Clinical Study Protocol	
Study Intervention	AZD1222
Study Code	D8110C00001
Version	Amendment 2
Date	17 September 2020

TITLE PAGE

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

Sponsor Name:	**AstraZeneca AB**
Legal Registered Address:	151 85 Södertälje, Sweden
Regulatory Agency Identifier Number(s):	**IND number 23522**

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: D8110C00001

Amendment Number: 2

Study Intervention: AZD1222

Study Phase: III

Short Title: Phase III Double-blind, Placebo-controlled Study of AZD1222 for the Prevention of COVID-19 in Adults

Study Physician Name and Contact Information will be provided separately

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	17 September 2020
Amendment 1	10 August 2020
Original Protocol	15 July 2020

Amendment 2 (17 September 2020)

Overall Rationale for the Amendment:

The principal reason for this amendment was to address US FDA feedback to the Investigational New Drug application. Additional changes included statistical revisions per DSMB request and other revisions to provide clarity or correct inadvertent errors. All the changes were considered non-substantial.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.1 Synopsis	Updated Objectives and Endpoints, Overall Design, Statistical Methods	To align with edits in the protocol body	Non-substantial
1.3 Schedule of Activities, Table 3	Removed 'at least' to clarify that PBMCs will be isolated from approximately 300 participants	Clarification	Non-substantial
1.3 Schedule of Activities, Table 4	a) Added new footnote 'b' to indicate that collection of saliva sample for viral shedding assessment is optional in Chile/Peru and may occur after a feasibility assessment has been completed b) Footnote 'c': removed the requirement for the RT-PCR test to be a rapid test	a) Feasibility of collection of saliva samples in Chile/Peru is underway b) Not a requirement per protocol and provides more flexibility to the sites	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
3 Objectives and Endpoints, Table 5	a) Revised definition of intercurrent event b) Revised secondary objective 1 to assess for all SARS-COV-2 infection c) Added an exploratory objective to estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for COVID-19-related deaths d) Added an exploratory objective to estimate the efficacy of AZD1222 compared to placebo for the prevention of COVID-19 following the first dose e) Renumbered exploratory objective 12: removed 'serum' prior to B- and T-cell responses	a) To align with changes in the primary analysis b) To align with analyses c) Per US FDA request d) Per DSMB request e) To correct a misstatement	Non-substantial
4.1 Overall Design	Removed requirement to limit initial enrollment to participants 18 to 55 years of age	The US FDA reviewed the accrued data from the ongoing University of Oxford studies and approved enrollment in all age groups prior to enrollment of the first subject.	Non-substantial
6.2.1 Dose Preparation and Administration	Clarified description for use of AZD1222 and placebo within the beyond-use-date	To avoid confusion in the time period from the first needle puncture of the AZD1222 vial or placebo vial/IV bag to dose administration	Non-substantial
6.2.1.1 AZD1222 (Additional change)	Removed specification for a 1 mL syringe to be used for AZD1222 dose preparation	To provide flexibility in dose administration	Non-substantial
6.5 Concomitant Therapy	Specified that all concomitant medication must be recorded in the eCRF	Per US FDA request	Non-substantial
6.5.1 Permitted Concomitant Medications	Clarified the concomitant medications permitted for the treatment of COVID-19 after receiving study intervention	Per US FDA request	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
6.5.2 Prohibited Concomitant Medications	a) For participants who received a prohibited concomitant medication, described the potential impact on participation in the study, including study withdrawal, discontinuation of study intervention, or evaluability in analysis data sets b) Added immunoglobulins and/or blood product	a) Per US FDA request b) For alignment with exclusion criterion 13	Non-substantial
7.1 Discontinuation of Study Intervention	a) Added new criterion for laboratory-confirmed SARS-CoV-2 infection b) Revised criterion that any allergic reaction related to study intervention, regardless of severity grade, will result in study discontinuation c) Added new criterion for receipt of prohibited concomitant medication that may jeopardize the safety of the participant or interpretation of the data	a) Clarification b) Per US FDA request c) Per US FDA request	Non-substantial
8.1.2 Illness Visits	Clarified that home collection requirements include digital health device and Illness e-Diary recordings, and saliva samples	Per US FDA request	Non-substantial
8.1.2.2 Digital Health Device	Described the monitoring protocols for triage and follow-up of alerts from the digital health device	Per US FDA request	Non-substantial
8.5.2.4 Assessment of Cell-mediated Immune Responses	Clarified the number of participants who will provide PBMC samples, ie, approximately 300 in the substudy and from up to approximately the first 3 000 during the Day 1 illness visit	To align with the SoA Table 3 and Table 4	Non-substantial
8.6.1.1 Virologic Assessments (additional change)	Clarified that a validated multiplexed respiratory panel may be utilized to assess the presence of respiratory pathogens	Multiplexed respiratory panel testing is not an absolute requirement	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
8.6.1.2 Assessment of Viral Shedding	a) Clarified that saliva collection is performed utilizing a Spectrum DNA (SDNA-1000) collection kit b) Removed 'qualitative' to describe the type of shedding assessment c) Added information that collection of saliva sample for viral shedding assessment is optional in Chile/Peru and may occur after a feasibility assessment has been completed	a) Clarification b) Updated due to an assay improvement c) Feasibility of collection of saliva samples in Chile/Peru is underway	Non-substantial
9 Statistical Considerations 9.1, 9.2, 9.4, 9.4.2.1, 9.4.4, and 9.5	Amended the testing strategy, sample sizing, as well as number of events required for the interim and primary analyses	Per DSMB request	Non-substantial
9.3 Populations for Analysis, Table 9	Added definition for immunogenicity analysis set	To describe the population to be used for the immunogenicity assessments	Non-substantial
9.4.1 General Considerations	Revised definition of intercurrent event	To align with changes in the primary analysis	Non-substantial
9.4.2 Efficacy	a) Added reference to new Appendix G (see description for Appendix G below) b) Added description of an adjudication committee that will review data of potential cases for the COVID-19-related efficacy endpoints	a) Per US FDA request b) To provide clarity on the process for determining cases to be included in the COVID-19-related efficacy evaluations	Non-substantial
9.4.2.1 Primary Endpoint (additional change)	Clarified a supportive analysis of the primary endpoint	Incorrect statement about censored observations removed	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
9.4.2.2 Secondary Endpoints	a) Bullet 1: Clarified that the endpoint will assess the proportion of participants who have a post-treatment response (negative at baseline to positive post treatment with study intervention) for SARS-CoV-2 Nucleocapsid antibodies over time b) Bullet 2: Included the endpoint to assess the incidence of SARS-CoV-2 RT-PCR positive symptomatic illness using the CDC criteria c) Bullet 3: Clarified the University of Oxford symptom criteria used to assess the incidence of SARS-CoV-2 RT-PCR positive symptomatic illness d) Specified the analyses for the incidence endpoints, and added a description of the analysis for participants positive for SARS-CoV-2 Nucleocapsid antibodies	a) To align with analyses b) Corrected an inadvertent omission c) Per US FDA request d) Clarification	Non-substantial
Appendix A5 Committee Structure	Added description of an adjudication committee that will review data of potential cases for the COVID-19-related efficacy endpoints	To provide clarity on the process for determining cases to be included in the COVID-19-related efficacy evaluations	
Appendix G Overview of Primary and Secondary Efficacy Objectives, Endpoints, and Associated Case Definitions	New overview table presenting the primary and secondary efficacy objectives, endpoints, and associated case definitions	Per US FDA request	Non-substantial
Appendix I Protocol Amendment History	Moved summary of changes for Protocol Amendment 1 to this new appendix	Per protocol template	Non-substantial

CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 2019; eCRF = electronic case report form; DSMB = Data Safety Monitoring Board; e-Diary = electronic diary; IM = intramuscular; NP = nasopharyngeal; PBMC = peripheral blood mononuclear cell; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus 2; SoA = schedule of activities; US FDA = United States Food and Drug Administration.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: 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

Short Title: Phase III Double-blind, Placebo-controlled Study of AZD1222 for the Prevention of COVID-19 in Adults

Rationale: The aim of the study is to assess the safety, efficacy, and immunogenicity of AZD1222 for the prevention of COVID-19. The COVID-19 pandemic has caused major disruption to healthcare systems with significant socioeconomic impacts. Currently, there are no specific treatments available against COVID-19 and accelerated vaccine development is urgently needed. A safe and effective vaccine for COVID-19 prevention would have significant public health impact.

Objectives and Endpoints

Objective [a]	Estimand [b] Description/Endpoint
PRIMARY	
1 To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of COVID-19 in adults ≥ 18 years of age	**Population:** Full analysis set, excluding participants who are seropositive at baseline.
	Endpoint: 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.
	Intercurrent events: 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 (ie, 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.
	Summary measure: VE, calculated as 1-relative risk. (Relative risk is the incidence of infection in the vaccine group relative to the incidence of infection in the control group.)
2 To assess the safety and tolerability of 2 IM doses of AZD1222 compared to placebo in adults ≥ 18 years of age	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

Objective [a]	Estimand [b] Description/Endpoint
3 To assess the reactogenicity of 2 IM doses of AZD1222 compared to placebo in adults ≥ 18 years of age (Substudy only)	Incidence of local and systemic solicited AEs for 7 days post each dose of study intervention
SECONDARY	
1 To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of SARS-CoV-2 infection	The proportion of participants who have a post-treatment response (negative at baseline to positive post treatment with study intervention) for SARS-CoV-2 Nucleocapsid antibodies over time
2 To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of symptomatic COVID-19 using CDC criteria	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
3 To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of University of Oxford-defined symptomatic COVID-19	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
4 To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of severe or critical symptomatic COVID-19	The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring ≥ 15 days post second dose of study intervention
5 To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of COVID-19-related Emergency Department visits	The incidence of COVID-19-related Emergency Department visits occurring ≥ 15 days post second dose of study intervention
6 To assess antibody responses to AZD1222 S antigen following 2 IM doses of AZD1222 or placebo (Substudy and Illness Visits only)	a) 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)
	b) The 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)
7 To determine anti-SARS-CoV-2 neutralizing antibody levels in serum following 2 IM doses of AZD1222 or placebo (Substudy and Illness Visits only)	a) 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)
	b) 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 AZD1222 as measured by SARS-CoV-2 neutralizing antibodies (wild-type assay or pseudo-neutralization assay)

Objective [a]	Estimand [b] Description/Endpoint

[a] Substudy: The first participants randomized in each age group, 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.
Illness Visits: Participants who present with qualifying symptoms will be tested for SARS-CoV-2 and if positive, will complete illness visits.

[b] Estimand is the target of estimation to address the scientific question of interest posed by the primary objective. Attributes of an estimand include the population of interest, the variable (or endpoint) of interest, the specification of how intercurrent events are reflected in the scientific question of interest, and the population-level summary for the variable.

AE = adverse event; AESI = adverse event of special interest; CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 2019; GMFR = geometric mean fold rise; GMT = geometric mean titer; IFN-γ = interferon-gamma; IM = intramuscular; MAAE = medically attended adverse event; MSD = Meso Scale Discovery; RT-PCR = reverse transcriptase polymerase chain reaction; RBD = receptor binding domain; S = Spike; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; VE = vaccine efficacy.

For exploratory objectives, see Section 3.

Overall Design: 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. Up to approximately 100 sites in the USA will participate in this study. Study sites outside of the USA will also be considered based on predicted transmission rates of SARS-CoV-2 in those locations.

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.

All participants will be assessed for efficacy and safety. The first participants randomized in each age group, 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.

A PSRT will provide safety surveillance during the study. Additionally, an independent COVID-19 Vaccine DSMB organized by the National Institutes of Health, National Institute for Allergy and Infectious Diseases, will provide oversight, to ensure safe and ethical conduct of the study.

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 may be offered AZD1222 if doses are available. Placebo participants treated with AZD1222 will continue to be followed in the study.

Disclosure Statement: This is a parallel-group preventive study with 2 arms that is participant-, investigator-, and Sponsor-blinded.

Number of Participants: Approximately 33 000 participants will be screened to achieve up to approximately 30 000 participants randomly assigned to study intervention, including 20 000 participants randomized to the AZD1222 arm and 10 000 participants randomized to the saline placebo arm.

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.'

Intervention Groups and Duration: Participants will be randomized in a 2:1 ratio to receive 2 IM doses of 5×10^{10} vp (nominal, $\pm 1.5 \times 10^{10}$ vp) AZD1222 or saline placebo. Study intervention will be administered on Day 1 and Day 29.

Data Monitoring Committee: Yes

Statistical Methods

Primary efficacy endpoint

The primary efficacy endpoint is a binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs ≥ 15 days post second dose of study intervention. Otherwise, a participant is not defined as a COVID-19 case.

Sample size

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, on Days 1 and 29.

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 these analyses 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 control the overall type I error at 5% with 0.31% alpha at the interim analysis and 4.9% at the primary analysis. 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 within the population of participants who are not seropositive at baseline are required across the active and control groups 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 endpoint definition have been reported across the active and control groups within the population of participants who are not seropositive 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% with 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.

Primary estimand

The primary estimand will be used for the analysis of the primary efficacy endpoint. It will be based on participants in the full analysis set, defined as all randomized participants who received at least 1 dose of study intervention excluding those participants who are seropositive at baseline, analyzed according to their randomized treatment. For participants with multiple events, only the first occurrence will be used for the primary efficacy endpoint analysis. The set of intercurrent events for this estimand consists of participants who withdraw from the study prior to having met the primary efficacy endpoint. The intercurrent events will be handled using the treatment policy strategy and the absence of data following these participants' withdrawal will be treated as missing (ie, 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.

