informed consent (i.e., ≥ 18 to < 65 years, and ≥ 65 years) as covariates. The logarithm of the participant's corresponding monitoring period at risk starting from 15 days post second dose of study intervention up to the study day 360 visit will be used as an offset variable in the model to adjust for participants having different exposure times during which the events occur. Participants who withdraw or have a non-COVID-19 related death prior to having met the criteria for the primary efficacy endpoint will not be counted as having the event and the follow up time for these participants will be at that time from 15 days post second dose. Participants who (1) were unblinded to treatment assignment and (2) received licensed COVID-19 vaccine but were not unblinded to treatment assignment, in both cases prior to having met the criteria for the efficacy endpoint will not be counted as having the event. Their follow up time will be censored at the date of unblinding/licensed COVID-19 vaccine administration, whichever is earlier. Calculation of follow-up time is detailed as follows:

- For participants who meet the primary endpoint before the end of monitoring period, the follow up time will be calculated as (Date of Onset of Primary Endpoint) – (Date of Second Dosing+15) + 1. Date of Onset of Primary Endpoint is defined as the collection date of central lab positive COVID-19 test, or local lab if central is not available.
- For participants who do not experience a primary endpoint event before the end of monitoring period, the efficacy follow-up time will be determined based on the following:
    - If a SARS-CoV-2 RT-PCR positive symptomatic or asymptomatic event not meeting the primary endpoint criteria occurs during the COVID-19 monitoring period, the efficacy follow-up time will be calculated as (Date of positive COVID-19 test) – (Date of Second Dosing+15) + 1.
    - If an end of study date occurs during the COVID-19 monitoring period, the efficacy follow-up time will be calculated as (Date of End of Study) – (Date of Second Dosing+15) + 1.

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- If an end of study date occurs after the COVID-19 monitoring period, the efficacy follow-up will be censored at the end of COVID-19 monitoring period.

For participants who continue to participate in the study at the time of Interim or Primary Analysis, the data cut-off date will be used as their last assessment date. Vaccine efficacy (VE), which is the incidence in the vaccine group relative to the incidence in the control group expressed as a percentage, will be calculated as relative risk reduction (RRR) = 1- relative risk. RRR and its corresponding 2-sided 99.69 or 95.10% CI depending on if efficacy is declared at the interim or primary analysis, respectively (95% will be used for primary efficacy analysis at the time of final DBL), will be estimated from the Poisson regression model with robust variance. In addition, the 2-sided p-value testing null hypothesis that the VE is equal to 30% will be obtained from the model. Statistical significance will be achieved if the 95.10 or 99.69% CI for VE is > 30%. The success criterion for the study will be statistical significance with an observed VE point estimate of at least 50%.

The Poisson regression with robust variance analysis will be implemented by using the SAS PROC GENMOD procedure with the REPEATED statement for participant ID and logarithm link as well as OFFSET option. The estimated parameter $\hat{\beta}$ [i.e., log($\widehat{RR}$)], 2-sided 99.69 or 95.10% (5% will be used for primary efficacy analysis at final DBL) confidence interval (CI) for $\hat{\beta}$, and the 2-sided p-value will be obtained from the SAS outputs. The estimated RR and corresponding CI for the RR is given by exponentiating $\hat{\beta}$ and its confidence limits. Therefore, the percent of RRR is given by [(1 – exp($\hat{\beta}$) * 100%]. The CI for the percent of RRR is given by ([1 – exp(upper confidence limit for $\hat{\beta}$) * 100%], [1 – exp(lower confidence limit for $\hat{\beta}$) * 100%]).

If the number of participants in any stratum is too small and/or convergence cannot be achieved with the Poisson regression analysis model, the model will be reduced to exclude the age group covariate. If convergence is not achieved by excluding the age group covariate, a stratified Exact Poisson Regression model will be used as the primary analysis model to test the treatment effect on SARS-CoV-2 RT-PCR-positive symptomatic illness between AZD1222 and placebo groups. The number of events for each combination of treatment and strata will be used as the response variable. The logarithm of total number of participants for each combination of treatments and strata will be used as an offset variable in the model. The Exact Poisson Regression test will be stratified by age group at the time of informed consent (i.e., ≥ 18 to < 65 years, and ≥ 65 years). SAS procedure of PROC GENMOD with EXACT statement will be used to perform the analysis. The RR of AZD1222 over placebo for the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention and the 99.69 or 95.10% CI will be obtained from the SAS procedure. The percent of RRR and the 99.69 or 95.10% CI will be reported following the relationship of RRR (%) = (1- RR) * 100%. In the event that active study arm has 0 events and Placebo has ≥ 1 event, the maximum likelihood estimate (MLE) for the RR is zero, corresponding to VE=100%, however PROC GENMOD gives a median unbiased estimate instead of the MLE and the upper

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confidence limit of VE cannot be estimated in this extreme situation. In such cases, the VE will be set to the MLE (100%) and the 1-sided (99.845% for interim, 97.55% for primary, and 97.5% for final analysis) confidence interval will be presented for completeness. The inverse will be treated similarly when there are 0 events in the placebo arm and ≥ 1 event in the active arm, such that the VE will be set to -Infinity and the one-sided confidence interval will be presented.

The number and percentages of participants with SARS-CoV-2 RT-PCR-positive symptomatic illness will also be presented for the following intervals: participants prior to 15 days post the first dose, between 15 days post the first dose and prior to the second dose, between the second dose and 15 days post the second dose, between 15 days post the second dose and prior to month 6, between month 6 and month 12, overall after first dose.

16.1.4. Sensitivity Analyses for Primary Efficacy Endpoint

As a sensitivity analysis to the handling of missing data in the analysis of the primary efficacy endpoint, the primary analysis of the primary efficacy endpoint (refer to Section 16.1.3) will be repeated with multiple imputation for intercurrent events, without using log follow-up time as offset. For participants who are in FVS but (1) do not have a SARS-CoV-2 RT-PCR-positive symptomatic illness status occurring ≥ 15 days post second dose of study intervention and withdraw from the study prior to the time of analysis, or (2) are in FVS and were unblinded to treatment assignment prior to having met the criteria for the efficacy endpoint or (3) received licensed COVID-19 vaccine but were not unblinded to treatment assignment prior to having met the criteria for the efficacy endpoint, their event status will be imputed assuming the observed placebo attack rate conditional on stratification factor using multiple imputation techniques as described in the following paragraphs.

