Clinical Study Protocol	
Study Intervention	AZD1222
Study Code	D8111C00002
Version	4.0
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A Phase I/II Randomized, Double-blind, Placebo-controlled Multicentre Study in Participants Aged 18 Years or Older to Determine the Safety and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19

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Regulatory Agency Identifier Number(s): NCT04568031

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: D8111C00002

Amendment Number: 3

Study Intervention: AZD1222
Study Phase: I/II

Short Title: Phase I/II Study in Participants Aged 18 Years or Older of AZD1222 for the Prevention of COVID-19

Study Physician Name and Contact Information will be provided separately

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	18 January 2021
Amendment 2	19 November 2020
Amendment 1	13 August 2020
Original Protocol	24 July 2020

Amendment 3 (18-January-2021)

Overall Rationale for the Amendment:

In the context of the current Japan health emergency, the primary analysis has been changed to include immunogenicity data up to Day 57 of a subset of participants in whom immunogenicity results will be available significantly earlier than in the rest of the study population. Delayed immunogenicity results availability for the rest of the study population which includes the participates who enrolled after restarting the study (30 September 2020) is a consequence of a temporary study interruption that occurred on the 07 September 2020 to allow a review of safety data, following the occurrence of a serious adverse event in a University Oxford-sponsored study in the UK. The immunogenicity data analysis including data up to Day 57 in all participants will be provided through an additional analysis, when available.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	The synopsis was updated to align with changes to the body of the protocol.	To ensure consistency between the protocol and the Synopsis.
2.2 Background	Updated information on the current situation of COVID-19 in Japan.	To include updated information.
2.2 Background	Added the situation of vaccine/license authorization of AZD1222 in UK.	To include updated information.
6.5.2 Prohibited Concomitant Medications	Added the description that the short courses of steroids are allowed as concomitant medication.	To make the management of participants conditions easier for the study sites.
8 STUDY ASSESSMENTS AND PROCEDURES	Changed the amount of blood collected from each participant at Visit 1.	Due to correct the erroneous description.
8.5.2.1 SARS-CoV-2 Serology Assessments	Changed the description of SARS-CoV-2 Serology Assessments.	Due to correct the erroneous description.

Section # and Name	Description of Change	Brief Rationale
9.1 Statistical Hypotheses	Added "where *p* is the proportion of seroresponse participants".	To describe the statistical hypotheses precisely.
9.2 Sample Size Determination	Changed the description about the power of the primary analysis for immunogenicity.	Due to a change in the number of participants to be included in the primary analysis for immunogenicity.
9.4 Statistical Analysis	Primary immunogenicity analysis plan has been changed to be based on a subset of the study population enrolled before the study interruption, and an additional analysis including Day 57 immunogenicity data in all subjects will be conducted when data will be available.	Acceleration in context of Japan health emergency.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase I/II Randomized, Double-blind, Placebo-controlled Multicentre Study in Participants Aged 18 Years or Older to Determine the Safety and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19

Short Title: Phase I/II Study in Participants Aged 18 Years or Older of AZD1222 for the Prevention of COVID-19

Rationale:

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.

Objectives and Endpoints

Objectives	Endpoints
Primary (Immunogenicity)	
• To assess antibody responses to AZD1222 Spike antigen following 2 IM doses of AZD1222 or placebo.	• The proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from Day 1 baseline value) to Spike antigen of AZD1222 (MSD serology assay) at Day 57.
Primary (Safety)	
• To assess the safety, tolerability, and reactogenicity profile of the candidate vaccine AZD1222.	(a) Occurrence of solicited local reactogenicity signs and symptoms for 7 days following throughout vaccination. (b) Occurrence of solicited systemic reactogenicity signs and symptoms for 7 days following throughout vaccination. (c) Occurrence of AEs, SAEs and AESIs for 28 days following throughout vaccination. (d) Change from baseline for safety laboratory measures.
Secondary (Immunogenicity)	
• To assess antibody responses to AZD1222 RBD antigen following 2 IM doses of AZD1222 or placebo.	• The proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from Day 1 baseline value) to RBD antigen of AZD1222 (MSD serology assay) at Day 57.

Objectives	Endpoints
• To assess time course of antibody to AZD1222 Spike and RBD antigens of AZD1222 (MSD serology assay)	• GMT and GMFR of immunogenicity against Spike and RBD antigens of AZD1222 (MSD serology assay) at each time point up to Day 365.
• To assess the function of nAb against SARS-CoV-2 spike protein	• Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from Day 1 baseline value) to AZD1222 as measured by SARS-CoV-2 nAb (wild-type assay or pseudoneutralisation assay) at Day 57. • GMT and GMFR of immunogenicity against Spike antigen of AZD1222 as measured by SARS-CoV-2 nAb at each time point up to Day 365.
Secondary (Safety)	
• To assess the safety of the candidate vaccine AZD1222.	• Occurrence of SAEs and AESIs throughout the study duration up to Day 365.
Exploratory (Descriptive efficacy)	
• To describe occurrence of symptomatic COVID-19 in recipients of AZD1222 and placebo.	• Virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19.
• To describe occurrence of severe COVID-19 and seroresponse to non-Spike SARS-CoV-2 antigens.	(a) Hospital admissions associated with COVID-19. (b) Intensive care unit admissions associated with COVID-19. (c) Deaths associated with COVID-19. (d) Seroresponse against non-Spike (nucleocapsid) SARS-CoV-2 antigens (MSD serology assay).

AE = adverse event; AESI = adverse event of special interest; GMFR = geometric mean fold rise; GMT = geometric mean titre; IM = intramuscular; MSD = Meso Scale Discovery; nAb = neutralising antibodies; RBD = receptor-binding domain; RT-PCR = reverse transcriptase-polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2

Overall Design

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

The study has 2 cohorts with different age populations. Cohort C will include healthy participants aged 18 to 55 years. Cohort D will include healthy elderly participants aged ≥ 56 years. In Cohort D, the elderly population is further divided into 2 different age subgroups; aged 56 to 69 years (Subcohort D1) and aged ≥ 70 years (Subcohort D2). At least 30% of

participants in Cohort D will be secured for participants with age ≥ 70 years. Regarding Cohorts C and D, 128 participants will be randomised in a 3:1 ratio to receive either AZD1222 or placebo within each cohort.

An independent Neurological AESI Expert Committee will be available to review and provide advice to the Company about the diagnosis and causality assessment of selected neurological AESIs.

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

Number of Participants:

Approximately 307 participants will be screened to achieve 256 participants randomly assigned in a 3:1 ratio to receive either AZD1222 or placebo.

Intervention Groups and Duration:

In this study, 256 eligible participants will be randomised in a 3:1 ratio to receive 2 IM doses of either AZD1222 with 5×10^{10} vp (nominal) or placebo, administered 4 weeks apart.

After completion of clinical data lock for primary analysis, the study will become single blind, where only participants are blinded from allocation of investigational product. All participants will be unblinded and participants on the placebo arm may be vaccinated when a licensed vaccine for COVID-19 becomes available in Japan for the general population. For participants who cannot make scheduled visits after the vaccinations, the follow-up should be made as much as possible using telephone call and/or other appropriate way until Day 365.

Data Monitoring Committee: Not applicable

Statistical Methods

Sample Size

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

It is difficult to calculate an accurate sample size necessary for comparing the proportion of participants who have a seroresponse to severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) spike protein between the AZD1222 and placebo arms because of insufficient

information on immunogenicity in both arms at the moment. It is expected that the minimum number of participants per cohort will be about 36 in the primary analysis. Under a slightly conservative assumption about seroresponse rates of 10% assumed on placebo and over 75% on AZD1222, it is expected that the sample size of 36 (27 for AZD1222 vs 9 for placebo) will provide 93% power for showing the superiority of seroresponse of the AZD1222 treatment compared with placebo based on Fisher's exact test at 2-sided 5% alpha.

Analysis steps

The analysis will be done in the following three steps:

- The Primary analysis will include immunogenicity data up to Day 57 from subjects enrolled before the study interruption and safety data gathered in all participants up to Day 57.
- The additional analysis will include immunogenicity data in all participants up to Day 57.
- The final analysis will include all endpoints up to Day 365 in all participants.