Primary efficacy analysis

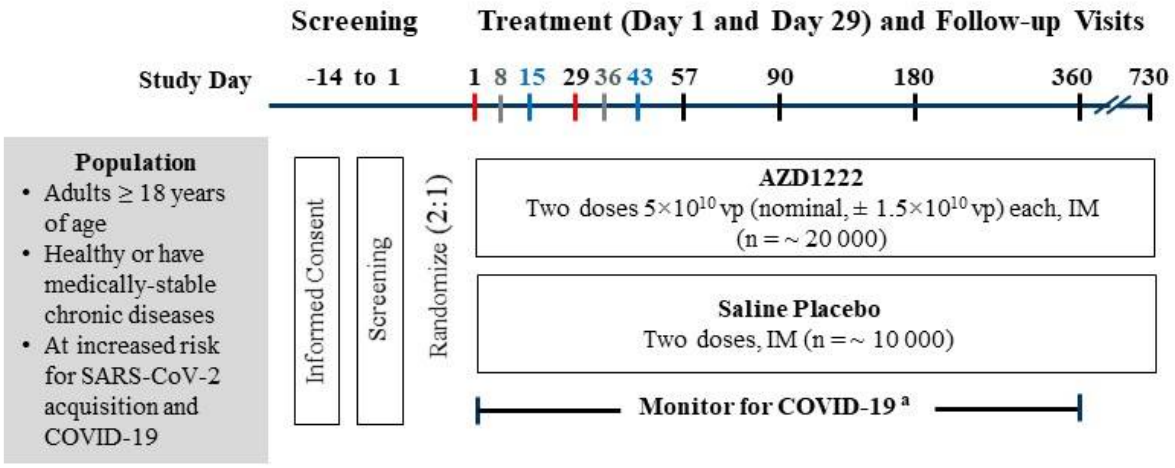
As the primary efficacy analysis, the plan is to use the primary estimand and a Poisson regression model with robust variance (Zou 2004) to analyze the primary efficacy endpoint, which will include age as a baseline covariate as well as the log of the follow-up time as an offset. The VE will be estimated from the model, which will give the RRR in the incidence of

SARS-CoV-2 RT-PCR-positive symptomatic illness. VE is calculated as RRR = 100*(1-relative risk), which is the incidence of infection in the vaccine group relative to the incidence of infection in the control group expressed as a percentage. 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%.

Model assumptions will be checked and the robustness of the primary analysis will be assessed. The Poisson regression model with robust variance has the flexibility for exploring multiple imputation approaches using, eg, the observed placebo attack rate to impute missing data. If the Poisson regression model with robust variance fails to converge, an alternative approach will be implemented. Full details will be documented in the SAP.

1.2 Schema

Figure 1 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, 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; vp = viral particles.

1.3 Schedule of Activities

The SoA tables include:

- Table 1, Screening Period
- Table 2, Treatment and Follow-Up Period – Main Study (Excluding Substudy Participants)
- Table 3, Treatment and Follow-Up Period - Substudy
- Table 4, Illness Visits (Participants with Qualifying Clinical Symptoms)

Table 1 Schedule of Activities: Screening Period

Procedure / Study Day	Day -14 to Day 1 [a]	For details see Section
Informed consent: main study	X	5.1
Informed consent: genetic sample and analysis (optional)	X	5.1, 8.7
Assignment SID number	X	6.3
Medical history	X	5.1, 5.2
Complete physical examination, including height and weight	X	8.2.1
Vital signs (including pulse oximetry)	X	8.2.2
Pregnancy test – urine or serum (WOCBP only) [b]	X	8.2.3
Assessment of SAEs	X	8.3
Concomitant medications	X	6.5
Verify eligibility criteria	X	5.1, 5.2

[a] If screening and dosing occur at the same visit, only one evaluation is required.

[b] If urine tests positive or indeterminate, a quantitative serum β-hCG will be performed for confirmation.

β-hCG = beta-human chorionic gonadotropin; SAE = serious adverse event; SID = subject identification; WOCBP = women of childbearing potential.

Table 2 Schedule of Activities: Treatment and Follow-up Period – Main Study (Excluding Substudy Participants)

Procedure	Treatment and Follow-up Period									For details see Section
Day	**1**	**8 [a]**	**29**	**36 [a]**	**57**	**90**	**180**	**360**	**730**	
Window (days)	**NA**	**± 3**	**± 3**	**± 3**	**± 3**	**± 5**	**± 10**	**± 15**	**± 30**	
Medical history	X									5.1, 5.2
Targeted physical examination	X									8.2.1
Vital signs (including pulse oximetry)	X									8.2.2
Pregnancy test – urine or serum (WOCBP only) [b]	X (predose)		X (predose)							8.2.3
Concomitant medications	X	X	X	X	X	As applicable, for treatment of SAE, MAAE, or AESI				6.5
Verify eligibility criteria	X									5.1, 5.2
Genomics Initiative optional, exploratory genetic sample	X (predose)									8.7, Appendix D
Study intervention administration	X		X							6.1, 6.2
Efficacy assessments										
Weekly telephone/email/text contacts - monitoring for COVID-19 qualifying symptoms [c]	←							→		8.1.1
Nasal swab for SARS-CoV-2 RT-PCR (local laboratory)	X (predose)									
Serum sample for SARS-CoV-2 serology testing	X (predose)		X (predose)		X	X	X	X	X	8.5.2
Immunogenicity assessments										
Serum sample for exploratory assessment	X (predose)		X (predose)		X					8.5.2.5
Safety assessments										
AEs	X	X	X	X	X					8.3
SAEs, MAAEs, and AESIs	X	X	X	X	X	X	X	X	X	

Table 2 Schedule of Activities: Treatment and Follow-up Period – Main Study (Excluding Substudy Participants)

Procedure	Treatment and Follow-up Period									For details see Section
Day	**1**	**8 [a]**	**29**	**36 [a]**	**57**	**90**	**180**	**360**	**730**	
Window (days)	**NA**	**± 3**	**± 3**	**± 3**	**± 3**	**± 5**	**± 10**	**± 15**	**± 30**	
Telephone contact for safety monitoring		X		X						

[a] Not a study site visit; participants will be contacted by telephone for safety monitoring

[b] If urine tests positive or indeterminate, a quantitative serum β-HCG will be performed for confirmation.

[c] Weekly contact with participants to remind them to present to the study site for SARS-CoV-2 testing if they have qualifying symptoms

AE = adverse event; AESI = adverse event of special interest; β-hCG = beta-human chorionic gonadotropin; MAAE = medically attended adverse event; NA = not applicable; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; WOCBP = women of childbearing potential.

Table 3 Schedule of Activities: Treatment and Follow-up Period – Substudy

Procedure	Treatment and Follow-up Period											For details see Section
Day	**1**	**8 [a]**	**15**	**29**	**36 [a]**	**43**	**57**	**90**	**180**	**360**	**730**	
Window (days)	**NA**	**± 3**	**± 1**	**± 3**	**± 3**	**± 3**	**± 3**	**± 5**	**± 10**	**± 15**	**± 30**	
Medical history	X											5.1, 5.2
Targeted physical examination	X											8.2.1
Vital signs (including pulse oximetry)	X											8.2.2
Pregnancy test – urine or serum (WOCBP only) [b]	X (predose)			X (predose)								8.2.3
Concomitant medications	X	X	X	X	X	X	X	As applicable, for treatment of SAE, MAAE, or AESI				6.5
Verify eligibility criteria	X											5.1, 5.2
Genomics Initiative optional, exploratory genetic sample	X (predose)											8.7, Appendix D
Study intervention administration	X			X								6.1.1
Efficacy assessments												
Weekly telephone/email/text contacts - monitoring for COVID-19 qualifying symptoms [c]	←										→	8.1.1
Nasal swab for SARS-CoV-2 RT-PCR (local laboratory)	X (predose)											
Serum sample for SARS-CoV-2 serology testing	X (predose)		X	X (predose)		X	X	X	X	X	X	8.5.2
Immunogenicity assessments												
Serum sample for ChAdOx1 nAbs assessment	X (predose)			X (predose)			X		X	X	X	8.5.2
Serum sample for seasonal CoV serology testing	X (predose)			X (predose)			X		X	X		

Table 3 Schedule of Activities: Treatment and Follow-up Period – Substudy

Procedure	Treatment and Follow-up Period											For details see Section
Day	**1**	**8 [a]**	**15**	**29**	**36 [a]**	**43**	**57**	**90**	**180**	**360**	**730**	
Window (days)	**NA**	**± 3**	**± 1**	**± 3**	**± 3**	**± 3**	**± 3**	**± 5**	**± 10**	**± 15**	**± 30**	
PBMCs for assessment of B-cell and T-cell responses [d]	X (predose)		X			X						8.5.2
Serum sample for SARS-CoV-2 nAbs assessment	X (predose)		X	X (predose)		X	X		X	X		
Nasal adsorption for SARS-CoV-2 mucosal responses	X (predose)		X	X (predose)		X	X		X	X		
Serum sample for ACE2 competition serology	X (predose)			X (predose)			X		X			
Safety assessments												
Local and systemic predefined solicited AEs (recorded daily by participant in Solicited AE e-Diary)	X (through Day 8)			X (through Day 36)								8.3.7
AEs	X	X	X	X	X	X	X					8.3
SAEs, MAAEs, and AESIs	X	X	X	X	X	X	X	X	X	X	X	
Telephone contact for safety monitoring		X			X							

[a] Not a study site visit; participants will be contacted by telephone for safety monitoring

[b] If urine tests positive or indeterminate, a quantitative serum β-hCG will be performed for confirmation.

[c] Weekly contact with participants to remind them to present to the study site for SARS-CoV-2 testing if they have qualifying symptom

[d] PBMCs will be isolated from approximately 300 participants at select study sites, as outlined in the laboratory manual.

ACE2 = angiotensin-converting enzyme 2; AE = adverse event (treatment-emergent); AESI = adverse event of special interest; β-hCG = beta-human chorionic gonadotropin; CoV = coronavirus; COVID-19 = coronavirus disease 2019; MAAE = medically attended adverse event; NA = not applicable; nAb = neutralizing antibody; PBMC = peripheral blood mononuclear cell; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; WOCBP = women of childbearing potential.

Table 4 Schedule of Activities: Illness Visits (Participants with Qualifying Clinical Symptoms)

Procedure [a]	Site Visit	Home Collection by Participant				Site Visit for SARS-CoV-2 Positive Participants Only			For details see Section
Day	**1**	**3**	**5**	**8**	**11**	**14**	**21**	**28**	
Window (days)	**NA**	**± 1**	**± 1**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	
Medical history	X					X	X	X	8.1
Brief physical examination	X					X	X	X	8.2.1
Vital signs (including pulse oximetry)	X					X	X	X	8.2.2
Concomitant medication	←	—	—	—	—	—	—	→	6.5
Efficacy assessments									
Digital health device	←	—	—	—	—	—	—	→	8.1.2.2
Symptoms associated with COVID-19 (recorded daily by participant in Illness e-Diary)	←	—	—	—	—	—	—	→	8.1.2.3
Virology assessments									
Nasal swab for SARS-CoV-2 RT-PCR (local laboratory)	X								8.1.2.1
Nasopharyngeal swab									
SARS-CoV-2 RT-PCR (central laboratory)	X					X	X	X	8.1.2.1
SARS-CoV-2 sequencing (central laboratory)	X					X			
Respiratory panel	X								8.6.1.1
Saliva sample for viral shedding [b]	X	X	X	X	X	X	X	X	8.6.1.2
Immunogenicity assessments									
PBMCs for B-cell and T-cell responses	X [c]					X			8.5.2
Serum sample for SARS-CoV-2 nAbs assessment	X					X		X	
Nasal adsorption for SARS-CoV-2 mucosal responses	X					X		X	

Table 4 Schedule of Activities: Illness Visits (Participants with Qualifying Clinical Symptoms)

Procedure [a]	Site Visit	Home Collection by Participant				Site Visit for SARS-CoV-2 Positive Participants Only			For details see Section
Day	**1**	**3**	**5**	**8**	**11**	**14**	**21**	**28**	
Window (days)	**NA**	**± 1**	**± 1**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	
Serum sample for ACE2 competition serology	X					X		X	8.5.2
Serum sample for exploratory assessments	X					X		X	
Safety assessments									
SAEs, MAAEs, and AESIs	←							→	8.3
Telephone contact for safety monitoring		X		X					

[a] Following availability of the SARS-CoV-2 RT-PCR results, only participants who test positive will continue with the illness visits, including any home collection requirements. Participants who test negative for SARS-CoV-2 will be instructed to stop all illness visit assessments and return the digital health device (see Section 8.1.2).

[b] Collection of saliva sample for viral shedding is optional in Chile/Peru and may occur after a feasibility assessment has been completed.

[c] PBMCs will be collected from up to approximately the first 3 000 participants on Day 1 illness visit and any participants with a Day 1 SARS-CoV-2 positive test result by local RT-PCR test (see Section 8.5.2.4)

ACE2 = angiotensin-converting enzyme 2; AESI = adverse events of special interest; CoV = coronavirus; COVID-19 = coronavirus disease 2019; MAAE = medically attended adverse event; NA = not applicable; nAb = neutralizing antibody; PBMC = peripheral blood mononuclear cell; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2.

2 INTRODUCTION

AZD1222 is being developed for the prevention of COVID-19. AZD1222 is a recombinant replication-defective chimpanzee adenovirus expressing the SARS-CoV-2 S surface glycoprotein driven by the human cytomegalovirus major immediate early promoter that includes intron A with a human tPA leader sequence at the N terminus.

2.1 Study Rationale

The aim of the study is to assess the safety, efficacy, and immunogenicity of AZD1222 for prevention of COVID-19. The COVID-19 pandemic has caused major disruption to healthcare systems with significant socioeconomic impacts. Currently, there are no licensed preventions available against COVID-19 and accelerated vaccine development is urgently needed. A safe and effective vaccine for COVID-19 prevention would have significant global public health impact.

2.2 Background

In December 2019, a cluster of patients with pneumonia of unknown cause was linked to a seafood wholesale market in Wuhan, China and were later confirmed to be infected with a novel coronavirus, known as 2019-nCoV (Zhu et al 2020). The virus was subsequently renamed to SARS-CoV-2 because it is similar to the coronavirus responsible for SARS-CoV, a lineage B *Betacoronavirus*. SARS-CoV-2 shares more than 79% of its sequence with SARS-CoV, and 50% with the coronavirus responsible for MERS-CoV, a member of the lineage C *Betacoronavirus* (Lu et al 2020). COVID-19 is the infectious disease caused by SARS-CoV-2. By January 2020 there was increasing evidence of human to human transmission as the number of cases rapidly began to increase in China. Spread of the virus has been rapid and now encompasses the globe. The WHO declared the novel coronavirus a pandemic on 11 March 2020. As of 13 July 2020, there have been more than 12.7 million confirmed cases and > 560 000 deaths, of which 3.2 million confirmed cases and > 130 000 deaths have been reported in the USA (WHO 2020). It is believed that evolution of the pandemic will vary across countries, affected in part by different containment strategies ranging from extreme lockdown to relative inaction. As a result, there may be regional waves of the disease and pockets of vulnerable populations. Globally, governments have acknowledged that an effective vaccine against COVID-19 is the only way to guarantee a safe and sustained exit strategy from repeated lockdowns.