The primary analysis uses Poisson regression with robust variance requires a participant-level dataset. A repeated imputation approach is introduced to impute the status of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention for missing observations at the participant-level for the model fitting. By incorporating the between-imputation variance, a reliable statistical inference in both hypothesis testing and CI estimation of the treatment effect is expected through the repeated imputation (Little and Rubin, 2002). In the primary analysis the missing outcome for participants who drop out (e.g., withdrawal, lost to follow-up, death not caused by SARS-CoV-2, etc) prior to reaching cut-off time for analysis without a SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention will be imputed per stratum determined by the stratification factor using placebo event rate. The imputation and subsequent analysis will be carried out using SAS PROC MI (Monotone Logistic Regression Method) and SAS PROC MIANALYZE. The detailed imputation steps are described as follows.

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- Step 1: For the FVS participants in the AZD1222 arm who (1) do not have an SARS-CoV-2 RT-PCR-positive symptomatic illness and are not followed through cut-off time of analysis or (2) were unblinded to treatment assignment prior to having met the criteria for the efficacy endpoint or (3) received licensed COVID-19 vaccine but were not unblinded prior to having met the criteria for the efficacy endpoint, their treatment code of "AZD1222" will be substituted with "placebo" to ensure the placebo SARS-CoV-2 RT-PCR-positive symptomatic illness rate is applied in the imputation for the AZD1222 dropouts adjusted for their stratification values. The imputation will be executed using SAS Proc MI (e.g., logistic regression with the recoded treatment term and stratification factor). The random seed is 12345.

- Step 2: The original treatment code will be restored after the SARS-CoV-2 RT-PCR-positive symptomatic illness statuses have been imputed. A complete dataset comprises the imputed SARS-CoV-2 RT-PCR-positive symptomatic illness status and observed SARS-CoV-2 RT-PCR-positive symptomatic illness status.

- Step 3: Analyse the complete dataset using a Poisson regression model with robust variance to estimate the RR on the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness between AZD1222 and placebo, with the term of study arm and the stratification factor. The point estimate of log-transformed RR and its variance will be extracted from the model.

- Steps 2-3 will be repeated 20 times. SAS procedure PROC MIANALYZE will be used to combine inferences from the 20 completed datasets, that will result in a combined point estimate of log-transformed RR and the variance.

Additional sensitivity analyses will be carried out as given below

- Multiple imputation as described above using the observed event rate per treatment group for their event status

16.1.5. Supplementary Analyses for Primary Efficacy Endpoint

To support the primary analysis, a Cox Proportional Hazards model using the same covariates as for the primary analyses as well as Kaplan-Meier curves will be presented for the active and control groups based on observed events, showing the cumulative incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention. Time to event, i.e., the duration in days since 15 days

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post second study dose to event or censoring, will be fit using the PH model with study arm as a factor and age group as stratum. Hazards ratios for each study arm along with the two-sided 95% CI will be obtained from the PH model. The number of participants with primary endpoint and the number of censored participants will also be provided. The censoring timing at each month will be displayed.

Another supplementary analysis is to break down the primary analysis described in Section 16.1.3 by repeating it for events occurring < 6 months from first dose of study intervention and ≥ 6 months from the first dose of study intervention up to the end of the COVID-19 monitoring period to show the efficacy over time.

The primary analysis described in Section 16.1.3 will also be repeated on PPS as a supplementary analysis. Same 2-sided p-value testing null hypothesis that the VE is equal to 30% will be present.

Additionally, the primary analysis will be repeated, excluding participants with out-of-window vaccination due to the clinical hold, i.e., participants who received their first dose of study intervention between 28 August 2020 and 06 September 2020.

The primary analysis will be repeated and will include participants in the FVS who (1) were unblinded to treatment assignment or (2) received licensed COVID-19 vaccine but were not unblinded, in both cases prior to having met the criteria for the efficacy endpoint. Censoring at study unblinding or licensed COVID-19 vaccine administration will not be performed.

16.1.6. Subgroup Analyses for Primary Efficacy Endpoint

Subgroup analysis will be performed for the primary efficacy endpoint, SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention. For subgroup analysis, FVS set is used except for the subgroup analysis for serostatus at baseline which will use the FVS regardless of baseline serostatus. Treatment-by-subgroup interaction will be tested using the Poisson regression with robust variance model adjusting for follow-up time with the terms of treatment, age group, subgroup, and treatment-by-subgroup interaction, which will be implemented using PROC GENMOD procedure. If this full model does not achieve convergence, a reduced model of treatment, subgroup, and treatment-by-subgroup interaction will be used. Within each level of a subgroup, the RRR and its corresponding 95% CI will be estimated using a Poisson regression model with robust variance with the term of treatment, age group at informed consent and adjusting for follow-up time. A forest plot of the RRR and the 95% CI will be presented.

The subgroup analysis will be conducted for the subgroups in Section 7.7, provided there are sufficient events observed for each subgroup level. In the case of sparse data for one or more levels of a subgroup, alternative

analysis approaches may be used, such as combining subgroup levels or fitting separate models for each subgroup, using the methods described in Section 16.1.3 for Exact Poisson Regression. Alternative approaches will be described in the study report.

For subgroups corresponding to one of the stratification factors included in the analysis model, the corresponding factor will not be included in the model.

16.2. SECONDARY EFFICACY

The secondary efficacy endpoints which are derived from binary outcomes are described in following sections.