Primary Immunogenicity Endpoint

The primary immunogenicity endpoint is the proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from Day 1 baseline value) to the Spike antigens of AZD1222 (Meso Scale Discovery [MSD] serology assay) at Day 57, and will be calculated along with its 95% confidence interval (CI) based on the Clopper-Pearson method in each treatment groups in each cohort (C and D) and also Subcohorts D1 and D2 separately. The proportion of participants who have a post-treatment seroresponse will be compared between AZD1222 treatment and placebo using Fisher's exact test for each cohort. Fisher's exact test will not be presented for Subcohorts D1 and D2. No adjustment for multiple testing will be made.

Primary Safety Endpoint

The safety of AZD1222 will primarily be assessed by:

- The incidence of local and systemic solicited reactogenicity signs and symptoms for 7 days following throughout vaccination (Day 1 to 8 and Day 29 to 36).
- The incidence of AEs, serious adverse events (SAEs) and adverse events of special interest (AESIs) collected from Day 1 through Day 57.
- The change from baseline for safety laboratory measures at Day 8, Day 29, Day 36, and Day 57.

AE severity will be graded according to the US Food and Drug Administration (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 1 event, where appropriate.

An overview of AEs will be presented for each treatment group, including the number and percentage of participants with any AE, AEs with outcome of death, 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.

Secondary Immunogenicity Endpoint

The proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from Day 1 baseline value) to the receptor-binding domain (RBD) antigens of AZD1222 (MSD serology assay) at Day 57, will be analysed in the same way as the primary immunogenicity endpoint.

Geometric mean titre (GMT) and geometric mean fold rise (GMFR) of immunogenicity against Spike and RBD antigens of AZD1222 (MSD serology assay) with the associated 95% CIs will be computed at each time point in each treatment arm in each cohort (C and D) and also in Subcohorts D1 and D2 separately.

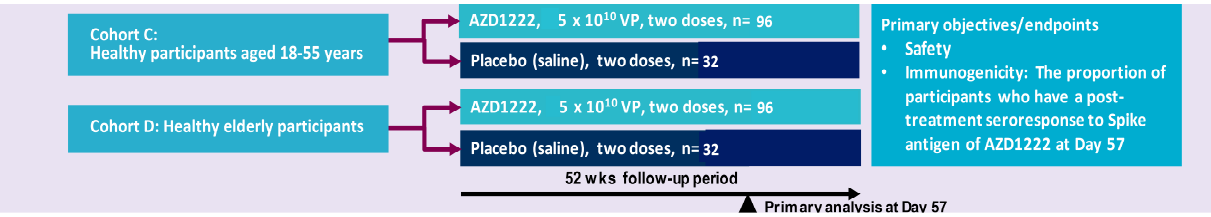
The proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from Day 1 baseline value) to AZD1222 as measured by SARS-CoV-2 neutralising antibodies (nAbs) (wild-type assay or pseudoneutralisation assay) at Day 57, will be analysed in the same way as the primary immunogenicity endpoint. GMT and GMFR of SARS-CoV-2 nAbs and the associated 95% CIs will be presented at each time point in each treatment arm in each cohort (C and D) and also in Subcohorts D1 and D2 separately.

Secondary Safety Endpoints

The secondary safety endpoints are the occurrence of SAEs and AESIs collected from Day 1 through Day 365.

1.2 Schema

Figure 1 Study Design



n = number of participants; VP = viral particles

1.3 Schedule of Activities

Table 1 Schedule of Activities

Study Procedure	**Screening**	**Vaccinations/Follow-up**											**Details in CSP Section or Appendix**
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	
Timeline (days)	**-14 to 1**	**1**	**4**	**8**	**15**	**29**	**32**	**36**	**43**	**57**	**183**	**365**	
Time window (days)			**± 1**	**± 2**	**± 2**	**± 2**	**± 1**	**± 2**	**± 2**	**± 2**	**± 7**	**± 30**	
Informed consent	X												Section 5.1
Verify eligibility criteria	X	X											Sections 5.1 and 5.2
Demography	X												
Medical and surgical history	X	X											
Prior/concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	
Vaccination		X				X							
Telephone call			X				X						
Vital signs	X	X		X	X	X		X	X	X	X	X	Section 8.2.2
Complete physical examination	X												Section 8.2.1
Targeted physical examination		X		X	X	X		X	X	X	X	X	Section 8.2.1
Urine pregnancy test (WOCBP only)	X	X (pre-dose)				X (pre-dose)							
AEs		X	X	X	X	X	X	X	X	X			Section 8.3
SAEs	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3
AESIs		X	X	X	X	X	X	X	X	X	X	X	Section 8.3.8
SARS-CoV-2 infection	X	←——————————————————————————————————→											

Study Procedure	Screening	Vaccinations/Follow-up											Details in CSP Section or Appendix
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	
Timeline (days)	**-14 to 1**	**1**	**4**	**8**	**15**	**29**	**32**	**36**	**43**	**57**	**183**	**365**	
Time window (days)			**± 1**	**± 2**	**± 2**	**± 2**	**± 1**	**± 2**	**± 2**	**± 2**	**± 7**	**± 30**	
e-Diary provided[a]		X				X							
e-Diary collected				X				X					
Clinical safety laboratory assessments	X	X		X		X		X		X			Section 8.2.3
Test for antibody against SARS-CoV-2 antigen (lateral flow type test)	X												Section 5.2
Saliva sample for RT-PCR test: SARS-CoV-2 genome detection	X												Section 5.2
Serum sample for SARS-CoV-2 serology (central test, MSD serology assay)	X	X (pre-dose)			X	X (pre-dose)			X	X	X	X	Section 8.5.2.1
Serum for SARS-CoV-2 nAb assessment (central test)		X (pre-dose)				X (pre-dose)				X	X	X	Section 8.5.2.2

AE = adverse event; AESI = adverse event of special interest; CSP = clinical study protocol; MSD = Meso Scale Discovery; nAb = neutralising antibody; RT-PCR = reverse transcriptase-polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; WOCBP = women of childbearing potential

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

a: If a participant has a smart phone, he/she will download app which is used for Diary. If a participant does not have one, e-Diary will be provided and he/she should use it in order to report their condition.

2 INTRODUCTION

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

2.1 Study Rationale

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 Middle East respiratory syndrome (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 World Health Organization (WHO) declared the novel coronavirus a pandemic on 11 March 2020. As of 18 October 2020, there have been more than 40 million confirmed cases and > 1.1 million deaths globally (WHO 2020a). As of 22 December 2020, there have been 198 523 cases of COVID-19 and 2 900 people have died due to the disease in Japan (https://www.mhlw.go.jp/stf/covid-19/kokunainohasseijoukyou_00006.html#1-1).

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.

Coronaviruses are spherical, enveloped, large positive-sense single-stranded RNA genomes. One-fourth of their genome is responsible for coding structural proteins, such as the S glycoprotein, envelope (E), membrane (M), and nucleocapsid (N) proteins. E, M, and N proteins are mainly responsible for virion assembly while the S protein is involved in receptor

binding, mediating virus entry into host cells during coronavirus infection via different receptors (Li, 2016). SARS-CoV-2 belongs to the phylogenetic lineage B of the genus *Betacoronavirus* and it recognises the angiotensin-converting enzyme 2 (ACE2) as the entry receptor (Zhou et al, 2020). It is the seventh coronavirus 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 protein. 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, ferret, porcine, and non-human primate (NHP) models. Whilst a single dose of AZD1222 induced antigen-specific antibody and T-cell responses, a booster immunization enhanced antibody responses, particularly in pigs, with significant increases in SARS-CoV-2 neutralising antibody titres (Graham et al 2020). Further, in a SARS-CoV-2 challenge model, a single administration of AZD1222 significantly reduced viral load in bronchoalveolar lavage fluid and respiratory tract tissue of vaccinated rhesus macaques as compared with vector controls. Importantly, no evidence of vaccine-associated enhanced respiratory disease （VAERD) following SARS-CoV-2 challenge in vaccinated rhesus macaques was observed (van Doremalen et al 2020b).

The clinical development program for AZD1222 was initiated by the University of Oxford, and currently has 4 ongoing studies being conducted in the UK (COV001 [NCT04324606], COV002 [NCT04400838]), Brazil (COV003 [ISRCTN89951424]), and South Africa (COV005 [NCT04444674]). The Sponsor, in addition to this study, has 2 ongoing studies in United States of America (D8110C00001[NCT04516746]) and Russia (D8111C00001 [NCT04540393]).