CoVs are spherical, enveloped viruses with positive-sense single-stranded RNA genomes. One fourth of their genome is responsible for coding structural proteins, such as the S glycoprotein, envelope, membrane, and nucleocapsid proteins. Envelope, membrane, and nucleocapsid proteins are mainly responsible for virion assembly whilst the S protein is involved in receptor binding, mediating virus entry into host cells during CoVs infection via different receptors (Li 2016). SARS-CoV-2 belongs to the phylogenetic lineage B of the

genus *Betacoronavirus* and it recognizes the ACE2 as the entry receptor (Zhou et al 2020). It is the seventh CoV known to cause human infections and the third known to cause severe disease after SARS-CoV and MERS-CoV.

AZD1222 is a recombinant replication-defective chimpanzee adenovirus expressing the SARS-CoV-2 S surface glycoprotein. Development of AZD1222, previously referred to as ChAdOx1 nCoV-19, was initiated by the University of Oxford with subsequent transfer of development activities to the Sponsor. Nonclinical studies found AZD1222 to be immunogenic in BALB/c and CD-1 mice, porcine, and NHP models. Further, in a SARS-CoV-2 challenge NHP model, a single administration of AZD1222 significantly reduced viral load in bronchoalveolar lavage fluid and respiratory tract tissue of vaccinated animals as compared to vector controls (van Doremalen et al 2020). Efficacy studies in ferret and NHP models are underway.

The clinical development program for AZD1222 was initiated by the University of Oxford, and currently has 4 ongoing studies being conducted in the UK (FIH COV001 [NCT04324606], COV002 [NCT04400838]), Brazil (COV003 [ISRCTN89951424], and South Africa (COV005 [NCT04444674]). Preliminary data are available for the FIH Study COV001 and Study COV002.

Study COV001 enrolled the first participant on 23 April 2020 and completed enrollment on 21 May 2020. As of 24 July 2020, a total of 1 077 participants have been enrolled including 544 participants who received at least one dose of 5×10^{10} vp AZD1222 and 10 participants who received a second dose of 5×10^{10} vp AZD1222 4 weeks later. Safety data found the vaccine was generally tolerated, with no treatment-related SAEs reported through 28 days post dose. The most common local solicited AEs were vaccination site pain and tenderness. The most common systemic solicited AEs were chills, feverishness, fever, headache, malaise, and myalgia. The majority of events were mild or moderate in severity and resolved within 1 to 7 days. Following the second dose, a general attenuation in the incidence and severity of local and systemic solicited AEs was observed.

Preliminary immunogenicity data from Study COV001 suggest that a single dose can elicit both humoral and cellular immunogenicity responses and that antibody responses are boosted after a second dose. S-specific T-cell responses peaked on Day 14. Anti-S IgG responses rose by Day 28, and were boosted 3-fold following a second dose.

Neutralizing antibody responses against SARS-CoV-2 were detected in 32 (91%) of 35 participants after a single dose when measured in microneutralization assay (MNA_{80}) and in 35 (100%) participants when measured in plaque reduction neutralization test ($PRNT_{50}$). After the second dose, all participants had neutralizing activity (9 of 9 in MNA_{80} at Day 42 and 10 of 10 in Marburg virus neutralization assay on Day 56). Neutralizing antibody responses correlated strongly with antibody levels measured by ELISA (Folegatti et al 2020b).

As of 24 July 2020, Study COV002 enrolled 8 344 participants, including 4 252 participants who received at least one dose of AZD1222 ranging from 2.2×10^{10} vp to 5×10^{10} vp. Based on preliminary data following a single dose of 5×10^{10} vp, the local and systemic solicited-AE profile in participants 18 to 55 years of age was generally comparable to results in Study COV001. In general, a decline in the incidence and severity of solicited AEs was observed across the age groups (18-55, 56-69, and ≥ 70 years) in Study COV002.

Another ChAdOx1-vectored vaccine expressing the full-length S protein from a related betacoronavirus, MERS-CoV, has been given to 53 participants as part of 2 ongoing dose-escalation Phase I studies (MERS001 [NCT03399578] and MERS002 [NCT04170829], sponsored by the University of Oxford) at doses ranging from 5×10^{9} vp to 5×10^{10} vp. Preliminary immunogenicity data from MERS001 suggested that a single dose of ChAdOx1 MERS can elicit both humoral and cellular responses. Overall, the vaccine was safe and generally well tolerated, with no serious adverse reactions reported in either study.

The ChAdOx1 platform has been used in 14 clinical studies sponsored by the University of Oxford with immunogens from multiple pathogens such as influenza, tuberculosis, malaria, chikungunya, Zika, MERS-CoV, and Meningitis B. Over 360 healthy adult participants have received ChAdOx1-vectored vaccines in these studies. These vaccines demonstrated robust immunogenicity after a single dose and favorable safety profiles, with no vaccine-related SAEs.

See the AZD1222 IB, Sections 4 and 5 for additional information on nonclinical and clinical studies, respectively, of AZD1222 and related ChAdOx1-vectored vaccines. Detail on the development and chemistry of AZD1222 is provided in the IB, Section 3.

Overall, the preliminary data from the AZD1222 clinical and nonclinical studies, and the acceptable safety and efficacy data for the MERS-CoV vaccine and other ChAdOx1-vectored vaccines, support further development of AZD1222 for the prevention of COVID-19.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of AZD1222 can be found in the AZD1222 IB.

2.3.1 Risk Assessment

AZD1222

Based on preliminary clinical data from Study COV001 and Study COV002, the most common local solicited AEs were vaccination site pain and tenderness. Common systemic solicited AEs across the 2 studies included chills, feverishness, fever, fatigue, headache, joint

pain, malaise, and myalgia. The majority of events were mild or moderate in severity and resolved within 1 to 7 days (Section 2.2 and AZD1222 IB).

There are no identified risks for AZD1222. Important potential risks are hypersensitivity including anaphylaxis/anaphylactic reactions, vaccine-associated enhanced respiratory disease, and Guillain-Barré syndrome and other immune-mediated reactions.

Serious allergic reactions including anaphylaxis may occur, as with any vaccine. Acute allergic reactions may include cardio-respiratory, skin, and gastrointestinal signs and symptoms, such as hypotension, bronchospasm, angioedema, urticaria, and diarrhea.

Vaccine-associated enhanced respiratory disease is a potential risk for AZD1222. The risks of inducing disease enhancement and lung immunopathology in the event of COVID-19 following AZD1222 vaccination are unknown.

As with many vaccines, temporary ascending paralysis (Guillain-Barré syndrome) or other immune-mediated reactions that can lead to organ damage may occur, but this should be extremely rare.

2.3.2 Benefit Assessment

Recipients of AZD1222 do not have any guaranteed benefit, however, AZD1222 may be efficacious and offer participants protection from COVID-19. The information gained from this study will inform development decisions.

2.3.3 Overall Benefit: Risk Conclusion

For the safety of participants, the protocol has incorporated various risk mitigation measures including appropriate inclusion and exclusion criteria, close monitoring of participants, and stopping criteria. An independent DSMB will provide study oversight, evaluating cumulative safety and other clinical data at regular intervals. Taking these measures into account, the potential risks identified in association with AZD1222 are justified by the anticipated benefit that may be afforded to participants for the prevention of COVID-19.

3 OBJECTIVES AND ENDPOINTS

Table 5 Objectives and Endpoints

Objective [a]	Estimand [b] Description/Endpoint
PRIMARY	
1 To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of COVID-19 in adults ≥ 18 years of age	**Population:** Full analysis set, excluding participants who are seropositive at baseline
	Endpoint: 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.
	Intercurrent events: 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 (ie, 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.
	Summary measure: VE, calculated as 1-relative risk. (Relative risk is the incidence of infection in the vaccine group relative to the incidence of infection in the control group.)
2 To assess the safety and tolerability of 2 IM doses of AZD1222 compared to placebo in adults ≥ 18 years of age	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
3 To assess the reactogenicity of 2 IM doses of AZD1222 compared to placebo in adults ≥ 18 years of age (Substudy only)	Incidence of local and systemic solicited AEs for 7 days post each dose of study intervention
SECONDARY	
1 To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of SARS-CoV-2 infection	The proportion of participants who have a post-treatment response (negative at baseline to positive post treatment with study intervention) for SARS-CoV-2 Nucleocapsid antibodies over time
2 To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of symptomatic COVID-19 using CDC criteria	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
3 To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of University of Oxford-defined symptomatic COVID-19	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

Table 5 Objectives and Endpoints

Objective [a]	Estimand [b] Description/Endpoint
4 To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of severe or critical symptomatic COVID-19	The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring ≥ 15 days post second dose of study intervention
5 To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of COVID-19-related Emergency Department visits	The incidence of COVID-19-related Emergency Department visits occurring ≥ 15 days post second dose of study intervention
6 To assess antibody responses to AZD1222 S antigen following 2 IM doses of AZD1222 or placebo (Substudy and Illness Visits only)	a) 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)
	b) The 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)
7 To determine anti-SARS-CoV-2 neutralizing antibody levels in serum following 2 IM doses of AZD1222 or placebo (Substudy and Illness Visits only)	a) 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)
	b) 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 AZD1222 as measured by SARS-CoV-2 neutralizing antibodies (wild-type assay or pseudo-neutralization assay)
EXPLORATORY	
1 To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the all-cause mortality	The incidence of all-cause mortality from Day 1 through Day 730
2 To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for COVID-19-related deaths	The incidence of COVID-19-related deaths occurring from Day 1 through Day 730
3 To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of COVID-19-related hospitalizations	The incidence of COVID-19-related hospitalizations occurring ≥ 15 days post second dose of study intervention
4 To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of COVID-19-related ICU admissions	The incidence of COVID-19-related ICU admissions occurring ≥ 15 days post second dose of study intervention
5 To estimate the efficacy of AZD1222 compared to placebo for the prevention of COVID-19 following the first dose	The incidence of COVID-19 SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post first dose of study intervention
6 To quantify SARS-Cov-2 viral loads in infected participants treated with 2 IM doses of AZD1222 or placebo (Illness Visits only)	Viral genome copies in NP swabs collected at Illness Visits as determined by qRT-PCR

Table 5 Objectives and Endpoints

Objective [a]	Estimand [b] Description/Endpoint
7 To characterize sequence variations in SARS-CoV-2 through genotypic analyses in participants treated with 2 IM doses of AZD1222 or placebo (Illness Visits only)	Genotypic analysis of SARS-CoV-2 from NP swabs collected on Day 1 illness visit
8 To quantify duration of viral shedding in symptomatic SARS-CoV-2 infected participants treated with 2 IM doses of AZD1222 or placebo (Illness Visits only)	Duration of SARS-CoV-2 shedding in saliva over time
9 To assess the biometric profiles associated with COVID-19 using a biosensor in participants treated with 2 IM doses of AZD1222 or placebo (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
10 To assess symptoms associated with COVID-19 using an e-Diary in participants treated with 2 IM doses of AZD1222 or placebo (Illness Visits only)	Symptoms recorded by participants in an Illness e-Diary from illness visits Day 2 through Day 28
11 To assess SARS-CoV-2 specific antibodies in an ACE2 competition assay following 2 IM doses of AZD1222 or placebo (Substudy only)	a) Post-treatment GMTs and GMFRs from Day 1 baseline value to 28 days post each dose in ACE2 competing antibodies from serum samples
	b) 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
12 To assess B- and T-cell responses following 2 IM doses of AZD1222 or placebo (Substudy only)	a) Quantification of (IFN-γ) ELISpot responses to SARS-CoV-2 S protein from day of dosing baseline to 14 days post each dose
	b) Intracellular cytokine staining and flow cytometry for B- and T-cell responses from day of dosing baseline to 14 days post each dose
13 To assess SARS-CoV-2 antibodies in nasal secretions following 2 IM doses of AZD1222 or placebo (Substudy only)	a) 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)
	b) 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)
14 To assess anti-vector responses to the ChAdOx-1 adenovirus vector following 2 IM doses of AZD1222 or placebo (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
15 To assess additional immune responses following 2 IM doses of AZD1222 or placebo	Other exploratory assays for humoral and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data

Table 5 Objectives and Endpoints

Objective [a]	Estimand [b] Description/Endpoint

[a] Substudy: The first participants randomized in each age group, 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.
Illness Visits: Participants who present with qualifying symptoms will be tested for SARS-CoV-2 and if positive, will complete illness visits.

[b] Estimand is the target of estimation to address the scientific question of interest posed by the primary objective. Attributes of an estimand include the population of interest, the variable (or endpoint) of interest, the specification of how intercurrent events are reflected in the scientific question of interest, and the population-level summary for the variable.

ACE2 = angiotensin-converting enzyme 2; AE = adverse event; AESI = adverse event of special interest; CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 2019; ELISpot = enzyme-linked immunospot; GMFR = geometric mean fold rise; GMT = geometric mean titer; ICU = intensive care unit; IFN-γ = interferon-gamma; IM = intramuscular; MAAE = medically attended adverse event; MSD = Meso Scale Discovery; NP = nasopharyngeal; RT-PCR = reverse transcriptase polymerase chain reaction; qRT-PCR = quantitative reverse transcriptase polymerase chain reaction, RBD = receptor binding domain; S = Spike; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; VE = vaccine efficacy.

4 STUDY DESIGN

4.1 Overall Design

D8110C00001 is a Phase III randomized, double-blind, placebo-controlled multicenter study assessing the safety, efficacy, and immunogenicity of AZD1222 compared to saline placebo for the prevention of COVID-19. 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 and < 65 years, and ≥ 65 years), with at least 25% of participants to be enrolled in the older age stratum.

Participants who present with at least one of the qualifying symptoms listed below through Day 360 will be assessed for COVID-19. With the exception of fever, shortness of breath, or difficulty breathing, the symptom must be present for 2 or more days. Participants with a COVID-19 qualifying symptom(s) will be tested for SARS-CoV-2, and if positive will complete illness visit assessments, as presented in Table 4. See Section 8.1 for details on COVID-19 assessments.