16.2.1. SECONDARY EFFICACY ENDPOINTS

16.2.1.1. The Incidence of the First Post-treatment Response (Negative at Baseline to Positive Post Treatment with Study Intervention) for SARS-CoV-2 Nucleocapsid Antibodies Occurring ≥ 15 Days Post Second Dose of Study Intervention

A key secondary endpoint, included in the multiplicity algorithm, is the incidence of the first post-treatment response (negative at baseline to positive post treatment with study intervention) for SARS-CoV-2 Nucleocapsid antibodies occurring ≥ 15 days post second dose of study intervention.

Blood samples will be collected as per the schedule of events (refer to protocol Section 1.3) for SARS-CoV-2 serology testing to monitor participants for infection.

16.2.1.2. The Incidence of the First Case of SARS-CoV-2 RT-PCR Positive Symptomatic Illness Occurring ≥ 15 Days Post Second Dose of Study Intervention Using CDC Criteria

A secondary endpoint is the incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention using adapted CDC criteria (Appendix 6 in this SAP), with no minimum duration of symptoms required to satisfy the endpoint criteria.

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16.2.1.3. Incidence of the First Case of SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring ≥ 15 Days Post Second Dose of Study Intervention Using University of Oxford Defined Symptom Criteria

A secondary endpoint is the Incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention using University of Oxford defined symptom criteria: new onset of fever (> 100 °F [> 37.8 °C]), cough, shortness of breath, or anosmia/ageusia.

16.2.1.4. Incidence of the First Case of SARS-CoV-2 RT-PCR Positive Symptomatic Illness Occurring ≥ 15 Days Post Second Dose of Study Intervention Regardless of Evidence of Prior SARS-CoV-2 Infection

A key secondary endpoint, included in the multiplicity algorithm, is the incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention regardless of evidence of prior SARS-CoV-2 infection.

16.2.1.5. Incidence of SARS-CoV-2 RT-PCR-positive Severe or Critical Symptomatic Illness Occurring ≥ 15 Days Post Second Dose of Study Intervention

A key secondary endpoint, included in the multiplicity algorithm, is the incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring ≥ 15 days post second dose of study intervention. The severity of COVID-19 will be evaluated in participants with symptoms of COVID-19. A diagnosis of severe or critical COVID-19 will include laboratory-confirmed COVID-19 (SARS-CoV-2 RT-PCR-positive symptomatic illness) plus any of the findings presented as following. The calculation of the follow up time (included as offset in model) will be calculated by using the date symptoms become severe (as assessed by the endpoint adjudication committee) as the reference date.

Findings Regarding Severe/Critical Symptomatic COVID-19 are listed as below.

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ⩾ 30 breaths per minute, heart rate ⩾ 125 beats per minute, oxygen saturation ⩽ 93% on room air at sea level, or partial pressure of oxygen to fraction of inspired oxygen ratio < 300 mm Hg)
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation)

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- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction
- Admission to an intensive care unit
- Death

The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring post first dose of study intervention will also be presented for participants in the FAS who are seronegative at baseline.

16.2.1.6. Incidence of COVID-19-related Emergency Department Visits Occurring ≥ 15 Days Post Second Dose of Study Intervention

A key secondary endpoint, included in the multiplicity algorithm, is the incidence of COVID-19-related emergency department visits occurring ≥ 15 days post second dose of study intervention. Adjudicated results as assessed by the endpoint adjudication committee will be used to identify COVID-19-related emergency department visits.

16.2.1.7. The Incidence of COVID-19 SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring Post First Dose of Study Intervention

The incidence of COVID-19 SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post first dose of study intervention will be analyzed in the same manner as the primary analysis of the primary efficacy endpoint (refer to Section 16.1.3) based on participants in FAS who were seronegative at baseline.

Kaplan-Meier curves will be presented for the active and control groups based on observed events, showing the cumulative incidence of the event. The Time to event is calculated as the duration in days since first study dose to event or censoring.

All incidence of COVID-19 SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post first dose of study intervention will be listed.

16.2.2. Missing Data Imputation Method for Secondary Efficacy Endpoints

No imputation method will be used for secondary efficacy endpoints.

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16.2.3. Analysis of Secondary Efficacy Endpoints

Incidence of event secondary efficacy endpoints in sections above will be analyzed in the same manner as the primary analysis of the primary efficacy endpoint (refer to Section 16.1.3) using the FVS, except for the key secondary endpoint of the incidence of the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose of study intervention regardless of evidence of prior SARS-CoV-2 infection, which will be evaluated using the FVS regardless of prior SARS-CoV-2 infection, where infection refers to both RT-PCR and serology.

Follow-up time for secondary endpoints based on symptom criteria (CDC, University of Oxford, and severe or critical COVID-19, symptomatic COVID-19 post first dose) will be derived as described in section 16.1.3. Follow-up time for other COVID-19-related secondary and exploratory endpoints will be derived similarly, however no censoring will occur at a SARS-CoV-2 RT-PCR positive symptomatic or asymptomatic event not meeting the endpoint.

For incidence of event secondary efficacy endpoints in sections above, Kaplan-Meier curves will also be presented for the active and control groups based on observed events, showing the cumulative incidence of the event. The time to event is calculated as Section 16.1.5.

Additionally, the proportion of participants with post-treatment response (negative at baseline to positive post treatment with study intervention) for SARS-CoV-2 Nucleocapsid Antibodies will also be summarized based on FAS by study arm and visit, overall and by PCR result. The proportion of participants will be derived for the vaccine and control group, with corresponding 95% Clopper-Pearson exact CIs at each nominal timepoint in Protocol Section 1.3.

For key secondary endpoints based on FVS, a subgroup analysis by baseline serostatus will be performed using the same methods described for the primary efficacy analysis in Section 16.1.6.