Preliminary unblinded data are available for the first in human Study COV001 and Study COV002. Study COV001 enrolled the first participant on 23 April 2020 and completed enrolment on 21 May 2020 with 1 077 participants. Preliminary data as of 24 July 2020 from 544 participants who received at least one dose of 5×10^{10} viral particles (vp) AZD1222 and 10 participants who received a second dose of 5×10^{10} vp AZD1222 28 days later found the vaccine was generally tolerated, with no treatment-related SAEs reported through 28 days post dose. The most common local solicited adverse events (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.

Neutralising antibody (nAb) 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 01 October 2020, Study COV002 enrolled 10 013 participants, including 5 152 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 as of 24 July 2020, the local and systemic solicited AE profile following a single dose of 5×10^{10} vp 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 $\geq$ 70 years).

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 immunogencity 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 participants have received ChAdOx1-vectored vaccines in these studies. The vaccines demonstrated robust immunogenicity after a single dose and favourable safety profiles, with no vaccine-related SAEs. As of 30 December 2020, vaccine/license authorization of AZD1222 was granted in UK.

See the AZD1222 Investigator's Brochure (IB), Sections 4 and 5 for additional information on nonclinical and clinical studies of AZD1222 and related ChAdOx1-vectored vaccines, respectively. 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 immunogenicity 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

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).

There are no identified risks for AZD1222. Important potential risks are immunologic reactions: serious hypersensitivity (anaphylactic reactions) and vasculitides; neurologic reactions: demyelinating diseases; and vaccine-associated enhanced respiratory disease. A summary of risks associated with AZD1222 and safety information reported across the AZD1222 clinical studies are provided in the current version of the AZD1222 IB.

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. Taking these measures into account, the potential risks identified in association with AZD1222 are justified by the anticipated benefits that may be afforded to participants for the prevention of COVID-19.

3 OBJECTIVES AND ENDPOINTS

Table 2 Objectives and Endpoints

Objectives	Endpoints
Primary (Immunogenicity)	
• To assess antibody responses to AZD1222 Spike antigen following 2 IM doses of AZD1222 or placebo.	• The proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from Day 1 baseline value) to Spike antigen of AZD1222 (MSD serology assay) at Day 57.
Primary (Safety)	
• To assess the safety, tolerability, and reactogenicity profile of the candidate vaccine AZD1222.	(a) Occurrence of solicited local reactogenicity signs and symptoms for 7 days following throughout vaccination. (b) Occurrence of solicited systemic reactogenicity signs and symptoms for 7 days following throughout vaccination. (c) Occurrence of AEs, SAEs and AESIs for 28 days following throughout vaccination. (d) Change from baseline for safety laboratory measures.
Secondary (Immunogenicity)	
• To assess antibody responses to AZD1222 RBD antigen following 2 IM doses of AZD1222 or placebo.	• The proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from Day 1 baseline value) to RBD antigen of AZD1222 (MSD serology assay) at Day 57.
• To assess time course of antibody to AZD1222 Spike and RBD antigens of AZD1222 (MSD serology assay)	• GMT and GMFR of immunogenicity against Spike and RBD antigens of AZD1222 (MSD serology assay) at each time point up to Day 365.
• To assess the function of nAb against SARS-CoV-2 spike protein	• Proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from Day 1 baseline value) to AZD1222 as measured by SARS-CoV-2 nAb (wild-type assay or pseudoneutralisation assay) at Day 57. • GMT and GMFR of immunogenicity against Spike antigen of AZD1222 as measured by SARS-CoV-2 nAb at each time point up to Day 365.
Secondary (Safety)	
• To assess the safety of the candidate vaccine AZD1222.	• Occurrence of SAEs and AESIs throughout the study duration up to Day 365.

Objectives	Endpoints
Exploratory (Descriptive efficacy)	
• To describe occurrence of symptomatic COVID-19 in recipients of AZD1222 and placebo.	• Virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19.
• To describe occurrence of severe COVID-19 and seroresponse to non-Spike SARS-CoV-2 antigens.	(a) Hospital admissions associated with COVID-19. (b) Intensive care unit admissions associated with COVID-19. (c) Deaths associated with COVID-19. (d) Seroresponse against non-Spike (nucleocapsid) SARS-CoV-2 antigens (MSD serology assay).

AE = adverse event; AESI = adverse event of special interest; GMFR = geometric mean fold rise; GMT = geometric mean titre; IM = intramuscular; MSD = Meso Scale Discovery; nAb = neutralising antibodies; RBD = receptor-binding domain; RT-PCR = reverse transcriptase-polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2

4 STUDY DESIGN

4.1 Overall Design

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

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

An independent Neurological AESI Expert Committee will be available to review and provide advice to the Company about the diagnosis and causality assessment of selected neurological AESIs.

4.1.1 Screening Visit

All potential participants will have a screening visit, which may take place up to 14 days prior to Day 1. Informed consent will be taken before screening/enrolment. At the time of obtaining consent, for female participants who are of childbearing potential it will be recorded that they verbally confirmed that they have used one highly effective form of birth control for at least 28 days prior to the planned vaccination. If written consent is obtained, the procedures indicated in the schedule of attendances will be undertaken including a medical history, physical examination, height and weight, and blood tests, including a SARS-CoV-2 screening test and clinical safety laboratory assessments (biochemistry and haematology). Abnormal blood tests at screening will be assessed. The eligibility of the participants will be reviewed at the end of the screening visit and again when all results from the screening visit have been considered. Decisions to exclude the participant from enrolling in the trial or to withdraw a participant from the trial will be at the discretion of the Investigator. If eligible, a Day 1 visit will be scheduled for the participant to receive AZD1222 or placebo and subsequent follow-up.

4.1.2 Vaccination Visit

Participants will be considered enrolled into the trial at the point of vaccination. Before vaccination, the eligibility of the participant will be reviewed. Body temperature will be observed and if necessary, a medical history and physical examination may be undertaken to determine need to postpone vaccination or withdraw the participation. Women who are of childbearing potential will be confirmed with negative pregnancy test (urine test) before

vaccination.

In this study, 2 doses of AZD1222 with 5×10^{10} vp (nominal) or 2 doses of placebo at 3:1 allocation will be distributed to healthy volunteers. Vaccines will be prepared out of sight of the participant.

All vaccines will be administered by IM injection. The injection site will be wiped with alcohol cotton and be covered with a sterile hermetic dressing and the participant will stay in the study site for observation for at least 30 minutes after vaccination, in case of immediate AEs. After the observation at the site, the study staff will attach a hermetic transparent dressing to the injection site. The application of the dressing will continue until the next visit. If the dressing comes off before the next visit, the participant should be instructed to put on the spare dressing. In addition, the peeled dressing should be properly stored in a sealed waste bag distributed beforehand. The participants will be instructed to bring it to the site at the next visit, and the study staff should collect it at the next visit. The staff will dispose of it properly.

All participants will be given an axillary thermometer, tape measure and app for e-Diary, with instructions on use. All participants will be asked to report on solicited signs and symptoms for 7 days following throughout vaccination (Days 1 to 8 and Days 29 to 36). e-Diary will collect information on the timing and severity of the solicited signs and symptoms shown in Table 6.

4.1.3 Subsequent Visits

Follow-up visits will take place as per the schedule of assessment described in Table 1 with respective windows. All participants will be assessed for local and systemic AE, physical examination, review of e-Diary and blood tests at these time points as detailed in the schedule of assessment. Blood will also be taken for immunology purposes. Visit 3 (Day 4) and Visit 7 (Day 32) are performed as a telephone visit to confirm solicited events.

After completion of clinical data lock for primary analysis, the study will become single blind, where only participants are blinded from allocation of investigational product. All participants will be unblinded and participants on the placebo arm may be vaccinated when a licensed vaccine for COVID-19 becomes available in Japan for the general population. For participants who cannot make scheduled visits after the vaccinations, the follow-up should be made as much as possible using telephone call and/or other appropriate way until Day 365 in order to collect information on event of SARS-CoV-2 infection, which includes 1) hospital admissions associated with COVID-19, 2) intensive care unit admissions associated with COVID-19, and 3) deaths associated with COVID-19, as well as any SAEs/adverse events of special interest (AESIs).

4.1.4 COVID-19 Symptomatic Participant

Participants who become symptomatic during follow-up will be instructed to call the trial staff who will then advise on how to proceed with clinical testing for COVID-19 if necessary. When participants are suspected of being infected with SARS-CoV-2 based on their symptom (fever or cough or shortness of breath or anosmia/ageusia) and/or positive reverse transcriptase-polymerase chain reaction (RT-PCR) testing, they will be advised to contact hospitals/clinics designated for treatment of COVID-19 per local guidance. Symptomatic participants may be regularly contacted over the phone for safety monitoring until symptom resolution.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Study Design and Participant Population

The placebo arm is needed for securing the objectivity of the safety evaluation of the AZD1222 arm and it is also needed as a control for evaluating immunogenicity.