COVID-19 Qualifying Symptoms

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

Adapted from (CDC 2020).

Safety will be assessed for the duration of the study. AEs will be recorded for 28 days post each dose of study intervention (ie, until Day 29 post first dose and Day 57 post second dose), and SAEs, MAAEs, and AESIs will be recorded through Day 730. See Sections 8.3, 8.3.8, and 8.3.9 for definitions of these events.

The first participants randomized in each age group, 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. These 3 000 participants in the substudy will have additional assessments for predefined solicited AEs for 7 days post each dose of study intervention and for humoral and cellular immune responses. Solicited AEs are defined in Section 8.3.7.

Table 2 and Table 3 provide the SoA for the main study and the substudy, respectively.

All participants will remain on study for 2 years following administration of first dose of study intervention (Day 730). If AZD1222 is proven to be safe and efficacious based on the primary

endpoint analysis (see Section 9.4.2.1), 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 may be offered AZD1222 if doses are available. Placebo participants treated with AZD1222 will continue to be followed in the study.

A PSRT will provide support for safety surveillance during the study. Additionally, an independent COVID-19 Vaccine DSMB will provide oversight, to ensure safe and ethical conduct of the study. The COVID-19 Vaccine DSMB will facilitate the interim analysis for 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. See Appendix A 5 for additional detail.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Study Design and Participant Population

The participant population is male and female adults ≥ 18 years of age who are not immunosuppressed, but are at increased risk of SARS-Cov-2 infection due to their locations or circumstances. Inclusion of older adults is based on data that are being gathered from the ongoing University of Oxford-sponsored studies. Study COV001 (NCT04324606) enrolled adults 18 to 55 years of age. Study COV002 (NCT04400838) is pursuing an age-escalation design and it is anticipated that at least 30 adults who are 56 to 69 years of age and that at least 30 adults who are aged ≥ 70 will have received 2 doses of AZD1222 prior to initiation of this study.

Adults with medically-stable chronic diseases may participate if, according to the judgement of the investigator, hospitalization within the study period is not anticipated and the participant appears likely to be able to remain on study through the end of protocol-specified follow-up.

The study will exclude females who are pregnant or breast-feeding and individuals less than 18 years of age. Women who are pregnant or breast-feeding are excluded at this point as nonclinical developmental and reproductive toxicity studies to support vaccinating these individuals have yet to be performed. Additionally, it is planned that children and adolescents will be evaluated for their response to the vaccine once safety and efficacy have been established in adults.

Participants who have been previously diagnosed with laboratory-confirmed SARS-CoV-2 infection are excluded from study participation. Participants with previous asymptomatic or undiagnosed infection are not excluded. Participant's baseline serostatus will be determined but baseline serostatus will not be used as a basis for exclusion from the study. Participants who are seropositive at baseline are enrolled in order to gather safety data in this group as it is anticipated that, if proven to be efficacious, the vaccine will rapidly be distributed to millions

of individuals and that these individuals will not be tested for serologic evidence of previous infection prior to vaccination. Participant's baseline serostatus will be determined so that subgroup analyses for both safety and efficacy can be performed by baseline serostatus.

The study population represents the initial target population for AZD1222. If AZD1222 demonstrates efficacy for the prevention of COVID-19, the safety and immunogenicity of the vaccine in additional groups such as the immunosuppressed, pregnant women, and children and adolescents may be assessed in future studies.

4.2.2 Rationale for Study Endpoints

The efficacy endpoints in this study are analogous to endpoints used for evaluating the efficacy of influenza vaccines. These definitions have 4 components: (1) a definition of clinical illness; (2) a method of respiratory specimen sampling for the detection of associated shedding of the relevant virus; (3) an assay method for laboratory confirmation; and (4) a defined surveillance period. Assessment of AZD1222 efficacy will begin ≥ 15 days after the second dose of study intervention as this time period is considered necessary for the vaccine to induce protective immune responses.

In the substudy, solicited AEs will be collected for 7 days post each dose of study intervention, a period that has proven adequate to describe reactogenicity events in previous vaccine studies. For all participants, AEs will be collected through 28 days post each dose of study intervention. SAEs, MAAEs, and AESIs and will be collected from Day 1 through end of the study. AESIs include terms identified by the Brighton Collaboration involving events associated with vaccination in general (SPEAC 2020).

4.3 Justification for Dose

The AZD1222 dose of 5×10^{10} vp was selected based on accumulated clinical experience with this vaccine in ongoing clinical studies sponsored by the University of Oxford (see Section 2.2). Safety and immunogenicity data from an additional clinical study, MERS001 (NCT03399578), using the same ChAdOx1 vector, also helped inform dose selection.

MERS001 was the first clinical study of a ChAdOx1-vectored vaccine expressing the full-length S protein from a separate, but related, betacoronavirus. ChAdOx1 MERS has been given to 31 participants to date at doses ranging from 5×10^{9} vp to 5×10^{10} vp. Despite higher reactogenicity observed at the 5×10^{10} vp, this dose was safe, with self-limiting AEs and no serious adverse reactions recorded. The 5×10^{10} vp was the most immunogenic, in terms of inducing neutralizing antibodies against MERS-CoV using a live virus assay (Folegatti et al 2020a). Given the immunogenicity findings and safety profile observed with the ChAdOx1-vectored vaccine against MERS-CoV, the 5×10^{10} vp dose was chosen for AZD1222. See the AZD1222 IB.

Based on accumulating nonclinical and clinical data gathered for AZD1222 as well as for other SARS-CoV-2 vaccines in development, a 2-dose regimen was selected for the study in order to enhance the immune responses to the virus (AZD1222 IB).

In an NHP challenge study, 6 macaques received a second dose of AZD1222 4 weeks after the first dose. The second dose resulted in increases in both ELISA and neutralizing antibody titers, and fewer areas of the lung contained viral RNA in prime boost group compared to the prime group. In a porcine model, 3 pigs also received a second dose of AZD1222 4 weeks after the first dose. In the animals that received the booster dose, both antibodies to the SARS-CoV-2 RBD and neutralizing antibodies were boosted after the second dose.

In Study COV001, 10 participants received a second dose of AZD1222 4 weeks after the first dose. Antibody responses to both the first and second doses were evaluated using an ELISA assay, through the MSD platform and by both neutralization and pseudo-neutralization assays. Notable increases in antibody levels to the S protein were seen with the ELISA assay and increases to both the S protein and RBD were noted using the MSD platform. Similarly, increases in antibody levels following the second dose were also seen with neutralization and pseudo-neutralization assays. Though based on small numbers, the second dose of the vaccine appeared to result in a lower rate of systemic solicited AEs.

The 4-week interval was selected based on the interval used in the nonclinical studies and Study COV001.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the SoA (Section 1.3).

The end of the study is defined as the date of the last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the study globally.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1 Adult, ≥ 18 years of age at the time of consent

Type of Participant

2 Increased risk of SARS-CoV-2 infection

– Defined as adults whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19, based on available risk assessment contemporaneous to enrollment (believed to be at risk/exposure)

3 Medically stable such that, according to the judgment of the investigator, hospitalization within the study period is not anticipated and the participant appears likely to be able to remain on study through the end of protocol-specified follow-up

– A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months prior to enrollment

4 Able to understand and comply with study requirements/procedures (if applicable, with assistance by caregiver, surrogate, or legally authorized representative) based on the assessment of the investigator

Reproduction

5 Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies

6 Female participants

(a) Women of childbearing potential must:

- Have a negative pregnancy test on the day of screening and on Day 1
- Use one highly effective form of birth control for at least 28 days prior to Day 1 and agree to continue using one highly effective form of birth control through 60 days following administration of the second dose of study intervention. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly (see Table 6). Periodic abstinence, the rhythm method, and withdrawal are NOT acceptable methods of contraception.

(b) Women are considered of childbearing potential unless they meet either of the following criteria:

- Surgically sterilized (including bilateral tubal ligation, bilateral oophorectomy, or hysterectomy), or
- Post-menopausal
  - For women aged < 50 years, post-menopausal is defined as having both:
    - A history of ≥ 12 months amenorrhea prior to randomization, without an alternative cause, following cessation of exogenous sex-hormonal treatment, and

- A follicle-stimulating hormone level in the post-menopausal range

Until follicle-stimulating hormone is documented to be within menopausal range, the participant is to be considered of childbearing potential

- For women aged ≥ 50 years, post-menopausal is defined as having a history of ≥ 12 months amenorrhea prior to randomization, without an alternative cause, following cessation of exogenous sex-hormonal treatment

Table 6 Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
• Intrauterine device • Intrauterine hormone-releasing system (IUS) [a] • Bilateral tubal occlusion • Vasectomized partner [b] • Sexual abstinence [c]	• Combined (estrogen- and progestogen-containing hormonal contraception) ° Oral (combined pill) ° Injectable ° Transdermal (patch) • Progestogen-only hormonal contraception ° Oral ° Injectable ° Implantable

[a] This is also considered a hormonal method
[b] Provided that partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success
[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study and if it is the preferred and usual lifestyle of the participant

Informed Consent

7 Capable of giving signed informed consent as described in Appendix A, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1 History of allergy to any component of the vaccine

2 History of Guillain-Barré syndrome or any other demyelinating condition

3 Significant infection or other acute illness, including fever > 100 °F (> 37.8 °C) on the day prior to or day of randomization

4 History of laboratory-confirmed SARS-CoV-2 infection

5 Any confirmed or suspected immunosuppressive or immunodeficient state, including asplenia

6 Recurrent severe infections and use of immunosuppressant medication within the past 6 months (≥ 20 mg per day of prednisone or its equivalent, given daily or on alternate days for ≥ 15 days within 30 days prior to administration of study intervention)
The following exceptions are permitted:

- Topical/inhaled steroids or short-term oral steroids (course lasting ≤ 14 days)
- Human immunodeficiency virus-positive stable participants on stable antiretroviral therapy, eg, (NIH 2020, Waldrop et al 2016)

7 History of primary malignancy except for:

(a) Malignancy with low potential risk for recurrence after curative treatment (for example, history of childhood leukaemia) or metastasis (for example, indolent prostate cancer) in the opinion of the site investigator.

(b) Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease

(c) Adequately treated uterine cervical carcinoma in situ without evidence of disease

(d) Localized prostate cancer

8 Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture

9 Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder, and neurological illness, as judged by the Investigator (mild/moderate well-controlled comorbidities are allowed)

10 Any other significant disease, disorder, or finding that may significantly increase the risk to the participant because of participation in the study, affect the ability of the participant to participate in the study, or impair interpretation of the study data

Prior/Concomitant Therapy

11 Receipt of, or planned receipt of investigational products indicated for the treatment or prevention of SARS-CoV-2 or COVID-19
Note: For participants who become hospitalized with COVID-19, receipt of licensed treatment options and/or participation in investigational treatment studies is permitted

12 Receipt of any vaccine (licensed or investigational) other than licensed influenza vaccines within 30 days prior to and after administration of study intervention

13 Receipt of immunoglobulins and/or any blood products within 3 months prior to administration of study intervention or expected receipt during the period of study follow-up

Other Exclusions

14 Involvement in the planning and/or conduct of this study (applies to both Sponsor staff and/or staff at the study site)

15 For women only - currently pregnant (confirmed with positive pregnancy test) or breast-feeding

16 Has donated ≥ 450 mL of blood products within 30 days prior to randomization or expects to donate blood within 90 days of administration of second dose of study intervention

5.3 Lifestyle Considerations

1 Participants must follow the contraception requirements outlined in Section 5.1

2 Restrictions relating to concomitant medications are described in Section 6.5

3 Agree to wear digital health device if diagnosed with COVID-19 as described in Section 8.1.2.2

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Only a single rescreening is allowed in the study. Rescreened participants are required to sign a new ICF (Appendix A 3), and will be assigned a new participant number.

6 STUDY INTERVENTION

In general, study intervention is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to or medical device(s) utilized by a study participant according to the study protocol. For this study, study intervention is defined as AZD1222 or saline placebo (Table 7). The third party medical device used for assessment of COVID-19 symptoms (ie, digital health device [Section 8.1.2.2]) is not considered a study intervention.

6.1 Study Interventions Administered

6.1.1 Investigational Products

Table 7 Investigational Products

Intervention Name	AZD1222	Placebo
Type	Vaccine	Placebo
Dose Formulation	10 mM histidine, 7.5% (w/v) sucrose, 35 mM sodium chloride, 1 mM magnesium chloride, 0.1% (w/v) polysorbate 80, 0.1 mM edetate disodium, 0.5% (w/v) ethanol, at pH 6.6.	0.9% (w/v) saline
Unit Dose Strength(s)	$\geq 0.7 \times 10^{11}$ vp/mL	
Dosage Level(s)	5×10^{10} vp (nominal, $\pm 1.5 \times 10^{10}$ vp)	
Route of Administration	Intramuscular	Intramuscular
Use	Experimental	Placebo
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Sourced locally
Packaging and Labeling	Will be provided in vials within a carton. Each carton and vial will be labelled as required per country requirement	Not applicable
Current/Former Name or Alias	ChAdOx1 nCoV-19	Not applicable

IMP = investigational medicinal product; NIMP = non-investigational medical product; vp = viral particles; w/v = weight/volume.

AZD1222

AZD1222 will be supplied by the Sponsor as a vial solution for injection. It is a sterile, clear to slightly opaque solution, practically free from visible particles, with a label-claim volume of 5 mL.

Unopened vials of AZD1222 vials must be stored at 2-8 °C (36-46 °F) for the duration of assigned shelf-life and must not be frozen. AZD1222 must be kept in original packaging until use to prevent prolonged light exposure.

Placebo

Commercially available 0.9% (w/v) saline for injection will be sourced locally for placebo.

6.1.2 Dosing Instructions

Participants will receive 2 doses of either AZD1222 or placebo; the first dose will be administered on Day 1 and the second dose on Day 29 (see Table 2 and Table 3).

It is recommended that the study interventions be administered as an IM injection into the deltoid of the non-dominant arm. Other injection sites may be used if necessary.

All study participants will be observed in the clinic for at least 15 minutes after vaccination.

Allergic reactions to vaccines are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

6.2 Preparation/Handling/Storage/Accountability

1 The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

2 Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

3 The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

4 Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual or specified handling instructions.