16.3. Exploratory Efficacy

The exploratory efficacy endpoints are:

- The incidence of all-cause mortality from Day 1 through Day 730
- The incidence of COVID-19-related deaths occurring from Day 1 through Day 730

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- The incidence of COVID-19-related hospitalizations occurring ≥ 15 days post second dose of study intervention
- The incidence of COVID-19-related ICU admissions occurring ≥ 15 days post second dose of study intervention
- Viral genome copies in NP swabs collected at Illness Visits as determined by qRT-PCR (Illness Visits only)
- Genotypic analysis of SARS-CoV-2 from NP swabs collected on Day 1 illness visit (Illness Visits only)
- Duration of SARS-CoV-2 shedding in saliva over time (Illness Visits only)
- Biophysical parameters, including but not limited to serial measurements of skin temperature, heart rate, respiratory rate, blood oxygen saturation, and physical activity, recorded using a biosensor from illness visits Day 1 through Day 28 (Illness Visits only)
- Symptoms recorded by participants in an Illness e-Diary from illness visits Day 2 through Day 28 (Illness Visits only)

An overview of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose will be provided and will include:

- Number of illness visits
- Number of SARS-CoV-2 RT-PCR-positive results for each visit

These summaries will be repeated for the following intervals: second dose date + 15 days to < 6 months from the first dose date and ≥ 6 months from first dose date to end of COVID-19 monitoring period.

16.3.1. Analysis of Exploratory Efficacy Endpoints

16.3.1.1. The Incidence of All-cause Mortality Occurring from Day 1 through Day 730

The incidence of all-cause mortality from Day 1 through Day 730 will be analyzed in the same manner as the primary analysis of the primary efficacy endpoint (refer to Section 16.1.3) based on participants in FAS who were seronegative at baseline. Follow-up time will be derived as described in section 16.2.3 for COVID-19-related

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secondary and exploratory events.

Kaplan-Meier curves will be presented for the active and control groups based on observed events, showing the cumulative incidence of the event. The time to event is calculated as Section 16.1.5.

All incidence of all-cause mortality from Day 1 through Day 730 will be listed.

16.3.1.2. The Incidence of COVID-19-related Deaths Occurring from Day 1 through Day 730

The incidence of COVID-19 related deaths occurring from Day 1 through Day 730 will be analyzed in the same manner as the primary analysis of the primary efficacy endpoint (refer to Section 16.1.3) based on participants in FAS who were seronegative at baseline. Follow-up time will be derived as described in section 16.2.3 for COVID-19-related secondary and exploratory events.

Kaplan-Meier curves will be presented for the active and control groups based on observed events, showing the cumulative incidence of the event. The time to event is calculated as Section 16.1.5.

All incidence of COVID-19 related deaths occurring from Day 1 through Day 730 will be listed.

16.3.1.3. The Incidence of COVID-19-related Hospitalizations Occurring ≥ 15 Days Post Second Dose of Study Intervention

The incidence of COVID-19-related hospitalizations occurring ≥ 15 days post second dose of study intervention will be analyzed in the same manner as the primary analysis of the primary efficacy endpoint (refer to Section 16.1.3) based on participants in FVS. Follow-up time will be derived as described in section 16.2.3 for COVID-19-related secondary and exploratory events.

Kaplan-Meier curves will be presented for the active and control groups based on observed events, showing the cumulative incidence of the event. The time to event is calculated as Section 16.1.5.

All incidence of COVID-19-related hospitalizations occurring ≥ 15 days post second dose of study intervention will be listed.

As a supportive analysis, the incidence of COVID-19-related hospitalizations occurring post first dose of study intervention will also be analyzed for participants in the FAS who are seronegative at baseline.

16.3.1.4. The Incidence of COVID-19-related ICU Admissions Occurring ≥ 15 Days Post Second Dose of Study Intervention

The incidence of COVID-19-related ICU admissions occurring ≥ 15 days post second dose of study intervention will be analyzed in the same manner as the primary analysis of the primary efficacy endpoint (refer to Section 16.1.3) based on participants in FVS. Follow-up time will be derived as described in section 16.2.3 for COVID-19-related secondary and exploratory events.

Kaplan-Meier curves will be presented for the active and control groups based on observed events, showing the cumulative incidence of the event. The time to event is calculated as Section 16.1.5. All incidence of COVID-19-related ICU admissions occurring ≥ 15 days post second dose of study intervention will be listed.

All incidence of COVID-19-related ICU admissions occurring ≥ 15 days post second dose of study intervention will be listed.

As a supportive analysis, the incidence of COVID-19-related ICU admissions occurring post first dose of study intervention will also be analyzed for participants in the FAS who are seronegative at baseline.

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

An exploratory efficacy endpoint is the Viral genome copies which will be collected via SARS-CoV-2 qRT-PCR test at central laboratory as scheduled in protocol section 1.3. Observed and change from illness visit baseline in viral load will be summarized by study arm and time points for the Illness Visits. If a participant has multiple sets of illness visits, the first set of illness visits with positive RT-PCR test result will be used for the summary. The analysis would be based on participants in IAS.

A listing will be provided for viral genome copies.

16.3.1.6. Genotypic Analysis of SARS-CoV-2 from NP Swabs Collected on Day 1 Illness visit

An exploratory efficacy endpoint is the Genotypic analysis of SARS-CoV-2 from NP swabs collected on illness visits. This analysis will be conducted by another party and will not be covered in this SAP.

16.3.1.7. Duration of SARS-CoV-2 Shedding in Saliva over Time

- **Viral Shedding**

An exploratory efficacy endpoint is the duration of SARS-CoV-2 shedding in saliva over time. If a participant has multiple sets of illness visits, the first set of illness visits with positive RT-PCR test result will be used for the summary. Saliva samples for viral shedding will be collected at illness visits as indicated in Protocol section 1.3. The number and proportion of participants shedding on illness visit days 1, 3, 5, 8, 11, 14, 21 and 28 will be summarized. Exact 95% CIs will be computed. The analysis would be based on participants in IAS.

The duration of SARS-CoV-2 shedding in saliva will be calculated as following:

Duration (days) = (Date of illness visit when viral shedding first tested as persistently negative or date of last illness visit when test was positive, if no negative test available) – Date of first positive + 1. A cumulative incidence plot for the time to clearance for shedding will be provided for participants with positive SARS-CoV-2 in saliva.