The participant population is males and females ≥ 18 years of age who have no seropositivity to SARS-CoV-2 and a negative RT-PCR test for SARS-CoV-2. Inclusion of older participants is based on data that are is being gathered from the ongoing University of Oxford-sponsored studies. Study COV001 enrolled participants 18 to 55 years of age. Study COV002 is pursuing an age-escalation design and it is anticipated that at least 60 participants who are 56 to 69 years of age and 100 participants aged ≥ 70 will have received AZD1222 prior to initiation of this study.

The study will exclude females who are pregnant or breastfeeding and children < 18 years of age. Women who are pregnant or breastfeeding 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 older participants.

4.2.2 Rationale for Study Endpoints

Seroresponse is defined as ≥ 4-fold rise in titres from Day 1 baseline value, and the proportion of participants who have a post-treatment seroresponse to Spike antigen of AZD1222 for the primary immunogenicity endpoint. Assessment of rise in titres of antibody is used in various development trials of vaccine as measurements of immunogenicity endpoint (https://www.pmda.go.jp/files/000206153.pdf.)

Solicited AEs will be collected for 7 days following each dose of study intervention, a period that has proven adequate to describe reactogenicity events. For all participants, AEs will be collected through 28 days post each dose of study intervention. SAEs and AESIs and will be

collected throughout 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, 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 nAbs against MERS-CoV using a live virus assay (Folegatti et al, 2020). 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 nAb titres, and fewer areas of the lung contained viral RNA in prime boost group compared with 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 receptor-binding domain and nAbs 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 Meso Scale Discovery (MSD) platform and by both neutralisation and pseudo-neutralisation assays. Notable increases in antibody levels to the S protein were seen with the ELISA assay and increases to both the S protein and receptor-binding domain were noted using the MSD platform. Similarly, increases in antibody levels following the second dose were also seen with neutralisation and pseudo-neutralisation assays. Safety data found the vaccine was generally tolerated, with no treatment-related SAEs reported through 28 days post dose.

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 their last scheduled procedure.

The end of the study is defined as the date of the last scheduled procedure for the last participant in the study.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment 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 Participants aged 18 to 55 years (Cohort C), aged 56 to 69 years (Subcohort D1), or aged ≥ 70 years (Subcohort D2).

Type of Participant

2 Willing to allow the investigators to discuss the participant's medical history with their General Practitioner and access all medical records when relevant to study procedures.

3 Agreement to refrain from blood donation during the course of the study.

Reproduction

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

5 Female participants:

(a) Women of childbearing potential must:

- Have a negative pregnancy test on 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 last 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 3). 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 sterilised (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 randomisation, 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 randomisation, without an alternative cause, following cessation of exogenous sex-hormonal treatment.

Table 3 Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
• Intrauterine device • Intrauterine hormone-releasing system (IUS) [a] • Bilateral tubal occlusion • Vasectomised partner [b] • Sexual abstinence [c]	• Combined (oestrogen- and progestogen-containing hormonal contraception) - oral (combined pill)

[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 vasectomised 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.

6 Male participants: Agree to continue contraception from the first vaccination until 74 days after the last vaccination.

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 informed consent form (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 Known past laboratory-confirmed SARS-CoV-2 infection.

2 Positive SARS-CoV-2 RT-PCR test at screening.

3 Seropositivity to SARS-CoV-2 at screening.

4 Significant infection or other illness, including fever > 37.8°C on the day prior to or day randomisation

5 Any confirmed or suspected immunosuppressive or immunodeficient state; asplenia; recurrent severe infections and use of immunosuppressant medication within the past 6 months, except topical steroids or short-term oral steroids (course lasting ≤ 14 days).

6 History of allergy to any component of the vaccine

7 Any history of anaphylaxis or angioedema.

8 Current diagnosis of or treatment for cancer (except basal cell carcinoma of the skin and uterine cervical carcinoma in situ).

9 History of serious psychiatric condition likely to affect participation in the study.

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

11 Suspected or known current alcohol or drug dependency.

12 History of Guillan-Barré syndrome or any other demyelinating condition.

13 Any other significant disease, disorder or finding which 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.

14 Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder and neurological illness (mild/moderate well controlled comorbidities are allowed).

Prior/Concomitant Therapy

15 Receipt of any vaccine (licensed or investigational) other than the study intervention within 30 days before and after each study vaccination.

16 Prior or planned receipt of an investigational or licensed vaccine or product likely to impact on interpretation of the trial data (eg, adenovirus vectored vaccines, any coronavirus vaccines). Note: Participants on the placebo arm are allowed to be vaccinated when a licensed vaccine for COVID-19 becomes available in Japan for the general population.

17 Administration of immunoglobulins and/or any blood products within the 3 months preceding the planned administration of the vaccine candidate.

18 Continuous use of anticoagulants, such as coumarins and related anticoagulants (ie, warfarin) or novel oral anticoagulants (ie, apixaban, rivaroxaban, dabigatran and edoxaban).

Prior/Concurrent Clinical Study Experience

19 Participation in COVID-19 prophylactic drug trials for the duration of the study. Note: Participation in COVID-19 treatment trials is allowed in the event of hospitalisation due to COVID-19.

Other Exclusions

20 For women only - currently pregnant (confirmed with positive pregnancy test) or breastfeeding.

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.

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 (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened only with the approval of the sponsor's physician (or designee). 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 for the rescreening.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilised by a study participant according to the study protocol. For this study, study intervention is defined as AZD1222 or placebo (Table 4).

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

Table 4 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 Labelling	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.

AZD1222

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

Unopened vials of AZD1222 must be stored at 2°C to 8°C (36°F to 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 doses of AZD1222 or placebo on Day 1 and Day 29.

It is recommended that the study interventions be administered as an IM injection into the

deltoid of the non-dominant arm. If IM injection in the deltoid of the non-dominant arm is not possible (local injury, tattoo, other) then IM injection in the deltoid of the dominant arm may be used.

The injection site should be wiped with alcohol cotton and covered with a dressing. All participants will be observed for 30 minutes after vaccination at the study site. After the observation at the site, the study staff will attach a hermetic transparent dressing to the injection site. The application of the dressing will continue until the next visit. If the dressing comes off before the next visit, the participant should be instructed to put on the spare dressing. In addition, the peeled dressing should be properly stored in a sealed waste bag distributed beforehand. The participants will be instructed to bring it to the site at the next visit, and the study staff should collect it at the next visit. The staff will dispose of it properly.

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 recognise 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 authorised 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 authorised 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 1 mL or equivalent 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 according to the beyond-use-date of the vial. If AZD1222 dose administration is not completed within the 4 hour 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 intravenous (IV) bag in a sterile 1 mL or equivalent 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 according to the beyond-use-date of the vial. If placebo dose administration is not completed within the 4-hour beyond-use-date, a new dose must be prepared from a new vial or IV bag.

6.3 Measures to Minimise Bias: Randomisation and Blinding

6.3.1 Randomisation

All participants will be centrally assigned to randomised study intervention using an Interactive Response Technology (IRT). Before the study is initiated, user guides, the log in information, and directions for the IRT will be provided to each site.

The randomisation will be done separately within each Cohort. In Cohort D, participants will be stratified at randomisation by age group within cohort, but in Cohort C stratification will not be done.

Where a participant does not meet all the eligibility criteria but is randomised in error, or incorrectly received study intervention, the investigator should inform the sponsor's physician immediately, and a discussion should occur between the sponsor's 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 until completion of clinical data lock for primary analysis. Only participants will be blinded from their investigational product assignment after clinical data lock for primary analysis. The study will become open label in order to inform participants of their investigational product assignment when a licensed vaccine for COVID-19 becomes available in Japan for the general population. Since AZD1222 and placebo are visually distinct prior to dose preparation (due to differences in container closure), investigational medicinal product 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 to the investigator(s) or pharmacists a dose tracking number to be allocated to the participant at the vaccination visit. Routines for this will be described in the IRT user manual that will be provided to each site.

The randomisation code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomisation.

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. Randomisation 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 electronic Case Report Form (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 enrolment or receives during the period specified in the Schedule of Activities (SoA, Section 1.3) must be recorded along with:

- 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 medical conditions and/or for health maintenance.