6.2.1 Dose Preparation and Administration

6.2.1.1 AZD1222

Doses of AZD1222 must be prepared by the unblinded pharmacist (or designee in accordance with local and institutional regulations) using aseptic technique. Each dose is prepared by withdrawing 0.5 mL from a vial of AZD1222 in a sterile syringe.

AZD1222 does not contain preservatives. Each vial must be assigned a beyond-use-date of 4 hours from first needle puncture of the AZD1222 vial, after which any unused portion must be discarded.

Once an AZD1222 dose is drawn into a syringe for administration, the dose must be administered within the beyond-use-date of the vial. If AZD1222 dose administration is not completed within the 4-hour vial beyond-use-date, a new dose must be prepared from a new vial.

Each vial of AZD1222 has a label-claim volume of 5 mL and can provide up to ten 0.5 mL doses.

6.2.1.2 Placebo

Doses of placebo must be prepared by the unblinded pharmacist (or designee in accordance with local and institutional regulations) using aseptic technique. Each placebo dose is prepared by withdrawing 0.5 mL from a 0.9% (w/v) saline vial or IV bag in a sterile syringe. If 0.9% (w/v) saline is extracted from IV bags, the manufacturers recommendation for maximum number of needle punctures of the IV bag port must not be exceeded.

Saline (0.9% [w/v]) does not contain preservatives. Each IV bag or vial must be assigned a beyond use date of 4 hours from first needle puncture, after which any unused portion must be discarded.

Once a placebo dose is drawn into a syringe for administration, the dose must be administered within the beyond-use-date of the vial/IV bag. If placebo dose administration is not completed within the 4-hour vial/IV bag beyond-use-date, a new dose must be prepared from a new vial or IV bag.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization

All participants will be centrally assigned to randomized study intervention using an IRT. Before the study is initiated, user guides, the log in information, and directions for the IRT will be provided to each study site. Randomization will be stratified by age ($\geq$ 18 to < 65 years, and $\geq$ 65 years), with at least 25% of participants to be enrolled in the older age stratum.

Where a participant does not meet all the eligibility criteria but incorrectly received study intervention, the investigator should inform the Study Physician immediately, and a discussion should occur between the Study Physician and the investigator regarding whether to continue or discontinue the participant.

6.3.2 Blinding

Neither the participant nor any of the investigators or Sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the study intervention received. Since AZD1222 and placebo are visually distinct prior to dose preparation (due to differences in container closure), IMP will be handled by an unblinded pharmacist (or designee in accordance with local and institutional regulations) at the study site. Once drawn into syringes for administration, AZD1222 and placebo are not visually distinct from each other.

The IRT will provide the investigator(s) or pharmacists a dose tracking number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IRT user manual that will be provided to each study site.

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization. The investigator documents and reports the action to the Sponsor, without revealing the treatment given to participant to the Sponsor staff.

The Sponsor retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational medicinal product and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

6.3.3 Procedures for Unblinding

The IRT will be programmed with blind-breaking instructions. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition (eg, antidote available), the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind.

6.4 Study Intervention Compliance

When participants are dosed at the study site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date, and time if applicable, of dose administered will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines) that the participant is receiving at the time of enrollment or receives during the period specified in the SoA (Section 1.3), must be recorded in the eCRF along with the information listed below. Vitamins and/or herbal supplements are not to be recorded.

- Reason for use
- Dates of administration including start and end dates

- Dosage information including dose and frequency

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Permitted Concomitant Medications

Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance. Primary care providers, or where appropriate investigators, should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study. Participants who develop COVID-19 after receiving study intervention should be treated with licensed medications and interventions according to standard of care. All routine vaccinations other than influenza are permitted beginning > 30 days after last dose of study intervention. Licensed influenza vaccines are permitted at any time.

6.5.2 Prohibited Concomitant Medications

The following medications are prohibited and the Sponsor must be notified if a participant receives any of these prohibited medications. The use of the following concomitant medications and/or vaccines, however, will not definitively require withdrawal of the participant from the study, but may determine a participant's eligibility to receive a second dose or evaluability in the per-protocol analysis set.

If a participant receives a prohibited concomitant medication, the investigator in consultation with the Sponsor will evaluate any potential impact on receipt of study intervention based on time the medication was administered, the medication's pharmacology and pharmacokinetics, and whether the medication will compromise the participant's safety or interpretation of the data (see Section 7.1).

- Investigational products indicated for the treatment or prevention of SARS-CoV-2 or COVID-19
  Note: For participants who become hospitalized with COVID-19, receipt of licensed treatment options and/or participation in investigational treatment studies is permitted
- Receipt of any vaccine (licensed or investigational) other than licensed influenza vaccines within 30 days prior to and after administration of study intervention
- Glucocorticoids at a dose ≥ 20 mg/day of prednisone or equivalent given daily or on alternate days for ≥ 14 consecutive days between randomization and the participant's scheduled final visit
- Other systemically administered drugs with significant immunosuppressive activity, such as azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy between randomization and the participant's scheduled final visit

- Immunoglobulins and/or any blood product

6.6 Dose Modification

Study intervention will be administered as described in Section 6.1.2. Dose modification is not permitted.

6.7 Intervention After the End of the Study

There is no intervention after the end of the study (see definition in Section 4.4).

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Each participant will receive 2 doses of study intervention (see Section 6). An individual participant will not receive the first or second dose of study intervention if any of the following occur in the participant in question:

1 Withdrawal of consent after signing informed consent
2 Participant meets one or more of the exclusion criteria or fails to meet all inclusion criteria for study participation
3 Laboratory-confirmed SARS-CoV-2 infection
4 Participant is pregnant or nursing
5 Any allergic reaction including anaphylaxis that is assessed as related to study intervention
6 Any SAE assessed as related to study intervention
7 Any AE that, in the judgment of the site investigator, is related to study intervention and may jeopardize the safety of the study participant
8 Receipt of a prohibited concomitant medication that may jeopardize the safety of the study participant or interpretation of the data

Each participant who has received at least one dose of study intervention will be followed for the full study period unless consent is withdrawn specifically from further study participation, or the participant is lost to follow-up. Participants who have not received study intervention, regardless of reason, will not be followed.

7.1.1 Study Suspension or Termination

The Sponsor reserves the right to temporarily suspend or permanently terminate this study or a component of the study at any time. The reasons for temporarily suspending the study may include, but are not limited, to the following:

- Any death, SAE, or other safety finding assessed as related to study intervention that in the opinion of the Sponsor may preclude further administration of study intervention

No additional participants will be randomized or treated with study intervention until review by the COVID-19 Vaccine DSMB is complete (see Appendix A 5 for COVID-19 Vaccine DSMB information).

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Sponsor Study Team.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The study site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local

equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3) is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 Efficacy Assessments

8.1.1 Monitoring COVID-19 Symptoms

Study sites will contact participants weekly (telephone/email/text) through Day 360 with reminders to monitor for COVID-19 symptoms. Participants who present with at least one of the COVID-19 qualifying symptoms listed below must contact the study team. With the exception of fever, shortness of breath, or difficulty breathing, the symptom must be present for 2 or more days. During the 7 days following administration of each dose of study intervention, investigator judgement should be used to determine which participants should initiate illness visits as symptoms may be due to the reactogenicity of the study intervention as opposed to potentially due to infection with SARS-CoV-2.

If a participant presents with a COVID-19 qualifying symptom(s) on Days 1-3, the nasal swab collected on Day 1 will be tested locally for SARS-CoV-2 (see Section 8.6.1.1). If positive, the participant will be instructed to initiate illness visits. If negative, the participant will continue with scheduled assessments per their assigned study (ie, main study [Table 2] or substudy [Table 3]).

Participants who present with a COVID-19 qualifying symptom(s) after Day 3 will be instructed to initiate illness visits and be tested for SARS-CoV-2.

COVID-19 Qualifying Symptoms

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

Adapted from (CDC 2020).

8.1.2 Illness Visits

Symptomatic participants (as defined in Section 8.1.1) will be instructed to visit the study site for initiation of illness assessments (Table 4); where supported, home or mobile visits may be substituted for the site visits. Symptomatic participants will complete the Day 1 illness visit and will be instructed to continue with the home collection requirements (eg, digital health device and Illness e-Diary recordings, and saliva samples). SARS-CoV-2 RT-PCR results will be available during the home collection period and participants will be informed of their status. The results of the COVID-19 RT-PCR testing should also be reported to the participants' primary care providers. Only participants who test positive will be instructed to continue with the illness visits, including home collection of saliva samples and digital health device and Illness e-Diary recordings. Participants who test negative for SARS-CoV-2 will be instructed to stop all illness visit assessments and return the digital health device. Participants

will continue with follow-up visits per their assigned study (ie, main study [Table 2] or substudy [Table 3]).

8.1.2.1 SARS-CoV-2 Testing and Other Virology Assessments

At the Day 1 illness visit, mid-turbinate nasal swabs and nasopharyngeal swabs will be collected and tested for SARS-COV-2 by authorized RT-PCR assays (see Section 8.6.1.1).

Saliva will be collected during site illness visits and by self-collection at home throughout the illness visits to quantify duration of viral shedding. Other virology assessments are described in Section 8.6.

8.1.2.2 Digital Health Device

At the Day 1 illness visit, participants will receive a wearable, digital health device (eg, Current Health Monitoring System) and be trained on use of the biosensor. The digital health device will continuously track biophysical parameters, including but not limited to, serial measurements of skin temperature, heart rate, respiratory rate, blood oxygen saturation, and physical activity.

Data will be obtained from the biosensor and transmitted via a wireless hub from the participant to the vendor platform. The vendor platform will be monitored remotely 24 hours a day by a team which includes registered nurses. The monitoring team will receive technical alerts if there are data or device issues, and physiologic alerts if participants' vital signs meet prespecified criteria. The physiologic alerts are intended to provide an early indication of worsening health status that would allow the monitoring team and investigator to provide appropriate follow-up. All alerts will be triaged and followed up by the monitoring team according to agreed-upon monitoring protocols. A registered nurse will review the alerts requiring clinical attention and will apply clinical judgement (based on the Schmitt-Thompson COVID-19 - Diagnosed or Suspected After Hours Telephone Triage Protocols) (Schmitt-Thompson 2020) to determine which alerts can be addressed directly with the participant via telephone, and which alerts should be escalated to the on-call clinician at the site. If escalation is required, the nurse will contact the on-call clinician by telephone and the clinician will then be responsible for subsequent follow-up. For all technical and physiologic alerts, details regarding the nature of the alert and action taken will be documented within the Current Health Monitoring System and an informational email will be sent to the investigator within 2 hours for further follow-up if required. The data from the biosensor and remote monitoring are not intended to substitute for protocol-mandated standard safety monitoring, participant self-reporting, or participant oversight, which remains the responsibility of the investigator.

Along with the device, participants will be provided with a paper-based Quick Start Guide containing general instructions for the device as well as frequently asked questions. A reference copy of the document will be retained in the Site Master File.

Participants who test positive for SARS-CoV-2 will be instructed to continue wearing the digital health device until the COVID-19-associated symptoms resolve or until the Day 28 illness visit. Participants who test negative and stop the illness visits will be instructed to return the digital health device.

8.1.2.3 Illness e-Diary

An Illness e-Diary will be used to collect self-reported information about COVID-19-associated symptoms (listed below per CDC (CDC 2020). At the Day 1 illness visit, participants (or, if applicable, their caregiver, surrogate, or legally authorized representative) will be given access to the Illness e-Diary and trained by study staff on how to record the information and assess the severity of the symptoms.

Participants who test positive for SARS-CoV-2 will be instructed to continue recording in the Illness e-Diary until symptoms resolve or until the Day 28 illness visit. Participants who test negative will be instructed to stop Illness e-Diary recording.

Study sites will monitor the health status of participants via Illness e-Diary responses after the Day 1 illness visit, and will call participants as needed based on these responses.

COVID-19 Symptoms

- 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

8.1.3 Severe COVID-19

The severity of COVID-19 will be evaluated in participants who test positive for SARS-CoV-2 by RT-PCR. A diagnosis of severe or critical COVID-19 will include laboratory-confirmed COVID-19 (SARS-CoV-2 RT-PCR-positive symptomatic illness) plus any of the following:

- 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)
- 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

8.1.4 Medical Notes Review

With the participant's consent, the study team will request access to medical notes or submit a data collection form for completion by attending clinical staff on any medically-attended COVID-19 episodes. Any data relevant for assessment of the efficacy endpoints or vaccine-associated enhanced respiratory disease (see Section 8.3.9) will be collected. These are likely to include, but not limited to, information on intensive care unit admissions, clinical parameters such as oxygen saturation, respiratory rates and vital signs, need for oxygen therapy, need for ventilatory support, imaging, blood tests results, and overall outcome (survival or death).

8.1.5 Monitoring for Asymptomatic Infection

Blood samples will be collected according to the SoA (Section 1.3) for SARS-CoV-2 serology testing to monitor participants for asymptomatic infection. See description of assessment in Section 8.5.2.1.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical Examinations

A complete physical examination will be performed at screening followed by targeted physical examinations as specified in the SoA (Section 1.3).

- A complete physical examination will include, but not be limited to, assessment of height, weight, general appearance, head, ears, eyes, nose, throat, neck, skin, as well as cardiovascular, respiratory, abdominal, and nervous systems. Each clinically significant abnormal finding at screening will be recorded in the medical history.
- A targeted physical examination will include areas suggested by the medical history. Each clinically significant abnormal finding following vaccination will be recorded as an AE.
- All physical examinations will be performed by a licensed healthcare provider (eg, physician, physician assistant, or licensed nurse practitioner).

8.2.2 Vital Signs

Vital signs, including heart rate, pulse oximetry, blood pressure, and body temperature, will be performed as specified in the SoA (Section 1.3). The participant should be resting prior to the collection of vital signs.

Data collected through the digital health device on heart rate, respiratory rate, temperature, and oxygen saturation level will be recorded as exploratory efficacy measurements and should not be reported as AEs unless resulting in an MAAE or SAE.

Situations in which vital sign results should be reported as AEs are described in Section 8.3.5.

8.2.3 Clinical Laboratory Assessments

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical study.

For women participants of childbearing potential, a urine sample for pregnancy testing will be collected according to the SoA (Section 1.3). Urine pregnancy tests for β-hCG may be performed at the site using a licensed test (dipstick). If urine tests positive or indeterminate, a quantitative serum β-hCG will be performed for confirmation.