The number of days of shedding will be summarized by descriptive statistics.

A listing will be provided for viral shedding.

- **Viral Quantitation**

For values reported as lower than the lower limit of quantitation (LLoQ), a value equal to half of the limit of quantification will be imputed in viral quantitation summaries. Missing values will not be imputed in viral quantitation summaries.

For the subset of participants in IAS who shed, viral quantities as measured by qRT-PCR will be summarized on illness visit days 1, 3, 5, 8, 11, 14, 21 and 28. Summary statistics will be presented describing the mean, standard deviation, median, minimum and maximum of Log_{10} (viral copies/mL) at baseline (Date of first positive) and each post-baseline time-points. Change from baseline at each post-baseline time point will also be summarized.

Time weighted change from baseline to each post-baseline time-point is derived on a by-participant basis using the linear trapezoidal rule with all available data from baseline to that specific time-point minus the baseline value. This is defined as (Area Under the Curve [AUC])/number of days – baseline value, between baseline to that specific post-baseline time-point. AUC from baseline to each post-baseline time-point will be reported as well.

Figures such as Log_{10} (viral copies/mL) over time (mean ± SD), AUC and time weighted change from baseline of Log_{10} (viral copies/mL) over time (box plots) will be provided.

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16.3.1.8. Biophysical Parameters, including but not limited to Serial Measurements of Skin Temperature, Heart rate, Respiratory Rate, Blood Oxygen Saturation, and Physical Activity, Recorded Using a Biosensor from Illness Visits Day 1 through Day 28

A group of efficacy endpoints are biophysical parameters collected from Current Health wearable device. The analysis of these exploratory results will be conducted by another party and are not covered by this SAP.

16.3.1.9. Symptoms Recorded by Participants in an Illness e-Diary from Illness Visits Day 2 through Day 28

A group of exploratory endpoints are symptoms collected by participants in an illness e-Diary. Symptoms from the first SARS-CoV-2 RT-PCR-positive symptomatic illness occurring ≥ 15 days post second dose will be summarized. If a participant has multiple sets of illness visits, the first set of illness visits with positive RT-PCR test result will be used for the summary. The number and percentage of participants with these symptoms, onset study day of these symptoms as well as the duration days will be summarized by study arm. Percentage is based on the number of participants with illness visits. The analysis would be based on participants in FVS.

All symptoms from each illness visit will be listed.

17. IMMUNOGENICITY ENDPOINTS

Unless otherwise indicated, all immunogenicity summaries will be presented by study arm and visit (visits from substudy and separately for visits from illness visits), when appropriate, based on the IAS.

All participants will be assessed for serum samples for SARS-COV-2 serology testing. The first participants randomized in each age group in the USA, including 1,500 participants 18 to 55 years of age, 750 participants 56 to 69 years of age, and 750 participants ≥ 70 years of age will also participate in a substudy assessing the immunogenicity of AZD1222.

For all immunogenicity endpoints, participants will be censored at the date of unblinding/licensed COVID-19 vaccine administration, whichever occurs first, such that data from all visits after the date of unblinding/licensed COVID-19 vaccine administration will be excluded from derivations and all by-visit summaries. All immunogenicity data regardless of unblinding/licensed COVID-19 vaccine administration will be listed for all participants, with unblinded/post licensed COVID-19 vaccine administration assessments flagged.

For summaries over time in participants from the substudy, participants who do not receive dose 2 of study

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intervention will be excluded from all time points post dose 2.

The immunogenicity secondary endpoints are:

- Post-treatment GMTs and GMFRs from day of dosing baseline value to 28 days post each dose in SARS-CoV-2 S, RBD antibodies (MSD serology assay) (Substudy and Illness Visits only)
- Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from day of dosing baseline value to 28 days post each dose) to the S, RBD antigens of AZD1222 (MSD serology assay) (Substudy and Illness Visits only)
- Post-treatment GMTs and GMFRs from day of dosing baseline value to 28 days post each dose in SARS-CoV-2 neutralizing antibodies (wild-type assay or pseudo-neutralization assay) (Substudy and Illness Visits only)
- Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from day of dosing baseline value (see Section 17.1.3) to 28 days post each dose) to AZD1222 as measured by SARS-CoV-2 neutralizing antibodies (wild-type assay or pseudo-neutralization assay) (Substudy and Illness visits only)

The exploratory immunogenicity endpoints are:

- Post-treatment GMTs and GMFRs from Day 1 baseline value to 28 days post each dose in ACE2 competing antibodies from serum samples (Substudy only)
- Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from day of dosing baseline value to 28 days post each dose) in ACE2 competing antibodies (Substudy only)
- Post-treatment GMTs and GMFRs from Day 1 baseline value to 28 days post each dose in SARS-CoV-2 S, RBD, and Nucleocapsid antibodies (MSD serology assay) (Substudy only, from participants enrolled in the immunogenicity cohort, from nasal secretions)
- Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from Day 1 baseline value to 28 days post each dose) to SARS-CoV-2 S, RBD, and Nucleocapsid antigens (MSD serology assay) (Substudy only, from participants enrolled in the immunogenicity cohort, from nasal secretions)
- Post-treatment GMTs and GMFRs from Day 1 baseline value to 28 days post each dose in ChAdOx1

neutralizing antibodies (Substudy only)

- Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titers from Day 1 baseline value to 28 days post each dose) to AZD1222 as measured by ChAdOx1 neutralizing antibodies (Substudy only)

The exploratory cell-mediated immune (CMI) response endpoints are:

- Quantification of (IFN-γ) ELISpot responses to SARS-CoV-2 S protein from day of dosing baseline to 14 days post each dose (Substudy only, from participants in the immunogenicity cohort)
- Intracellular cytokine staining and flow cytometry for B- and T-cell responses from day of dosing baseline to 14 days post each dose (Substudy only, from participants in the immunogenicity cohort)

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.