6.5.2 Prohibited Concomitant Medications

- Receipt of any vaccine (licensed or investigational) other than the study intervention (within 30 days before and after each study vaccination).
- Receipt of a product likely to impact on interpretation of the trial data (eg, adenovirus vectored vaccines, any coronavirus vaccines) (within 30 days before study vaccination until the end of study). Note: Participants on the placebo arm are allowed to be vaccinated when a licensed vaccine for COVID-19 becomes available in Japan for the general population.
- Receipt of any investigational drug (from provision of informed consent to the end of study).
- Receipt of any immunosuppressant medication (within 6 months prior to enrolment until the end of study) other than the topical steroids and short courses of steroids (course lasting ≤ 14 days).
- Receipt of immunoglobulins and/or any blood products (from provision of informed consent to the end of study).
- Receipt of oral anticoagulants, such as coumarins and related anticoagulants (ie, warfarin) or novel oral anticoagulants (ie, apixaban, rivaroxaban, dabigatran and edoxaban) (from provision of informed consent to the end of study).

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

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Each participant will receive 2 doses of study intervention. An individual participant will not receive study intervention if any of the following occur in the participant in question:

- Withdrawal of consent after signing informed consent
- Participant meets one or more of the exclusion criteria or fails to meet all inclusion criteria for study participation
- Participant is pregnant or nursing
- Any Grade ≥ 3 allergic reaction including anaphylaxis that is assessed as related to AZD1222
- Any SAE assessed as related to study intervention
- Any AE that, in the judgment of the site investigator, is related to study intervention and may jeopardise the safety of the study participant

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.

7.2 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, behavioural, 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 and not tested 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 Global Study Team.

- For participants who cannot make scheduled visits after the vaccinations, the follow-up should be made as much as possible using telephone call and/or other appropriate way until Day 365.

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 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.

7.4 Criteria for Discontinuation or Suspension of All or Part of the Study

The study sponsor may decide to prematurely terminate or suspend the whole study or a component of the study at any time. The reasons for prematurely terminating or temporarily suspending the study may include, but are not limited to, 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.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised 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 utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).

The amount of blood collected from each participant will be as follows:

- The amount of blood collected from each participant is Visit 1: 14.0 mL, Visit 2: 13 mL, Visit 4: 4.5 mL, Visit 5: 8.5 mL, Visit 6: 13 mL, Visit 8: 4.5 mL, Visit 9: 8.5 mL, Visit 10: 13 mL, Visit 11: 8.5 mL, Visit 12: 8.5 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Descriptive Efficacy Assessments

Primary and secondary immunogenicity endpoint assessments are described in Section 8.5.2.1 and Section 8.5.2.2, respectively.

In addition, the following occurrences will be described in AZD1222 and placebo recipients:

- Virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19.
- Evaluation of severe COVID-19 in virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19:
  - Hospital admissions associated with COVID-19.
  - Intensive care unit admissions associated with COVID-19.
  - Deaths associated with COVID-19.
- Seroresponse against non-spike (nucleocapsid) SARS-CoV-2 antigens (MSD serology assay); see Section 8.5.2.1 for details.

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 and 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 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).

8.2.2 Vital Signs

Vital signs, including heart rate, 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.

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

8.2.3 Clinical Safety 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 beta human chorionic gonadotropin (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.

Blood samples for determination of clinical chemistry and haematology will be taken at the visits indicated in the SoA (Section 1.3).

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date and time of collection will be recorded on the appropriate eCRF.

The clinical chemistry and haematology analyses will be performed at a central laboratory.

The following laboratory variables will be measured.

Table 5 Laboratory Safety Variables

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

B = blood; P = plasma; S = serum

NB. In case a participant shows an aspartate aminotransferase (AST) **or** alanine aminotransferase (ALT) ≥ 3 × upper limit of normal (ULN) together with total bilirubin (TBL) ≥ 2 × ULN please refer to Section 8.3.6.

8.3 Adverse Events and Serious Adverse Events

The Principal investigator (PI) 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 categorised as solicited AEs.

Solicited AEs are local or systemic predefined events for assessment of reactogenicity. Solicited AEs will be collected in an e-Diary (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.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant’s legally authorised 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 28 days after each dose of study intervention.

Solicited AEs will be recorded for 7 days following each dose of study intervention.

SAEs will be recorded from the time of signing of the ICF through the last participant contact.

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

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. AstraZeneca 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.

Adverse event variables

The following variables will be collected for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Severity grade/max severity grade/changes in severity grade
- Whether the AE is serious or not
- Investigator causality rating against the investigational product(s) (yes or no)
- Action taken with regard to investigational product(s)
- 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 hospitalisation

- 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 Food and Drug Administration (FDA) guidance for healthy volunteers enrolled in a preventive vaccine clinical study (FDA, 2007) will be utilised for all unsolicited events with an assigned severity grading.

8.3.3 Causality Collection

The investigator should assess causal relationship between investigational product 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 to the Clinical Study Protocol.

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 laboratory tests and vital signs will be summarised in the Clinical Study Report (CSR).

Deterioration as compared with baseline in protocol-mandated laboratory values or vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the investigational product 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 laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

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 ≥ 3 × ULN together with TBL ≥ 2 × ULN and confirmed as a Hy's law case should be reported as SAEs.

Hy's Law

AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN, where no other reason, other than the study intervention, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug. The elevation in aminotransferases 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 aminotransferases and TBL must occur.

8.3.7 Solicited Adverse Events

Local and systemic predefined solicited AEs for reactogenicity assessment will be collected in an e-Diary for 7 days following administration of each dose of study intervention.

Solicited AEs should not be reported as unsolicited AEs (see Section 8.3). However, solicited AEs should be reported as SAEs if they fulfil the criteria (see Section 8.3.9).

Table 6 List of Predefined Solicited Adverse Events for Reactogenicity Assessment

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

[a] Fever measured by any route. Investigators who consider a temperature lower than this cutoff as a fever or a 'fever' reported by participants without documentation by a thermometer should record the event as 'elevated body temperature.'

[b] Swelling, redness, and induration must be ≥ 0.6 centimetres in diameter.

e-Diary for Recording Solicited AEs

On Day 1, participants will be given an axillary thermometer, tape measure, and access to app for 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 according to toxicity grading scales adopted from US FDA Guidance (FDA, 2007) as defined in Appendix D. Because solicited AEs are expected to occur after vaccination, they will not be assessed for relationship to study intervention.

8.3.8 Adverse Events of Special Interest

AESIs will be collected according to the time points 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. AESIs for AZD1222 are based on Brighton Collaboration case definitions (SPEAC, 2020), clinical experience, and scientific interest. See Appendix E for a listing and description of AZD1222 AESIs.