Additional safety samples may be collected if clinically indicated at the discretion of the investigator

8.3 Adverse Events and Serious Adverse Events

The principal investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

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.

Solicited AEs are local or systemic predefined events for assessment of reactogenicity. Solicited AEs will be collected in a Solicited AE e-Diary only for participants in the substudy (see Section 8.3.7), and will be assessed separately from the (unsolicited) AEs collected during the study.

General information for AEs in this protocol excludes solicited AEs.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

AEs will be recorded for 28 days post each dose of study intervention.

Solicited AEs will be recorded only for participants in the substudy for 7 days post each dose of study intervention.

SAEs will be recorded from the time of signature of the informed consent form through the last participant contact.

MAAEs and AESIs will be recorded from Day 1, post treatment, through the last participant contact.

See the SoA (Section 1.3) for the scheduled timepoints.

If the investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the Sponsor.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the

eCRF. The Sponsor retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

AE variables

The following variables will be collected for each AE:

- AE (verbatim)
- Date when the AE started and stopped
- Severity grade/maximum severity grade/changes in severity grade
- Whether the AE is serious or not
- Investigator causality rating against the study intervention (yes or no)
- Action taken with regard to study intervention
- AE caused participant's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

The grading scales from US FDA guidance for healthy volunteers enrolled in a preventive vaccine clinical study (FDA 2007) will be utilized for all unsolicited events with an assigned severity grading.

8.3.3 Causality Collection

The investigator should assess causal relationship between study intervention and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes.'

A guide to the interpretation of the causality question is found in Appendix B.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the Clinical Study Protocol-mandated vital signs will be summarized in the CSR.

Deterioration as compared to baseline in protocol-mandated vital signs should therefore only be reported as AEs if they fulfil any of the SAE or MAAE criteria or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required).

If deterioration in a vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an SAE or MAAE, and the associated vital sign will be considered as additional information.

8.3.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation. Any occurrences of AST or ALT $\geq 3 \times$ ULN together with total bilirubin $\geq 2 \times$ ULN *and* confirmed as a Hy's Law case should be reported as an SAE.

Hy's Law

AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN, where no other reason, other than the study intervention, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

8.3.7 Solicited Adverse Events (Only for Substudy)

Local and systemic predefined solicited AEs for reactogenicity assessment (Table 8) will be collected in a Solicited AE e-Diary for 7 days following administration of each dose of study intervention only from participants in the substudy.

Solicited AEs should not be reported as unsolicited AEs (see Section 8.3). However, solicited AEs should be reported as SAEs or MAAEs if they fulfil the criteria (see Sections 8.3 and 8.3.8, respectively).

Table 8 List of Predefined Solicited Adverse Events for Reactogenicity Assessment

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

[a] Fever measured by any route. Investigators who consider a temperature lower than this cutoff as a fever or a 'fever' reported by participants without documentation by a thermometer should record the event as 'elevated body temperature.'
[b] Swelling and redness must be ≥ 0.25 inches (≥ 0.6 centimeters) in diameter.

Solicited AE e-Diary

On Day 1, participants in the substudy (or, if applicable, their caregiver, surrogate, or legally authorized representative) will be given an oral thermometer, tape measure, and access to the Solicited AE e-Diary, with instructions on use, along with the emergency 24-hour telephone number to contact the on-call study physician if needed.

Participants will be instructed to record for 7 days following administration of each dose of study intervention, the timing and severity of local and systemic solicited AEs, if applicable, and whether medication was taken to relieve the symptoms.

Severity Assessment of Solicited AEs

Severity will be assessed for solicited AEs by the participant (or, if applicable, their caregiver, surrogate, or legally authorized representative) according to toxicity grading scales modified and abridged from the US FDA guidance (FDA 2007) as defined in Appendix E. Because

solicited AEs are expected to occur after vaccination, they will not be assessed for relationship to study intervention.

8.3.8 Medically Attended Adverse Events

MAAEs will be collected according to the timepoints specified in the SoA (Section 1.3).

MAAEs are defined as 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.

8.3.9 Adverse Events of Special Interest

AESIs will be collected according to the timepoints specified in the SoA (Section 1.3).

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. An AESI can be serious or non-serious. All AESIs will be recorded in the eCRF. Serious AESIs will be recorded and reported as per Section 8.3.10.

AESIs for AZD1222 are listed below. They are based on Brighton Collaboration case definitions (SPEAC 2020), as described in Appendix F. See also the AZD1222 IB, Section 5.5, for additional information on AESIs.

Brighton Collaboration AESIs

AESIs relevant to vaccination in general include:

- Neurologic
  - Generalized convulsion
  - Guillain-Barre syndrome
  - Acute disseminated encephalomyelitis
- Immunologic
  - Vasculitides
  - Anaphylaxis
  - Vaccine-associated enhanced respiratory disease
- Hematologic
  - Thrombocytopenia

8.3.10 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the study intervention, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, investigators or other site personnel will inform the appropriate Sponsor representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform Sponsor representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but no later than 24 hours of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated Sponsor representative.

If the EDC system is not available, then the investigator or other study site staff reports an SAE to the appropriate Sponsor representative by telephone or other method.

The Sponsor representative will advise the investigator/study site staff how to proceed.

For further guidance on the definition of an SAE, see Appendix B.

The reference document for definition of expectedness is the AZD1222 IB, Section 5.6.

8.3.11 Pregnancy

All pregnancies and outcomes of pregnancy with conception dates following administration of study intervention should be reported to the Sponsor, except if the pregnancy is discovered before the participant has received any study intervention.

8.3.11.1 Maternal Exposure

Female participants who are pregnant or have a confirmed positive pregnancy test at screening or Day 1 will be excluded from the study (see Section 5.2). Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without

complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate Sponsor representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.10) and **within 30 days** for all other pregnancies that are not associated with an SAEs.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module may be used to report the outcome of the pregnancy.

8.3.12 Medication Error

If a medication error occurs, then the investigator or other site personnel informs the appropriate Sponsor representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative works with the investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) **or 5** (other serious initial and follow up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.10) and **within 30 days** for all other medication errors.

The definition of a Medication Error can be found in Appendix B 4.

8.3.13 Medical Device Deficiencies

Any deficiency observed with the digital health device (third-party medical device) will be collected and reported to the manufacturer by the investigators or other site personnel within one day ie, immediately but no later than 24 hours of when he or she becomes aware of it.

A medical device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Medical device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

The manufacturer’s medical device complaint report will be used to collect the deficiency.

8.4 Overdose

For this study, any dose of study intervention exceeding that specified in the protocol will be considered an overdose.

There is no specific treatment for an overdose with AZD1222. If overdose occurs, the participant should be treated supportively with appropriate monitoring as necessary.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module
- An overdose without associated symptoms is only reported on the Overdose eCRF module

If an overdose occurs in the course of the study, the investigator or other site personnel inform appropriate Sponsor representatives immediately, but **no later than 24 hours** after when he or she becomes aware of it.

The designated Sponsor representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.10) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study-specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. Further details on Handling of Human Biological Samples are provided in Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

Remaining biological sample aliquots will be retained at the Sponsor or its designee for a maximum of 15 years following issue of the CSR. Additional use excludes genetic analysis unless participant has consented to the Optional Genomics Initiative, Section 8.7 and includes but is not limited to, analysis of COVID-19 and other coronavirus-related diseases or vaccine-related responses, eg, exploratory immunology, such as systems serology and profiling of B- and T-cell repertoire. The results from further analysis will not be reported in the CSR.

8.5.1 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5.2 Immunogenicity Assessments

Serum samples for immunogenicity assessments will be collected according to the SoA (Section 1.3). Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual. Results for exploratory immunogenicity analyses may be reported separately from the CSR.

8.5.2.1 SARS-CoV-2 Serology Assessments

Serum samples will be collected to assess SARS-CoV-2 antigen-specific antibody levels from all participants according to the SoA (Section 1.3). Authorized laboratories will assess serologic responses to AZD1222 by the rate of participants seroconverting from negative to positive as defined by a validated immunoassay directed at the SARS-CoV-2 S antigen. The rate of asymptomatic SARS-CoV-2 infection in participants receiving AZD1222 vs placebo will be determined by seroconversion in a SARS-CoV-2 Nucleocapsid assay operated by an authorized laboratory. Serologic assessment to S, RBD, and Nucleocapsid antigens will also be assessed quantitatively using a validated multiplexed MSD immunoassay.

8.5.2.2 SARS-CoV-2 Neutralizing Antibody Assessments

Serum samples to measure SARS-CoV-2 neutralizing antibody levels will be collected from participants in the substudy according to the timepoints specified in the SoA (Section 1.3). Authorized laboratories will measure neutralizing antibodies to SARS-CoV-2 using validated wild-type neutralization assay or pseudo-neutralization assays.

8.5.2.3 Assessment of Mucosal Responses

Nasal samples to evaluate SARS-CoV-2 antigen-specific antibody responses in nasal secretions will be collected from participants in the substudy and during illness visits according to the SoA (Section 1.3). Nasal adsorption specimens will be collected by synthetic absorptive matrix sampling as outlined in the laboratory manual. Antibody responses to SARS-CoV-2 S, RBD, and Nucleocapsid antigens may be assessed in a qualified multiplexed MSD immunoassay and stratified by antibody isotype (IgA, IgG, IgM).

8.5.2.4 Assessment of Cell-mediated Immune Responses

Cell-mediated immune responses (ie, B-cell and T-cell responses) will be assessed by characterizing PBMCs using methods that may include T-cell ELISpot assays to SARS-CoV-2 antigens, flow cytometry after intracellular cytokine staining, single-cell RNA sequencing, B-cell and T-cell receptor sequencing, and other methodology as determined by the Sponsor and/or authorized laboratories. Data on Th1/Th2 polarization after AZD1222 vaccination will be provided and may be reported separately from the CSR. Samples will be collected from approximately 300 participants in the substudy and from up to approximately the first 3 000 participants during the Day 1 illness visit, as well as participants who have a positive SARS-CoV-2 RT-PCR result at timepoints specified in the SoA (Section 1.3).

Additionally, plasma will be isolated from the whole blood samples collected to isolate PBMCs, which may be utilized for exploratory immunogenicity and biomarker analyses as outlined in Section 8.6.2.

8.5.2.5 Additional Serum Immunogenicity

Additional serum samples for exploratory immunogenicity evaluation will be obtained according to the SoA (Section 1.3). Serologic assessment to seasonal coronavirus antigens will also be assessed quantitatively using a qualified multiplexed MSD immunoassay, while anti-vector immune responses (ie ChAdOx1 neutralizing antibody responses) will characterize the induction of antibodies to the ChAdOx1vector and the persistence of these antibodies over time. Exploratory sera samples may be utilized to investigate additional humoral and cellular immune responses as well as potential correlates of protection as determined by the Sponsor and/or authorized laboratories based upon emerging safety, efficacy, and immunogenicity data.

8.5.3 Pharmacodynamics

Pharmacodynamics are not evaluated in this study.

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

By consenting to participate in the study, the participant consents to participate in the mandatory research components of the study.

Samples for biomarker research are required and will be collected from participants during illness visits as specified in the SoA (Section 1.3). Mid-turbinate nasal and nasopharyngeal swabs will be collected at site illness visits for virologic assessments. Saliva samples will be collected at site illness visits and by the participants during the home-collection period. These biomarker measurements will support our understanding of potential correlates of protection, duration of immune responses, and correlations between immunogenicity and reactogenicity. Details for sample collection, processing, and testing will be provided in the Laboratory Manual.

Any results from such analyses may be reported separately from the CSR.

8.6.1.1 Virologic Assessments

Instructions for obtaining and processing mid-turbinate nasal swabs and nasopharyngeal swab samples are provided in the Laboratory Manual. Mid-turbinate nasal and nasopharyngeal swabs will be assessed by authorized RT-PCR assays for the detection of SARS-CoV-2 by local and central laboratories, respectively. Genotypic analysis of the viral S protein will be performed by next generation sequencing modalities. Additionally, a validated multiplexed

respiratory panel may be utilized to assess for the presence of other respiratory pathogens in nasopharyngeal swabs in a central laboratory operated on behalf of the Sponsor.

8.6.1.2 Assessment of Viral Shedding

Viral shedding will be assessed in saliva samples collected using a Spectrum DNA (SDNA-1000) collection kit at site illness visits or self-collected at home, by an authorized RT-PCR assay for the measurement of SARS-CoV-2. Collection of saliva sample for viral shedding is optional in Chile and Peru and may occur after a feasibility assessment has been completed.

8.6.2 Other Study-related Biomarker Research

Already collected samples may be analyzed for different biomarkers thought to play a role in COVID-19 severity or outcomes including, but not limited to serum, plasma or mucosal cytokines, quantification of RNA, micro-RNA, and/or non-coding RNA using quantitative RT-PCR, microarray, sequencing, or other technology in blood, PBMCs, or mucosal specimens to evaluate their association with observed clinical responses to AZD1222. Other study-related biomarker research excludes genetic analysis unless participant has consented to the Optional Genomics Initiative, Section 8.7.

For storage, re-use, and destruction of biomarker samples see Section 8.5.

8.7 Optional Genomics Initiative Sample

Collection of optional samples for Genomics Initiative research is also part of this study as specified in the SoA (Section 1.3) and is subject to agreement in the Optional Genetic Research Information ICF.

Blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

See Appendix D for information regarding the Genomics Initiative genetic sample. Details on processes for collection and shipment and destruction of these samples can be found either in the appendices or in the Laboratory Manual.

For storage and destruction of genetic samples see Appendix D.

8.8 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics are not applicable in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary efficacy endpoint is a binary response, whereby a participant is defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs ≥ 15 days post second dose of study intervention. Otherwise, a participant is not defined as a COVID-19 case. VE will be calculated as 1-relative risk, which is the incidence of infection in the vaccine group relative to the incidence of infection in the control group. The null hypothesis 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%.

9.2 Sample Size Determination

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, ± 1.5×10^{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/assigned in the study, are considered ‘screen failures,’ unless otherwise specified by the protocol.

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 these analyses 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, where the Type I error at the interim and primary analyses is 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 not seropositive 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 not seropositive 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% with 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.