17.1. Analysis of Immunogenicity Endpoints

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

17.1.1. Geometric Mean Titers and Geometric Mean Fold Rise

GMTs and GMFRs will be calculated for the vaccine and control groups and will be summarized at each scheduled visit as per protocol section 1.3 for the following titer measurements and participants:

- SARS-CoV-2 S, RDB antibodies from serum samples for participants in substudy and separately for participants positive for SARS-CoV-2
- SARS-CoV-2 neutralizing antibodies from serum samples for participants in substudy and separately for participants positive for SARS-CoV-2
- ACE2 competing antibodies from serum samples for participants in substudy
- SARS-CoV-2 S, RDB and Nucleocapsid antibodies from nasal samples by antibody isotype (IgG, IgA) for participants in substudy and enrolled in the immunogenicity cohort.

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

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.

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.

The GMT and GMFR endpoints will be analyzed using an analysis of variance (ANOVA) model which includes the log base 2-transformed value of titer (or log base 2-transformed value of fold rise for GMFR) as the dependent variable and study arm and age group as factors. On the log scale, the models will be used to estimate a mean response for the vaccine and control groups and the difference (vaccine - control), with corresponding 95% confidence limits. These values will then be back-transformed to give geometric means for the vaccine and control groups and a ratio of geometric means (vaccine/control), with corresponding 95% confidence limits. A p-value, corresponding to a 2-sided test, will be presented to compare the vaccine against the control. The p-value will be nominal as secondary endpoints are not controlled for multiplicity. This analysis will be performed on participants who are seronegative at baseline (i.e. participants having a titer value < LLoQ at baseline).

The above analyses for serum samples of SARS-CoV-2 S, RBD and Nucleocapsid antibodies as well as SARS-CoV-2 neutralizing antibodies will also be performed separately by baseline serostatus. Additionally, summaries for participants in the substudy will be presented by age group (18-64 years, ≥65 years) and by clinical hold status (randomized prior to clinical hold, randomized after clinical hold).

17.1.2. SERORESPONSE RATE

Seroresponse is a binary outcome where a success is when the fold rise in titers compared to baseline is ≥4. Seroresponse will be calculated for the vaccine and control groups and will be summarized at each scheduled visit as per protocol section 1.3 for the following titer measurements and participants:

- SARS-CoV-2 S, RDB antibodies from serum samples for participants in substudy and separately for participants positive for SARS-CoV-2

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[redacted]

- SARS-CoV-2 neutralizing antibodies from serum samples for participants in substudy and separately for participants positive for SARS-CoV-2
- ACE2 competing antibodies from serum samples for participants in substudy
- SARS-CoV-2 S, RDB and Nucleocapsid antibodies from nasal samples by antibody isotype (IgG, IgA) for participants in substudy and enrolled in the immunogenicity cohort
- ChAdOx1 neutralizing antibodies from serum samples for participants in substudy

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. These seroresponse summaries for serum samples of SARS-CoV-2 S, RBD and Nucleocapsid antibodies as well as SARS-CoV-2 neutralizing antibodies will also be performed separately by baseline serostatus. Additionally, summaries for participants in the substudy will be presented by age group (18-64 years, ≥65 years) and by clinical hold status (randomized prior to clinical hold, randomized after clinical hold).

17.1.3. Missing Data Imputation Method for Immunogenicity Endpoints

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 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.

Titer values measured as above ULoQ will be imputed at the ULoQ value.

17.2. Analysis of Cell-mediated Immune Response Endpoints

CMI responses (i.e., B-cell and T-cell responses) will be collected from up to 300 participants in the substudy, approximately 300 participants in the immunogenicity cohort and from up to 3 000 participants, where operationally feasible, during the Day 1 illness visit, and any participants with a Day 1 SARS-CoV-2 positive test result by local RT-PCR test. CMI data will be reported separately from CSR.

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18. SAFETY ENDPOINTS

The safety of AZD1222 will primarily be assessed by:

- Incidence of AEs for 28 days post each dose of study intervention
- Incidence of SAEs from Day 1 post treatment through Day 730
- Incidence of MAAE (defined in Protocol Section 8.3.8) and AESIs (defined in Protocol Section 8.3.9) from Day 1 post treatment through Day 730
- Incidence of local and systemic solicited AEs for 7 days post each dose of study intervention (substudy only)

There are also other safety endpoints such as vital signs.

All safety summaries will be presented by study arm based on the SAF. There will be no statistical comparisons between the study arms for safety data.

For participants who are unblinded to treatment assignment during the study and received licensed COVID-19 vaccine but were not unblinded, the unblinding/licensed COVID-19 vaccine administration will be treated as an intercurrent event. Safety data collected during the unblinded/post licensed COVID-19 vaccine administration follow up period will be excluded from all summaries directly comparing the AZD1222 and placebo study arms, using exposure adjusted rates to account for differences in duration of double-blinded follow up for SAEs, MAAEs, and AESIs which are collected through the full 2-year study period. SAEs, MAAEs, and AESIs will also be summarized for the double-blinded period, unblinded period/post licensed COVID-19 vaccine period, and overall, separately for each study arm.

Summary statistics of follow up time, as well as number and percentage of participants at risk at each month post first study intervention will also be provided on SAF. This summary will include the follow-up time post first dose as well as the follow-up time post second dose.

18.1. ADVERSE EVENTS

All AEs are considered to be unsolicited AEs (collected by ‘open question’ at study visits) unless categorized as solicited AEs recorded in the substudy only.

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[redacted]

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

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

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

All AE summary tables listed below will be repeated respectively for participants who are seronegative at baseline and participants who are seropositive at baseline.

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

- All AEs
- 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
- MAAEs
- AEs with outcome of death
- AESIs

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

An overall summary of number and percentage of participants, 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 study arm based on the SAF.

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An overall summary of number and percentage of participants, including exposure adjusted rates, and number of events within categories of all SAEs, related SAEs, related SAEs by severity, AEs leading to study discontinuation, related AEs leading to study discontinuation, MAAEs, AEs with outcome of death and AESIs during the entire period of study will be provided by study arm based on the SAF. 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.