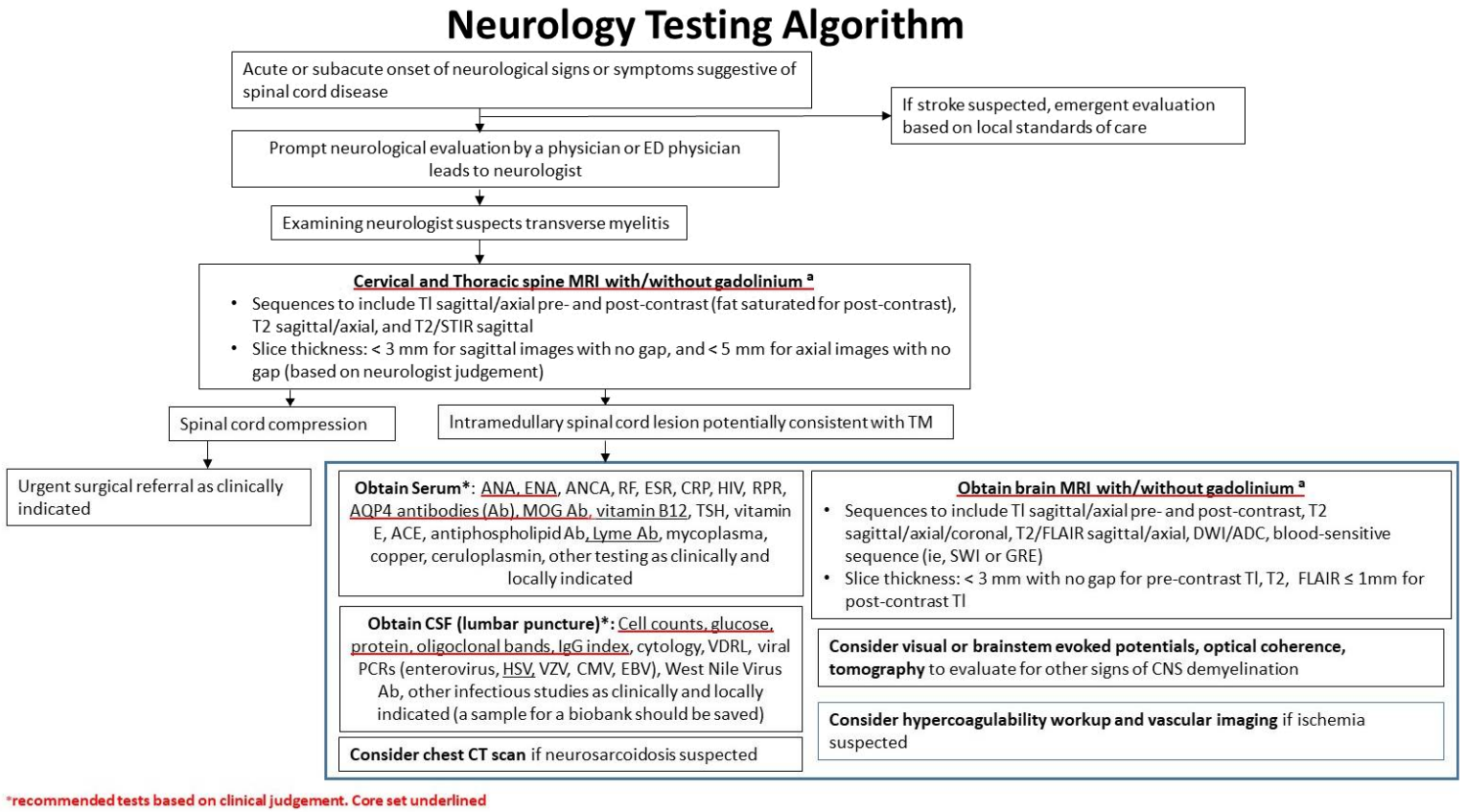
An AESI can be serious or non-serious. All AESIs will be recorded in the eCRF. If any AESI occurs in the course of the study, investigators or other site personnel will inform the appropriate Sponsor representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it. Serious AESIs will be recorded and reported as per Section 8.3.9.

8.3.8.1 Potential Neurological AESIs

If a participant experiences new onset (acute or subacute) motor and sensory disturbances (eg, weakness, numbness, paresthesias, hypoesthesia, hyperesthesia, dysesthesias), bowel/bladder dysfunction, gait impairment, visual disturbance, or any event of myelitis, encephalomyelitis, transverse myelitis, or other sudden neurological deficit, there should be prompt neurological evaluation. See Figure 2 for a recommended testing algorithm.

An independent Neurological AESI Expert Committee will review and provide advice on the diagnosis and causality assessment of selected neurological AESIs occurring in the AZD1222 clinical development program (see Appendix A 5).

Figure 2 Neurology Testing Algorithm



[a] Adapted from (Rovira et al 2015)

Ab = antibody; ACE = angiotensin converting enzyme; ADC = apparent diffusion coefficient; ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibodies; AQP4 = aquaporin 4; CMV = cytomegalovirus; CNS = central nervous system; CRP = c-reactive protein; CSF = cerebral spinal fluid; CT = computed tomography; DWI = diffusion-weighted image; EBV = Epstein-Barr virus; ED = emergency department; ENA = extractable nuclear antigen antibodies; ESR = erythrocyte sedimentation rate; FLAIR = fluid-attenuated inversion recovery; GRE = gradient echo; HIV = human immunodeficiency virus; HSV = herpes simplex virus; IgG = immunoglobulin G; MOG = myelin oligodendrocyte glycoprotein; MRI = magnetic resonance image; PCR = polymerase chain reaction; RF = rheumatoid factor; RPR = rapid plasma reagin; STIR = short T1 inversion recovery; SWI = susceptibility-weighted imaging; TSH = thyroid stimulating hormone; TM = transverse myelitis; VDRL = Venereal Disease Research Laboratories; VZV = varicella-zoster virus.

8.3.9 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the investigational product, 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 AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca 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 AstraZeneca 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 electronic data capture system, an automated email alert is sent to the designated AstraZeneca representative.

If the electronic data capture system is not available, then the investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

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

For further guidance on the definition of a SAE, see Appendix B of the Clinical Study Protocol.

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

8.3.10 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention

8.3.10.1 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 investigational product under study 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 AstraZeneca representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca 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 8.3.9) and **within 30 days** for all other pregnancies.

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 is used to report the outcome of the pregnancy.

8.3.11 Medication Error

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

The designated AstraZeneca 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 8.3.9) and **within 30 days** for all other medication errors.

The definition of a medication error can be found in Appendix B 4.

8.4 Overdose

For guidance refer to AstraZeneca standard operating procedure Reporting of Individual Safety Events in Clinical Studies.

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

The designated AstraZeneca 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 overdoses associated with an SAE (see Section 8.3.9) 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. For 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.

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.

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). Authorised laboratories will assess seroresponse to AZD1222 by a validated immunoassay directed at the SARS-CoV-2 S antigen. The rate of asymptomatic SARS-CoV-2 infection in participants receiving AZD1222 versus placebo will be determined by seroresponse to SARS-CoV-2 N by an immunoassay operated by an authorised laboratory. Serologic assessment to S and receptor-binding domain (RBD) antigens will also be assessed quantitatively using a validated multiplexed MSD immunoassay.

8.5.2.2 SARS-CoV-2 Neutralising Antibody Assessments

Serum samples to measure SARS-CoV-2 nAb levels will be collected according to the time points specified in the SoA (Section 1.3). Authorised laboratories will measure nAbs to SARS-CoV-2 using validated wild-type neutralisation assay or pseudoneutralisation assays.

8.5.3 Pharmacodynamics

Pharmacodynamics are not evaluated in this study.

8.6 Human Biological Sample Biomarkers

Biomarkers are not evaluated in this study.

8.7 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable in this study.

8.8 Medical Resource Utilisation and Health Economics

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

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

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

Let p_{active} and $p_{placebo}$ denote the proportion of participants who have a post-treatment seroresponse for the AZD1222 treatment and placebo group, respectively, then the null hypothesis and alternative hypothesis are defined as follows:

- Null hypothesis: $p_{active} = p_{placebo}$
- Alternative hypothesis: $p_{active} \neq p_{placebo}$

where p is the proportion of seroresponse participants.

The proportion of participants who have a post-treatment seroresponse will be compared between AZD1222 treatment and placebo using the Fisher's exact test at the 2-sided 5% alpha level for each cohort. No adjustment for multiple testing will be made.

9.2 Sample Size Determination

Regarding Cohort C, 128 participants will be randomised in a 3:1 ratio to receive either AZD1222 or placebo. Regarding Cohort D, in a similar way, 128 participants will be randomised in a 3:1 ratio to receive either AZD1222 or placebo, but participants will be

stratified at randomisation by age group (ie Subcohorts D1 vs D2). At least 30% of participants in Cohort D will be secured for participants with age ≥ 70 years.

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

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

9.3 Populations for Analyses

The following populations are defined:

Table 7 Populations for Analysis

Population/Analysis set	Description
All participants analysis set	All participants screened who signed informed consent form for the study, to be used for reporting disposition and screening failures.
Total vaccinated analysis set (TVS)	All participants who have received at least one dose of study intervention. Erroneously vaccinated participants (eg, those randomised to placebo treatment but were actually given active vaccine treatment) are accounted for in this analysis set by assigning them to the treatment they actually received. This analysis set will be used for the analysis of safety, exploratory efficacy and immunogenicity endpoints.

Population/Analysis set	Description
Fully vaccinated analysis set (FVS) for immunogenicity	All participants in the TVS who have received two doses of study intervention and have no important protocol deviations judged to have the potential to interfere with the generation or interpretation of immune responses. Protocol deviations will be reviewed by the study team before unblinding to determine exclusion from the immunogenicity. Participants who have a postbaseline seroresponse (≥ 4-fold rise in titres from Day 1 baseline value) to nucleocapsid antibodies by MSD serology assay at post-baseline up to Day 57 will be excluded from this analysis set. This analysis set will be used for the analysis of immunogenicity endpoints.
Fully vaccinated analysis set (FVS) for efficacy	All participants in the TVS who have received two doses of study intervention, and who remain on-study 15 days after their second dose without having had a prior SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) positive confirmed COVID-19 infection. This analysis set will be used for applicable exploratory endpoints.