9.3 POPULATIONS FOR ANALYSES

The following populations are defined:

Table 9 Populations for Analysis

Population	Description
All participants analysis set	All participants screened for the study, to be used for reporting disposition and screening failures.
Full analysis set	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 or assent to participate in the study will be included up to the date of their study withdrawal.
Per-protocol analysis set	The per-protocol analysis set will include subjects in full analysis set who receive the correct dose of randomized treatment and who do not have a serious protocol deviation. Detailed criteria defining this analysis set will be documented in the Statistical Analysis Plan.
Safety analysis set	The safety analysis set consists of all participants who have received at least one dose of study intervention. Erroneously-treated participants (eg, those randomized to treatment A but were actually given treatment B) are accounted for in this analysis set by assigning them to the treatment they actually received. A participant who has on one or several occasions received active study intervention is classified as active.
Immunogenicity analysis set	The immunogenicity analysis population will include all participants in the safety analysis set who have no protocol deviations judged to have the potential to interfere with the generation or interpretation of an immune response. Examples of protocol violations will be documented in the Statistical Analysis Plan.

9.4 Statistical Analyses

The primary DBL will occur after approximately 150 events have been observed for the primary endpoint (see Section 9.2) within the population of participants who are not seropositive at baseline. All participants in the study will be assessed for efficacy 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.

This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints. A more technical and detailed description of the statistical analyses will be described in the SAP, and an approved version will be finalized prior to the interim analyses (see Section 9.5).

All personnel involved in the analyses of the study will remain blinded until the primary DBL and protocol deviations are identified.

Analyses will be performed by the Sponsor or its representatives.

Categorical variables will be summarized using frequency and percentages, where the denominator for calculation is the underlying analysis set population unless otherwise stated.

Continuous variables will be summarized with descriptive statistics of number of available observations, mean, standard deviation, median, minimum and maximum, and quartiles where more appropriate.

All point estimates will be presented together with a 95% CI, unless otherwise stated. P-values, corresponding to a 2-sided test, will be presented for comparisons between treatments. Methods for controlling multiplicity across endpoints are discussed in Section 9.4.4.

9.4.1 General Considerations

The primary efficacy analysis will be based on the double-blind, placebo-controlled phase of the study, and will compare participants randomized to receive 2 nominal doses of 5×10^{10} vp ($\pm 1.5 \times 10^{10}$ vp) AZD1222 against participants randomized to saline placebo.

The primary estimand will be used for the analysis of the primary efficacy endpoint. It will be based on participants in the full analysis set, defined as all randomized participants who received at least 1 dose of study intervention excluding those participants who are seropositive at baseline, analyzed according to their randomized treatment. For participants with multiple events, only the first occurrence will be used for the primary efficacy endpoint analysis. The set of intercurrent events for this estimand consists of participants who withdraw from the study prior to having met the primary efficacy endpoint. The intercurrent events will be handled using the treatment policy strategy and the absence of data following these participants' withdrawal will be treated as missing (ie, 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.

Additional estimands will be specified for the primary efficacy endpoint to carry out sensitivity analyses for assessing the robustness of results. These sensitivity analyses will explore different methods for handling intercurrent events and different assumptions for missing data. Estimands will also be specified for the analysis of secondary endpoints. Full details will be provided in the SAP.

Demography and baseline characteristics will be summarized by treatment for the full analysis set. If there are major differences between the full analysis set and the safety analysis set, the summaries will be repeated and presented for the safety analysis set.

9.4.2 Efficacy

An overview of the primary and secondary efficacy objectives, endpoints, and the associated case definitions is presented in Appendix G.

A blinded independent efficacy adjudication committee will review relevant data of potential cases for the COVID-19-related efficacy endpoint evaluations. More detail on this process will be provided in the SAP and the Efficacy Adjudication Committee Charter (see also Appendix A 5).

9.4.2.1 Primary 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. 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

OR

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)

The primary efficacy endpoint will be assessed at 2 milestones during the study, giving an interim analysis (see Section 9.5) and a primary analysis. The timing of these analyses will be driven by the number of events observed in the study within the subset of participants who are not seropositive at baseline. The interim analysis will be carried out when approximately 75 events meeting the primary efficacy endpoint definition have been observed, and the primary analysis will be carried out when approximately 150 events meeting the primary efficacy endpoint definition have been observed (see Section 9.2). A final analysis will also be carried out when all participants have completed the 2-year study. However, the final analysis will not be controlled for multiplicity and statistical hypotheses will be tested at a nominal 5% significance level (based on a 2-sided test).

As the primary efficacy analysis, the plan is to use the primary estimand and a Poisson regression model with robust variance (Zou 2004) to analyze the primary efficacy endpoint, which will include age as a baseline covariate as well as the log of the follow-up time as an offset. The VE will be estimated from the model, which will give the RRR in the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness. VE is calculated as RRR = 100*(1-relative risk), which is the incidence of infection in the vaccine group relative to the incidence of infection in the control group expressed as a percentage. For 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%. The CIs are based on a Lan-DeMets alpha-spending function for 2-group sequential tests.

Model assumptions will be checked and the robustness of the primary analysis will be assessed. The Poisson regression model with robust variance has the flexibility for exploring multiple imputation approaches using, eg, the observed placebo attack rate to impute missing data. If the Poisson regression model with robust variance fails to converge, an alternative approach will be implemented. Full details will be documented in the SAP.

To support the primary analysis, a Cox proportional hazard model will be fitted to the data as well as Kaplan-Meier curves presented for the active and control groups, 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. In addition, descriptive statistics for the vaccine and control groups will also be produced. Full details will be documented in the SAP.

9.4.2.2 Secondary Endpoints

The set of secondary endpoints include the following summary measures, derived from binary outcomes:

- Proportion of participants who have a post-treatment response (negative at baseline to positive post treatment with study intervention) for SARS-CoV-2 Nucleocapsid antibodies over time
- 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 (see Section 8.1.1 for definition)
- 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. Cases are defined as RT-PCR-confirmed SARS-CoV-2 and having at least one of the following symptoms
  1 New onset of fever (> 100 °F [> 37.8 °C]), OR
  2 Cough, OR
  3 Shortness of breath, OR
  4 Anosmia/ageusia
- Incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic COVID-19 (see Section 8.1.3 for definition)
- Incidence of COVID-19-related Emergency Department visits occurring ≥ 15 days post second dose of study intervention

The proportion of participants who have a post-treatment response (negative at baseline to positive post treatment with study intervention) to SARS-CoV-2 Nucleocapsid antibodies will be derived for the vaccine and control groups by visit, with corresponding 95% Clopper-Pearson exact CIs.

Following the same methodology outlined for the primary endpoint, each of these secondary incidence endpoints will be analysed by a separate Poisson regression model with robust variance (Zou 2004), and they will include age as a baseline covariate. RRR will be estimated from each model, with a corresponding 95% CI. 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. To support these analyses, descriptive statistics will be produced for the vaccine and control groups. Full details will be documented in the SAP.

To assess immune response, the set of secondary endpoints also includes:

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

The proportion of participants who have a post-treatment seroresponse to the S and RBD anitgens of AZD1222 will be derived for the vaccine and control groups, with corresponding 95% Clopper-Pearson exact CIs. Similarly, the proportion of participants who have a post-treatment seroresponse to AZD1222 as measured by SARS-CoV-2 neutralizing antibodies will be derived for the vaccine and control groups, with corresponding 95% Clopper-Pearson exact CIs.

The GMT and GMFR endpoints will be analysed on the natural log scale by separate analysis of variance (ANOVA) models, and will include treatment and age as categorical covariates. 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.

To support these analyses, descriptive statistics will be produced for the vaccine and control groups. Full details will be documented in the SAP.

9.4.2.3 Exploratory Endpoints

Full details of the analyses for the exploratory endpoints will be specified in the SAP.

9.4.3 Safety

9.4.3.1 Primary Endpoints

Overview

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 Section 8.3.8) and AESIs (defined in 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

AE severity will be graded according to the US FDA guidance (FDA 2007) and coded using the most recent version of the Medical Dictionary for Regulatory Activities. AEs will be presented for each treatment group by system organ class and preferred term. Summaries will include the number and percentage of participants reporting at least one event, number of events and exposure adjusted rates, where appropriate.

An overview of AEs will be presented for each treatment group, including the number and percentage of participants with any AE and SAEs. Summaries will present the relationship to study intervention as assessed by the investigator, maximum intensity, seriousness, and death.

A listing will cover details for each individual AE. Full details of all AE analyses will be provided in the SAP.

9.4.3.2 Other Safety Endpoints

Vital Signs

For SARS-CoV-2-positive participants, vital sign measurements will be performed as specified in the SoA (Section 1.3). The set of assessments will include pulse oximetry, blood pressure, and body temperature.

Details of all vital sign analyses will be provided in the SAP, which will include descriptive statistics presented for observed and change from baseline values for all vital sign parameters.

9.4.4 Methods for Multiplicity Control

The primary efficacy endpoint 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, where the Type I error 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%. 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 CIs are > 30%. At the interim or primary analysis the success criterion for the study will be statistical significance with an observed VE point estimate of at least 50%.

Note that 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.

9.4.5 Sensitivity Analyses

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

9.4.6 Subgroup Analyses

Subgroup analyses will be carried out to assess the consistency of the treatment effect across key, pre-defined, subgroups. These analyses will focus on the primary efficacy endpoint, and they may be performed on secondary and exploratory endpoints if deemed appropriate. The list of subgroups includes, but may not be limited to: gender, age, and serostatus at baseline. Full details of all subgroup analyses will be described in the SAP, including hypotheses that will be tested and the covariates and interaction terms to be included in the statistical models.

9.5 Interim Analyses

The study has been powered to include an interim efficacy analysis, based on the primary efficacy endpoint. The statistical analysis described in Section 9.4.2.1 will be carried out by the COVID-19 Vaccine DSMB when approximately 75 events have been reported across the active and control groups (ie, when approximately 50% of the total amount of statistical information is available) within the population of participants who are not seropositive at baseline. A statistically significant finding at the interim analysis (ie, 2-sided 99.69% CI is > 30%) will not be considered a reason to stop the study, but instead will be interpreted as early assessment of efficacy. The SAP will describe the planned interim analyses in greater detail.

9.6 Data Safety Monitoring Committee

An independent COVID-19 Vaccine DSMB will provide oversight, to ensure safe and ethical conduct of the study. During the study, the benefit/risk assessment will be continuously monitored by the COVID-19 Vaccine DSMB to ensure that the balance remains favorable. Further details, composition, and operation of the COVID-19 Vaccine DSMB will be described in a separate COVID-19 Vaccine DSMB charter.

For details on the COVID-19 Vaccine DSMB, refer to Appendix A 5.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Sponsor will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with the Sponsor.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all Food and Drug Administration (FDA) Regulations, as applicable and all other applicable local regulations

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will

review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The study medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study if required by the IRB.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant

names or any information which would make the participant identifiable will not be transferred.

- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committee Structure

The safety of all Sponsor clinical studies is closely monitored on an ongoing basis by Sponsor representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the Clinical Study Protocol and letters to investigators.

A PSRT comprised of Sponsor, COVID-19 Prevention Network, Biomedical Advanced Research and Development Authority, and NIAID medical officers will be convened to oversee the safety of participants during the study. Further details, composition, and operation of the PSRT will be described in a separate COVID-19 Prevention Network PSRT Charter.

A COVID-19 Vaccine DSMB organized by the National Institutes of Health, National Institute for Allergy and Infectious Diseases, comprised of independent experts will be convened to provide oversight, to ensure safe and ethical conduct of the study. The COVID-19 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. Specifically, the study will be paused for DSMB review if a statistically significantly higher risk ratio (> 1), at the 1-sided 5% significance level, is seen for cases of severe COVID-19 in the vaccine arm compared to the placebo arm. This assessment for a potentially increased risk ratio will begin after 8 cases of severe COVID-19 have accrued in the study. Based on the output of the review, 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.

A blinded independent efficacy adjudication committee will review relevant data of potential cases for the COVID-19-related efficacy endpoint evaluations. More detail on this process will be provided in the SAP and the Efficacy Adjudication Committee Charter.

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the relevant study plans.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A 9 Study and Site Start and Closure

The first act of recruitment is the first participant screened and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites may have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support

publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both SAEs and non-SAEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

AEs for **malignant tumors** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-SAE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life Threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the study intervention would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability, or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of important medical events include such events as listed below:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by acetaminophen overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

Intensity Rating Scale

The grading scales found in the US FDA guidance for healthy volunteers enrolled in a preventive vaccine clinical study (FDA 2007) will be utilized for all events with an assigned severity grading.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe

intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the IMP.

- Time Course. Exposure to suspect drug. Has the participant actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect IMP?
- Consistency with known IMP profile. Was the AE consistent with the previous knowledge of the suspect IMP (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect IMP?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected IMP was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the IMP?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study intervention that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the IMP, but rather a human or process related failure while the IMP is in control of the study site staff or participant.

Medication error includes situations where an error.

- Occurred
- Was identified and intercepted before the participant received the IMP
- Did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- IMP name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- IMP not administered as indicated, for example, wrong route or wrong site of administration
- IMP not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- IMP not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT errors)
- Wrong IMP administered to participant (excluding IRT errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed IMP dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each study site keeps full traceability of collected biological samples from the participants while in storage at the study site until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

The Sponsor or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

The Sponsor ensures that biological samples are destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, the Sponsor is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes.

The investigator:

- Ensures participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to the Sponsor or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and the Sponsor are informed about the sample disposal.

The Sponsor ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

Appendix D Optional Genomics Initiative Sample

D 1 Use/Analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant´s DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

D 2 Genetic Research Plan and Procedures

Selection of Genetic Research Population

- All participants will be asked to participate in this genetic research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this genetic research, participants must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol and: Provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

- Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
  - Previous allogeneic bone marrow transplant
  - Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Withdrawal of Consent for Genetic Research

- Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2.

Collection of Samples for Genetic Research

- The blood sample for this genetic research will be obtained from the participants on Day 1 prior to administration of study intervention. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn on Day 1, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

Coding and Storage of DNA Samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years, from the date of last participant last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA).
- The link between the participant enrollment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

Informed Consent

- The genetic component of this study is optional and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study the participant must sign and date both the consent form for the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the participant and the original filed at the study center. The principal investigator(s) is responsible for ensuring that consent is given freely and that the participant understands that they may freely withdrawal from the genetic aspect of the study at any time.