18.1.1. Adverse Events

Adverse events post the first study intervention occurring within 28 days of each dose will be summarized by SOC and PT by study arm. Specific AEs will be counted once for each participant for calculating percentages.

Non-serious AEs reported by > 1% participants in any study arm, including exposure adjusted rates, will be summarized by PT. AEs reported by > 1% participants in any study arm within 28 days of each study intervention will also be summarized by PT.

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.

Listings of AEs will be provided, with events occurring after unblinding/licensed COVID-19 vaccine administration flagged.

18.1.1.1. Severity for AEs

Severity will be classified as mild, moderate or severe (increasing severity) by using FDA Grading for AEs. Severity 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 severity FDA grade will be counted for that SOC or PT.

18.1.1.2. 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.

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[redacted]

18.1.2. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" 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 study arm. Specific SAEs will be counted once for each participant for calculating percentages.

Summary of SAEs post the first study intervention, including exposure adjusted rates, will also be broken down further by post each dose, maximum severity and events related to study intervention. 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 study arm as well.

SAEs will also be summarized for the double-blinded period, unblinded period/post COVID-19 licensed vaccine administration, and overall, separately for each study arm. This summary will be repeated for related SAEs.

Listings of SAEs will be provided, with events occurring after unblinding/licensed COVID-19 vaccine administration flagged. SAEs prior to the first study intervention will only be presented in the listings. For SAEs with partial dates, if the known part of the date indicates that SAE stopped before the 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.

18.1.3. AEs Leading to Discontinuation of Study Intervention

AEs leading to permanent discontinuation of study intervention are those participants recorded as not complete the full course of study intervention on the "Adverse Event" pages of the eCRF. AEs leading to permanent discontinuation of study intervention will be recorded within 28 days post first dose of study intervention. A summary of AEs leading to permanent discontinuation of study intervention by SOC and PT will be prepared.

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

A listing of all AEs leading to permanent discontinuation of study intervention will be provided, with events occurring after unblinding/licensed COVID-19 vaccine administration flagged.

18.1.4. AEs Leading to Discontinuation of Study

AEs leading to permanent discontinuation of study are those participants recorded as not complete the study on the "Adverse Events" pages of the eCRF. Non-serious AEs leading to permanent discontinuation of study will be recorded within 28 days post each dose of study intervention. SAEs, MAAEs, and AESIs leading to permanent discontinuation of study will be recorded through to end of study. A summary of AEs within 28 days post each dose of study intervention leading to permanent discontinuation of study by SOC and PT will be prepared. A summary of SAEs, MAAEs, and AESIs during the entire period of study leading to permanent discontinuation of study by SOC and PT will be prepared, including exposure adjusted rates.

A summary of related AEs occurring within 28 days post each dose of study intervention leading to permanent discontinuation of study by SOC and PT will be prepared. A summary of related SAEs, MAAEs, and AESIs during the entire period of study leading to permanent discontinuation of study by SOC and PT will also be prepared, including exposure adjusted rates.

SAEs, MAAEs, and AESIs leading to permanent discontinuation of study will also be summarized for the double-blinded period, unblinded period/post licensed COVID-19 vaccine administration period, and overall, separately for each study arm. This summary will be repeated for related SAEs, MAAEs, and AESIs leading to permanent discontinuation of study.

A listing of all AEs leading to permanent discontinuation of study will be provided, with events occurring after unblinding/licensed COVID-19 vaccine administration flagged.

18.1.5. AEs with Outcome of Death

AEs with outcome of death are those participants recorded as having an AE with "Fatal" outcome on the "Adverse Event" pages of the eCRF. A summary of AEs with outcome of death by SOC and PT will be prepared, including exposure adjusted rates. A summary of related AEs with outcome of death by SOC and PT will also be prepared, including exposure adjusted rates.

AEs with outcome of death will also be summarized for the double-blinded period, unblinded period/post licensed COVID-19 vaccine administration period, and overall, separately for each study arm. This summary will be repeated for related AEs with outcome of death.

A listing of all AEs with outcome of death will be provided, with events occurring after unblinding/licensed COVID-19 vaccine administration flagged.

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18.1.6. Medically Attended Adverse Events

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 study arm 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.

MAAEs will also be summarized for the double-blinded period, unblinded period/post licensed COVID-19 vaccine administration, and overall, separately for each study arm.

A listing of all MAAEs will be provided, with events occurring after unblinding/licensed COVID-19 vaccine administration flagged.

18.1.7. Adverse Events of Special Interest

AEs 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 study arm 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. AESIs will also be summarized for the double-blinded period, unblinded period/post licensed COVID-19 vaccine administration period, and overall, separately for each study arm. This summary will be repeated for related AESIs.

AESIs will be summarized by the subgroups of baseline serostatus, age group, sex, and race.

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A listing of all AESIs will be provided, with events occurring after unblinding/licensed COVID-19 vaccine administration flagged.

18.1.8. Additional Summaries of Adverse events

A summary of adverse events in the SOC of Nervous System Disorders by PT and study arm will be prepared, including exposure adjusted rates. Should a participant experience multiple events within a PT, the participant will be counted only once for that PT. AEs in the SOC of Nervous System Disorders will also be summarized by baseline serostatus, age group, sex, and race. These events will also be summarized for the double-blinded period, unblinded period/post licensed COVID-19 vaccine administration, and overall, separately for each study arm.

The above summaries will be repeated for the following:

- Vascular Disorders of Embolism and Thrombosis.
- Potentially Immune-Mediated Conditions (see Appendix 7)
- Standard MedDRA Queries (SMQs):
    - Demyelination
    - Peripheral neuropathy
    - Guillain-Barre Syndrome
    - Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous
    - Immune mediated/autoimmune disorders
    - Anaphylactic reaction
    - Hypersensitivity

18.2. Solicited Adverse Events (Only for Substudy)

For participants in the substudy, safety will be assessed daily for 7 days after vaccination (symptoms reported in the last 24 hours are collected on Days 2-8) via e-diary collection of solicited AEs. These include local events (pain, tenderness, redness/erythema, swelling) and systemic events (fever [body temperature > 100 °F or 37.8 °C], chills,

muscle pains, fatigue, headache, malaise, nausea, and vomiting). Measurements of the largest diameter for each of the injection site reactions (erythema/redness, swelling) are collected. These measurements will be used to derive severity grades based on the criteria presented in Appendix 4. Severity categories for systemic solicited AE are defined in Appendix 5.