FVS = fully vaccinated analysis set; MSD = Meso Scale Discovery; RT-PCR = reverse transcriptase-polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; TVS = total vaccinated analysis set

9.4 Statistical Analyses

9.4.1 General Considerations

The study has been interrupted to allow a safety review, following the occurrence of a SAE in an Oxford University-sponsored trial in the UK. By that time (07 September 2020), 99 participants had been vaccinated. In order not to delay the local (Japan) vaccine assessment, the analysis strategy has been updated.

The analysis will be done in the following three steps:

- The Primary analysis will include immunogenicity data up to Day 57 from subjects enrolled before the study interruption and safety data gathered in all participants up to Day 57.
- The additional analysis will include immunogenicity data in all participants up to Day 57.
- The final analysis will include all endpoints up to Day 365 in all participants.

The clinical data lock for the primary analysis will occur after all participants have completed visit Day 57 or discontinued early, whichever occurs first. All safety data up to Day 57 in all subjects will be included. This primary analysis will also include immunogenicity data up to Day 57 from subjects enrolled before the study interruption.

After completion of the clinical data lock for the primary analysis, the study will become single blind, where only participants are blinded from allocation of investigational product.

Final clinical data lock will occur when all participants have completed the study or discontinued early.

The statistical analysis plan (SAP) will be finalised prior to the clinical data lock for the primary analysis and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and main secondary endpoints.

All personnel involved in the analyses of the study will remain blinded until the clinical data lock for the primary analysis is achieved and protocol deviations are identified.

The additional analysis including immunogenicity data up to Day 57 in all participants will be performed when these data become available. In addition, the final analysis will be performed when all participants have completed Day 365 visit or discontinued early.

Analyses will be performed by the Sponsor or its representatives.

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

Continuous variables will be summarised 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% confidence interval (CI), unless otherwise specified. P-values, corresponding to a 2-sided test, will be presented for comparisons between treatments.

Demography and baseline characteristics will be summarised by treatment for the total vaccinated analysis set (TVS) and fully vaccinated analysis set (FVS) for efficacy.

9.4.2 Efficacy (Including Immunogenicity)

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

9.4.2.1 Primary Endpoint(s)

The primary immunogenicity endpoint is the proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from Day 1 baseline value) to the Spike antigens of AZD1222 (MSD serology assay) at Day 57, and will be calculated along with its 95% CI based on the Clopper-Pearson method in each treatment groups in each cohort (C and

D) and also Subcohorts D1 and D2 separately. The proportion of participants who have a post-treatment seroresponse will be compared between AZD1222 treatment and placebo using Fisher's exact test for each cohort. Fisher's exact test will not be presented for Subcohorts D1 and D2. No adjustment for multiple testing will be made.

9.4.2.2 Secondary Endpoint

The proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from Day 1 baseline value) to RBD antigen of AZD1222 (MSD serology assay) at Day 57, will be analysed in the same way as the primary immunogenicity endpoint.

Geometric mean titre (GMT) and geometric mean fold rise (GMFR) of immunogenicity against Spike and RBD antigens of AZD1222 (MSD serology assay) with the associated 95% CIs will be computed at each time point in each treatment arm in each cohort (C and D) and also in Subcohorts D1 and D2 separately.

The proportion of participants who have a post-treatment seroresponse (≥ 4-fold rise in titres from Day 1 baseline value) to AZD1222 as measured by SARS-CoV-2 nAbs (wild-type assay or pseudoneutralisation assay) at Day 57, will be analysed in the same way as the primary immunogenicity endpoint. GMT and GMFR of SARS-CoV-2 nAbs and the associated 95% CIs will be presented at each time point in each treatment arm in each cohort (C and D) and also in Subcohorts D1 and D2 separately.

9.4.2.3 Exploratory Endpoint(s)

Exploratory analyses will be conducted to describe occurrence of symptomatic COVID-19 in recipients of AZD1222 and placebo and occurrence of severe COVID-19 and seroresponse to non-Spike SARS-CoV-2 antigens. The exploratory efficacy endpoint will be the incidence of the first virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19 post first dose of study intervention, analysed for the TVS, and the incidence of the first virologically confirmed (RT-PCR positive) symptomatic cases of COVID-19 occurring ≥ 15 days post second dose of study intervention, analyzed for the FVS for efficacy.

Kaplan-Meier curves will be presented for each cohort in the AZD1222 and placebo treatment group, showing the cumulative incidence of the first case of RT-PCR positive symptomatic COVID-19 post first dose of study intervention or occurring ≥ 15 days post second dose of study intervention, respectively. In addition, descriptive statistics will also be produced.

Similar descriptive analysis will be conducted on the following more severe cases of COVID-19.

- Hospital admissions associated with COVID-19
- Intensive care unit admissions associated with COVID-19
- Deaths associated with COVID-19

- Seroresponse against non-Spike (nucleocapsid) SARS-CoV-2 antigens (MSD serology assay) will also be assessed using a methodology similar to the one described in Section 9.4.2.1.

Full details of these exploratory efficacy analyses will be documented in the SAP.

9.4.3 Safety

9.4.3.1 Primary Endpoints

The safety of AZD1222 will primarily be assessed by:

- The incidence of local and systemic solicited reactogenicity signs and symptoms for 7 days following throughout vaccination (Day 1 to 8 and Day 29 to 36). A list of predefined solicited AEs for reactogenicity assessment can be found in Table 6.
- The incidence of AEs, SAEs and AESIs collected from Day 1 through Day 57.
- The change from baseline for safety laboratory measures at Day 8, Day 29, Day 36, and Day 57.

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 1 event, where appropriate.

An overview of AEs will be presented for each treatment group, including the number and percentage of participants with any AE, AEs with outcome of death, 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 Secondary Endpoints

The secondary safety endpoints are the occurrence of SAEs, AESIs (defined in Section 8.3.8) collected from Day 1 through Day 365.

9.5 Subgroup Analyses

Subgroup analyses will be carried out to assess the consistency of the treatment effect across subgroups. These analyses will focus on the primary and secondary immunogenicity endpoints, and they may be performed on primary safety endpoint of unsolicited AEs. The list of subgroups includes, but may not be limited to: gender, and BMI at baseline. Full details of all subgroup analyses will be described in the SAP.

9.6 Interim Analyses

Not applicable.

9.7 Data Monitoring Committee

Not applicable.

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:
  - Standards stipulated in Article 14, Paragraph 3 and Article 80-2 of the "Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices", and "Ministerial Ordinance on Good Clinical Practice for Drugs".
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (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.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a Contract Research Organisation but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to ICH guidelines and all applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a 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, IRB/IEC, and investigators.
- For all studies except those utilising medical devices, investigator safety reports must be prepared for SUSARs 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 a 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 authorised 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 authorised 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 (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- The 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 authorised 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.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

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

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 authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees 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.

An independent Neurological AESI Expert Committee will be available to review and provide advice to the Company about the diagnosis and causality assessment of selected neurological AESIs.

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com 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 Monitoring Plan.

- 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 organisations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised 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 study start date is the date on which the clinical study will be open for recruitment of participants.

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 organisation(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 multicentre 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 unfavourable 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 serious and non-serious AEs 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 hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse events (AEs) for **malignant tumours** reported during a study should generally be assessed as **Serious AEs**. 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 tumour event should be assessed and reported as a **non-serious AE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, 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 product 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).

Hospitalisation

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, hospitalisation, disability or incapacity but may jeopardise 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.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (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 utilised 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 a 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 a 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 drug.

- 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 drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (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 drug?
- 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 drug 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 recognised feature of overdose of the drug?
- 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 drug, but rather a human or process related failure while the drug 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 drug
- 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:

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

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

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)

- Participant failed to return unused medication or empty packaging
- 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 centre keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples while 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.

AstraZeneca 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 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 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 8 : Clinical Abnormalities, Local Reactions to Injectable Product
- Table 9 : Clinical Abnormalities, Vital Signs
- Table 10 : Clinical Abnormalities, Systemic (General or Illness)

Table 8 Tables for Clinical Abnormalities: Local Reactions to Injectable Product

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

[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable. Reactions < ¼ inch (< 0.6 cm) in diameter will not be recorded.

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

ER = emergency room.

Table 9 Tables for Clinical Abnormalities: Vital Signs

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

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

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

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

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

ER = emergency room; Hg = mercury.