Participant Data Protection

- AstraZeneca will not provide individual genotype results to participants, any insurance company, any employer, their family members, their physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a participant's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data Management

- Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyse the samples.
- AstraZeneca and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organizations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual participant data or any personal identifiers.
- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Appendix E Toxicity Grading Scales for Solicited Adverse Events

The toxicity grading scales for the solicited AEs were modified and abridged from the US FDA Guidance on Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (FDA 2007).

- Table 10: Clinical Abnormalities, Local Reactions to Injectable Product
- Table 11: Clinical Abnormalities, Vital Signs
- Table 12: Clinical Abnormalities, Systemic (General or Illness)

Table 10 Tables for Clinical Abnormalities: Local Reactions to Injectable Product

Local Reaction to Injectable Product	Reaction Grade			
	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Life Threatening (Grade 4)**
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or 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.

Table 11 Tables for Clinical Abnormalities: Vital Signs

Vital Sign [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.

Table 12 Tables for Clinical Abnormalities: Systemic (General or Illness)

Systemic (General)	Systemic Grade			
	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Nausea/vomiting	No interference with activity or 1-2 episodes/24 hrs	Some interference with activity or > 2 episodes/24 hrs	Prevents daily activity, required outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Chills	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hrs or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Systemic Illness				
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring intervention	Prevents daily activity and required medical intervention	ER visit or hospitalization

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

Appendix F Adverse Events of Special Interest

AESIs Based on Brighton Collaboration Case Definitions (SPEAC 2020)

Generalized Convulsion

Generalized convulsion is considered an AESI due to the association with immunization encompassing several different vaccines.

Guillain-Barré Syndrome and Other Immune-mediated Reactions

As with many vaccines, temporary ascending paralysis (Guillain-Barré syndrome) or immune-mediated reactions that can lead to organ damage may occur, but this should be extremely rare. Guillain-Barré syndrome is often preceded by an infection. This could be a bacterial or viral infection (gastrointestinal, upper respiratory infections including influenza). The exact mechanism that triggers Guillain-Barré syndrome is unknown, but it is thought to be triggered by antigenic stimulation resulting in demyelination and damage to the peripheral nerves. This is a condition in which people can develop severe weakness and can be fatal. Weakness or tingling in the legs or arms and upper body are characteristic symptoms of Guillain-Barré syndrome. Severe cases of Guillain-Barré syndrome cause paralysis and are life-threatening.

Other immune-mediated reactions considered AESIs include acute disseminated encephalomyelitis and vasculitides, which are a theoretical concerns based on immunopathogenesis.

Hypersensitivity Including Anaphylaxis/Anaphylactic Reactions

Serious allergic reactions including anaphylaxis may occur, as with any vaccine. The incidence of this is unknown, but in general is estimated at one per 10^5 to 10^6 vaccinations. These acute reactions may be severe and result in death. Acute allergic reactions may include cardio-respiratory, skin-subcutaneous, and gastrointestinal signs and symptoms, such as chest pain, hypotension, dyspnea, bronchospasm, respiratory failure, urticaria, pruritus, angioedema, nausea, vomiting, diarrhea, and collapse.

Vaccine-associated Enhanced Respiratory Disease

Disease enhancement following vaccination as judged by the investigator will be monitored. Detailed clinical parameters will be collected from medical records and aligned with agreed definitions as they emerge. These are likely to include, but are not limited to, oxygen saturation, need for oxygen therapy, respiratory rate, need for ventilatory support, imaging, blood test results, and other clinically relevant assessments. Events of potential

vaccine-associated enhanced respiratory disease will be evaluated by regular reviews of COVID-19 cases.

Thrombocytopenia

Thrombocytopenia is considered an AESI due to the association with immunization encompassing several different vaccines.

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. General symptoms of thrombocytopenia include bleeding in the mouth and gums, bruising, nosebleeds, and petechiae (pinpoint red spots/rash). Severe bleeding is the major complication, which may occur in the brain or gastrointestinal tract.

Appendix G Overview of Primary and Secondary Efficacy Objectives, Endpoints, and Associated Case Definitions

Table 13 Overview of Primary and Secondary Efficacy Objectives, Endpoints, and Associated Case Definitions

Objective		Endpoint	Case Definition
Primary	To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of COVID-19 in adults ≥ 18 years of age	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.	Participant must 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 **OR** 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)
Secondary	To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of SARS-CoV-2 infection	Proportion of participants who have a post-treatment response (negative at baseline to positive post treatment with study intervention) for SARS-CoV-2 Nucleocapsid antibodies over time	Participants who have a post-treatment response (negative at baseline to positive post treatment with study intervention) for SARS-CoV-2 Nucleocapsid antibodies over time

Table 13 Overview of Primary and Secondary Efficacy Objectives, Endpoints, and Associated Case Definitions

Objective		Endpoint	Case Definition
Secondary	To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of symptomatic COVID-19 using CDC criteria	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	The first case of SARS-CoV-2 RT-PCR-positive symptomatic illness for a participant occurring ≥ 15 days post second dose of study intervention using criteria from the CDC ((CDC 2020): *No minimum duration:* Fever Shortness of breath Difficulty breathing *Present for ≥ 2 days:* Chills Cough Fatigue Muscle aches Body aches Headache New loss of taste New loss of smell Sore throat Congestion Runny nose Nausea Vomiting Diarrhea

Table 13 Overview of Primary and Secondary Efficacy Objectives, Endpoints, and Associated Case Definitions

Objective		Endpoint	Case Definition
Secondary	To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of University of Oxford-defined symptomatic COVID-19	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	First case of SARS-CoV-2 RT-PCR-positive symptomatic illness for a participant occurring ≥ 15 days post second dose of study intervention using University of Oxford-defined symptom criteria. Cases are defined as RT-PCR-confirmed SARS-CoV-2 and having at least one of the following symptoms: 1 New onset of fever (> 100 °F [> 37.8 °C]), OR 2 Cough, OR 3 Shortness of breath, OR 4 Anosmia/ageusia
	To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of severe or critical symptomatic COVID-19	The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring ≥ 15 days post second dose of study intervention	Participant must have laboratory-confirmed COVID-19 (SARS-CoV-2 RT-PCR-positive symptomatic illness) plus any of the following: • 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) • 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

Table 13 Overview of Primary and Secondary Efficacy Objectives, Endpoints, and Associated Case Definitions

Objective		Endpoint	Case Definition
Secondary	To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of COVID-19-related Emergency Department visits	The incidence of COVID-19-related Emergency Department visits occurring ≥ 15 days post second dose of study intervention	COVID-19-related Emergency Department visits occurring ≥ 15 days post second dose of study intervention
	To assess antibody responses to AZD1222 S antigen following 2 IM doses of AZD1222 or placebo (Substudy and Illness Visits only)	a) 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)	a) 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)
		b) The 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)	b) 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)

Table 13 Overview of Primary and Secondary Efficacy Objectives, Endpoints, and Associated Case Definitions

Objective		Endpoint	Case Definition
Secondary	To determine anti-SARS-CoV-2 neutralizing antibody levels in serum following 2 IM doses of AZD1222 or placebo (Substudy and Illness Visits only)	a) 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)	a) 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)
		b) 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 AZD1222 as measured by SARS-CoV-2 neutralizing antibodies (wild-type assay or pseudo-neutralization assay)	b) Post-treatment seroresponse (≥ 4-fold rise in titers from day of dosing 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)

CDC = Centers for Disease Control and Prevention; COVID-19 = coronavirus disease 2019; GMFR = geometric mean fold rise; GMT = geometric mean titer; IM = intramuscular; MSD = Meso Scale Discovery; S =Spike; RBD = receptor binding domain; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2.

Appendix H Abbreviations

Abbreviation or special term	Explanation
ACE2	angiotensin-converting enzyme 2
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
CDC	Centers for Disease Control and Prevention
ChAdOx1 MERS	chimpanzee adenovirus Ox1 with MERS Spike antigen
ChAdOx1 nCoV-19	name of AZD1222 when initially developed by the University of Oxford
CI	confidence interval
CoV	coronavirus
COVID-19	coronavirus disease 2019
CRO	contract research organization
CSR	clinical study report
DBL	database lock
DSMB	Data Safety Monitoring Board
E	envelope
eCRF	electronic case report form
EDC	electronic data capture
e-Diary	electronic diary
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot
FIH	first-in-human
GCP	Good Clinical Practice
GMFR	geometric mean fold rise
GMT	geometric mean titer
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IM	intramuscular

Abbreviation or special term	Explanation
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
M	membrane
MAAE	medically attended adverse event
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
MSD	Meso Scale Discovery
NHP	non-human primate
PBMC	peripheral blood mononuclear cell
PSRT	Protocol Safety Review Team
RBD	receptor binding domain
RRR	relative risk reduction
RT-PCR	reverse transcriptase polymerase chain reaction
S	Spike
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV	severe acute respiratory syndrome-coronavirus
SARS-CoV-2	severe acute respiratory syndrome-coronavirus 2
SoA	Schedule of Activities
TBL	total bilirubin
tPA	tissue plasminogen activator
ULN	upper limit of normal
US FDA	United States Food and Drug Administration
USA	United States of America
VE	vaccine efficacy
vp	viral particles
WHO	World Health Organization
w/v	weight/volume

Appendix I Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 1 (10 August 2020)

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.1 Synopsis	Updated Objectives and Endpoints, Overall Design, and Statistical Methods	To align with edits in main body	Non-substantial
1.2 Schema	Revised the footnote to identify the number of randomized participants in each age group to participate in the substudy	To identify by age group the 3 000 randomized participants who will participate in the substudy	Non-substantial
1.3 Schedule of Activities Table 2 Treatment and Follow-up Period - Main Study	Added assessment for recording any concomitant medication administered for the treatment of an SAE, MAAE, or AESI from Day 90 through Day 730	To support evaluation of SAEs, MAAEs, or AESIs	Non-substantial
1.3 Schedule of Activities Table 3 Treatment and Follow-up Period - Substudy	a) Added assessment for recording any concomitant medication administered for the treatment of an SAE, MAAE, or AESI from Day 90 through Day 730 b) Footnote d: identified that 'at least 300' participants in the substudy can have PBMCs collected	a) To support evaluation of SAEs, MAAEs, or AESIs b) To help ensure PBMCs can be collected in participants across age groups	Non-substantial
2.2 Background	a) Corrected the study number for the University of Oxford South African clinical study b) Updated preliminary clinical data from Study COV001 and Study COV002	To align with: a) The study number correction made by the University of Oxford b) The updated AZD1222 IB, Edition 1.1	Non-substantial
2.3.1 Risk Assessment	Updated common solicited AE information	To align with the updated AZD1222 IB, Edition 1.1	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
3 Objectives and Endpoints	a) Clarified that secondary objective 6 is performed in substudy and illness visits only b) Footnote a: identified the number of randomized participants in each age group to participate in the substudy	a) Humoral responses to AZD1222 are not required for main study participants b) To identify by age group the 3 000 randomized participants who will participate in the substudy	Non-substantial
4.1 Overall Design	a) Clarified that enrollment will begin with participants 18 to 55 years of age, followed by older age groups after FDA review of accruing clinical data b) Identified the number of randomized participants in each age group to participate in the substudy	a) To provide for review of immunogenicity data in older subjects prior to enrollment' b) To identify by age group the 3 000 randomized participants who will participate in the substudy	Non-substantial
4.2.1 Rationale for Study Design and Participant Population	Updated the number of participants 56 to 69 and ≥ 70 years of age anticipated to have received AZD1222 at time of study initiation	To align with updated study status	Non-substantial
5.1 Inclusion Criteria	Corrected number formatting to separate Criteria 3 and 4	Inclusion criterion 4 was erroneously included under inclusion criterion 3	Non-substantial
5.2 Exclusion Criteria	a) Clarified Criterion 2 to include participants with any other demyelinating condition b) Clarified Criterion 6 to state ≥ 20 mg per day vs ≥ 20 mg/kg/day of prednisone	Per NIH request Correct typographical error	Non-substantial
6.1.2 Dosing Instructions	Deleted instructions to cover the injection site with a sterile dressing	Erroneously included in original protocol	Non-substantial
6.2.1 Dose Preparation and Administration; 6.2.1.1 AZD1222 6.2.1.2 Placebo	Clarified that AZD1222 and placebo doses drawn into syringes for administration must be administered according to the beyond-use-date of the vial or IV bag	To align with the beyond-use-date of the vial or IV bag as AZD1222 and placebo do not contain preservatives	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
7.2 Participant Withdrawal from the Study	Clarified that all collected samples will be destroyed if the participant withdraws consent for use of existing samples	To align with current process	Non-substantial
8.1.1 Monitoring COVID-19 Symptoms	Clarified that investigator judgement should be used when determining which participants should initiate illness visits during the 7 days following administration of each dose of study intervention	To help ensure that qualifying symptoms for illness visits are due to potential infection with SARS-CoV-2 and not to reactogenicity of the study intervention	Non-substantial
8.1.2.2 Digital Health Device	Clarified that the monitoring team will receive and triage alerts associated with participants' digital health device data rather than the investigator	To align with current process	Non-substantial
9.1 Statistical Hypotheses 9.4.2.1 Primary Endpoint 9.4.4 Methods for Multiplicity Control 9.5 Interim Analyses	Clarified the statistical significance for determining vaccine efficacy	To add greater detail to the statistical analysis approach for the primary estimand	Non-substantial
9.4 Statistical Analyses	Clarified that the SAP will be approved prior to the interim analysis vs the primary analysis	Per standard practice	Non-substantial
Appendix A 5 Committee Structure	Added criteria for pausing the study for DSMB review	To ensure safety oversight	Non-substantial
Appendix E Toxicity Grading Scales for Solicited Adverse Events			
Table 11 Clinical Abnormalities: Vital Signs	Revised the temperature range for fever	To align with definition of fever throughout the main body	Non-substantial
Table 12 Clinical Abnormalities: Systemic	Added information for assessing severity grade of chills and deleted diarrhea	To align with solicited adverse events being collected, which includes chills but not diarrhea	Non-substantial

AESI = adverse event of special interest; MAAE = medically attended adverse event; NIH = National Institutes of Health; SAE = serious adverse event; SAP = Statistical Analysis Plan.

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