Each solicited AE will be summarized at the following time intervals: overall during the interval Days 1-7 (captured on days 2-8 post vaccination), and daily during the interval Days 1-7 (individually, captured on days 2-8 post each vaccination). 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, participants with mild events, participants with moderate events, participants with severe events, and participants with 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 "Overall" and solicited systemic AEs "Overall". Same summaries for solicited AEs will also be presented by subgroups of serostatus and age groups (18-55, 56-69, ≥70 years; 18-64, ≥65 years).

A 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 2, Day 3, and Day 5 would be included with a duration of 3 days).

A listing of all solicited AEs will be provided, with events occurring after unblinding/licensed COVID-19 vaccine administration flagged.

18.3. VITAL SIGNS

The following vital sign parameters will be collected for SARS-CoV-2-positive participants for this study as per the schedule of events (refer to protocol, Section 1.3):

- Systolic blood pressure (SBP) (mmHg)
- Diastolic blood pressure (DBP) (mmHg)
- Heart rate (beats per minute [bpm])
- Pulse rate (beats per minute [bpm])

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- Respiratory rate (breaths/min)
- Body temperature (C/F)
- Oxygen saturation (%)

The severity grade of abnormal Vital Signs can be referred to Appendix 3.

The following summaries will be provided by study arm based on the SAF for each vital sign parameter:

- Observed and change from study baseline at the first illness visit associated with a positive SARS-CoV-2 RT-PCR result;
- Number and percentages of participants with at least one abnormal post-baseline observed value (refer to Appendix 3);

All vital sign data will be listed, with assessments after unblinding/licensed COVID-19 vaccine administration flagged.

18.4. PHYSICAL EXAMINATION

18.4.1. GENERAL PHYSICAL EXAMINATION

Physical examinations (completed and targeted) 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) or AE summaries (refer to Section 18.1), as appropriate. That is, no summaries will be specifically provided for the general physical examination.

18.4.2. CHEST IMAGING

Listing of chest imaging results for participants with a chest imaging assessment will be provided, with assessments occurring after unblinding/licensed COVID-19 vaccine administration flagged.

19. REFERENCES

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

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

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 STUDY ARMS

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

Study arm	Tables and Graphs	Listings
AZD1222	1	1
Placebo	2	2
Total [1]	3	n/a
Randomized, Not Vaccinated	n/a	3
Screen Failure	n/a	4

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

PRESENTATION OF NOMINAL VISITS

For outputs, analysis visits regarding non-illness visit will be represented as follows and in that order:

Long Name (default)	**Short Name**
Screening	Scrn
Day 1	D1
Day 8	D8
Day 15 (Substudy only)	D15
Day 29	D29
Day 36	D36
Day 43 (Substudy only)	D43
Day 57	D57
Day 90	D90
Day 180	D180
Day 360	D360
Day 730	D730

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

Long Name (default)	**Short Name**
Illness Visit Day X, X=1,3,5,8,11,14,21,28	ILDXX, X=1,3,5,8,11,14,21,28

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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: N;
- Mean, median, Q1, Q3, 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.

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 study arm (or study intervention received if it's a safety output);
- Participant ID;
- Parameter, when applicable;
- Date/Time, when applicable.
- Timepoint, when applicable

APPENDIX 3. CLINICAL ABNORMALITIES

Clinical Abnormalities: Vital Signs

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

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

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

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

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

ER = emergency room; Hg = mercury.

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APPENDIX 4. 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 centimeters) 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 e-Diary.

ER = emergency room.

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APPENDIX 5. CLINICAL ABNORMALITIES: SYSTEMIC

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. COVID-19 SYMPTOMS PER CDC CRITERIA

COVID-19 Symptoms Per CDC Criteria

Participant must present with at least one of the following symptoms
Symptom
Fever
Shortness of breath
Difficulty breathing
Chills
Cough
Fatigue
Muscle aches
Body aches
Headache
New loss of taste
New loss of smell
Sore throat
Congestion
Runny nose
Nausea
Vomiting
Diarrhea

CDC, 2020.

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APPENDIX 7. ADVERSE EVENTS OF SPECIAL INTEREST

AZD1222 AESIs 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 AESIs.

AESI	Medical Concept
Neurologic	Generalized convulsion: Seizures are episodes of neuronal hyperactivity most commonly resulting in sudden, involuntary muscular contractions. They may also manifest as sensory disturbances, autonomic dysfunction and behavioral abnormalities, and impairment or loss of consciousness.
	Guillain-Barré syndrome: GBS is a peripheral nerve demyelinating disease, which can present as temporary ascending paralysis.
	Acute disseminated encephalomyelitis: ADEM is 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 pediatric population.
	Other neurologic events: These events would include new onset event (acute or subacute) motor and sensory disturbances (eg, weakness, numbness, paresthesias, 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: These are 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: Thrombocytopenia is 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: Vasculitides are a group of related disorders characterized by inflammation of blood vessels (vasculitis) leading to tissue or end-organ injury.
	Anaphylaxis: 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.

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AESI	Medical Concept
Immunologic (Continued)	Vaccine-associated enhanced respiratory disease: The pathogenicity of VAERD 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 (Lambert et al 2020). 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 (Rajão et al 2016).
	Potential immune-mediated conditions: These conditions are a group of autoimmune inflammatory disorders characterized by an alteration in cellular homeostasis, which may or may not have an autoimmune aetiology. A list of events is provided in **Error! Reference source not found.** of the clinical study protocol.

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

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