Table 10 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 E Adverse Events of Special Interest

AZD1222 AESIs are based on Brighton Collaboration case definitions (SPEAC, 2020), clinical experience, and scientific interest. There is no current evidence to suggest that AZD1222 is associated with these AESIs.

Table 11 Adverse Events of Special Interest

AESI	Medical Concept
Neurologic	Generalized convulsion: Seizures are episodes of neuronal hyperactivity most commonly resulting in sudden, involuntary muscular contractions. They may also manifest as sensory disturbances, autonomic dysfunction and behavioral abnormalities, and impairment or loss of consciousness.
	Guillain-Barré syndrome: GBS is a peripheral nerve demyelinating disease, which can present as temporary ascending paralysis.
	Acute disseminated encephalomyelitis: ADEM is defined as a uniphasic syndrome of brain inflammation and demyelination occurring in temporal association with an antecedent immunologic challenge, such as infection or an immunization. ADEM most commonly occurs in the pediatric population.
	Other neurologic events: These events would include new onset event (acute or subacute) motor and sensory disturbances (eg, weakness, numbness, paresthesias, hypoesthesia, hyperesthesia, dysesthesias), bowel/bladder dysfunction, gait impairment, or visual disturbance, or any event of myelitis, encephalomyelitis, myelitis transverse, or other sudden neurological deficit.
Vascular	Thrombotic, thromboembolic, and neurovascular events: These are events that can manifest as transient or permanent vision problems, dizziness, trouble understanding, facial droop, slurred speech, unilateral weakness, deep vein thrombosis with swollen, warm or painful leg, pulmonary embolism with shortness of breath, chest pain or irregular heart rate
Hematologic	Thrombocytopenia: Thrombocytopenia is a disorder in which there is an abnormally low platelet count; a normal platelet count ranges from 150 000 to 450 000 platelets per μL.
Immunologic	Vasculitides: Vasculitides are a group of related disorders characterized by inflammation of blood vessels (vasculitis) leading to tissue or end-organ injury.
	Anaphylaxis: Anaphylaxis an acute hypersensitivity reaction with multi-organ-system involvement that can present as, or rapidly progress to, a severe life-threatening reaction requiring immediate medical attention.

AESI	Medical Concept
Immunologic (Continued)	Vaccine-associated enhanced respiratory disease: The pathogenicity of VAERD has been linked to a vaccine immune response characterized by induction of non-neutralizing antibodies, and a T-cell response of the Th2 type with hypereosinophilia (Lambert et al 2020). VAERD may manifest as a severe form of respiratory disease with prolonged fever, and diverse clinical manifestations of disease severity and pathological changes marked by increased areas of lung consolidation, broncho-interstitial pneumonia, and necrotizing bronchiolitis (Rajão et al 2016).
	Potential immune-mediated conditions: These conditions are a group of autoimmune inflammatory disorders characterized by an alteration in cellular homeostasis, which may or may not have an autoimmune aetiology. A list of events is provided in Table 12.

ADEM = acute disseminated encephalomyelitis; AESI = adverse event of special interest; GBS = Guillain-Barré syndrome; VAERD = vaccine-associated enhanced respiratory disease.

Table 12 List of Potential Immune-mediated Medical Conditions

Category	Condition
Gastrointestinal disorders	Celiac disease
	Crohn's disease
	Ulcerative colitis
	Ulcerative proctitis
Liver disorders	Autoimmune cholangitis
	Autoimmune hepatitis
	Primary biliary cirrhosis
	Primary sclerosing cholangitis
Metabolic diseases	Addison's disease
	Autoimmune thyroiditis (including Hashimoto thyroiditis)
	Diabetes mellitus type I
	Grave's or Basedow's disease
Musculoskeletal disorders	Antisynthetase syndrome
	Dermatomyositis
	Juvenile chronic arthritis (including Still's disease)
	Mixed connective tissue disorder
	Polymyalgia rheumatic
	Polymyositis
	Psoriatic arthropathy
	Relapsing polychondritis
	Rheumatoid arthritis
	Scleroderma, including diffuse systemic form and CREST syndrome
	Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis
	Systemic lupus erythematosus
	Systemic sclerosis

Category	Condition
Neuroinflammatory disorders	Acute disseminated encephalomyelitis, including site specific variants (eg, non-infectious encephalitis, encephalomyelitis, myelitis, radiculomyelitis)
	Cranial nerve disorders, including paralyses/paresis (eg, Bell's palsy)
	Guillain-Barré syndrome, including Miller Fisher syndrome and other variants
	Immune-mediated peripheral neuropathies and plexopathies, including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy
	Multiple sclerosis
	Neuromyelitis optica spectrum disorder
	Narcolepsy
	Optic neuritis
	Transverse myelitis
	Myasthenia gravis, including Eaton-Lambert syndrome
Skin disorders	Alopecia areata
	Autoimmune bullous skin diseases, including pemphigus, pemphigoid and dermatitis herpetiformis
	Cutaneous lupus erythematosus
	Erythema nodosum
	Morphoea
	Lichen planus
	Psoriasis
	Rosacea
	Sweet's syndrome
	Vitiligo
Vasculitides	Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis
	Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg– Strauss syndrome (allergic granulomatous angiitis), Buerger's disease, thromboangiitis obliterans, necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis

Category	Condition
Other	Antiphospholipid syndrome
	Autoimmune hemolytic anemia
	Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis)
	Autoimmune myocarditis/cardiomyopathy
	Autoimmune thrombocytopenia
	Goodpasture syndrome
	Idiopathic pulmonary fibrosis
	Pernicious anemia
	Raynaud's phenomenon
	Sarcoidosis
	Sjögren's syndrome
	Stevens-Johnson syndrome
	Uveitis

Appendix F Abbreviations

Abbreviation or special term	Explanation
β-hCG	beta human chorionic gonadotropin
ACE2	angiotensin-converting enzyme 2
ADEM	acute disseminated encephalomyelitis
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body-mass index
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CSR	Clinical Study Report
E	envelope (protein)
eCRF	electronic Case Report Form
ELISA	enzyme-linked immunosorbent assay
FDA	United States Food and Drug Administration
FVS	Fully vaccinated analysis set
GCP	Good Clinical Practice
GMFR	geometric mean fold rise
GMT	geometric mean titre
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IM	intramuscular
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous

Abbreviation or special term	Explanation
M	membrane (protein)
MERS	Middle East respiratory syndrome
MSD	Meso Scale Discovery
N	nucleocapsid (protein)
nAb	neutralising antibody
NHP	non-human primate
PI	Principal investigator
RBD	receptor-binding domain
RT-PCR	reverse transcriptase-polymerase chain reaction
RTSM	Randomisation and Trial Supply Management
S	Spike (protein)
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome-coronavirus 2
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin
TVS	Total vaccinated analysis set
tPA	tissue plasminogen activator
ULN	upper limit of normal
VAERD	vaccine-associated enhanced respiratory disease.
vp	viral particles
WHO	World Health Organization

Appendix G Protocol Amendment History

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

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Amendment 2 (19-November-2020)

Overall Rationale for the Amendment:

The major reasons for this amendment were to expand AESI evaluation, add secondary immunogenicity objective and endpoint, revise the analysis sets and statistical analyses, and add an independent Neurological AESI Expert Committee. Other key revisions included updating the AZD1222 safety profile.

Section # and Name	Description of Change	Brief Rationale
Title Page	Added ClinicalTrials.gov number	To align with updated information
1.1 Synopsis	The synopsis was updated to align with changes to the body of the protocol.	To ensure consistency between the protocol and the Synopsis.
2.2 Background	Updated information on the nonclinical and clinical AZD1222 development program	To align with information in the updated AZD1222 IB
2.3.1 Risk Assessment	Revised important potential risks	
3 Objectives and Endpoints	Added secondary immunogenicity endpoints.	To aligned with protocol D8110C00001
3 Objectives and Endpoints	Added the term of “receptor-binding domain (RBD)” for secondary immunogenicity objective and endpoints.	To align with protocol D8110C00001.
3 Objectives and Endpoints	Added geometric mean fold rise (GMFR) for secondary immunogenicity endpoints.	To align with protocol D8110C00001.
3 Objectives and Endpoints	Removed ‘throughout the study duration up to Day 365’ from exploratory efficacy endpoints.	The analysis of exploratory efficacy will be based on different periods throughout the study.
4.1 Overall Design	Added a description of the independent Neurological AESI Expert Committee	New committee to provide advice on selected neurological AESIs

Section # and Name	Description of Change	Brief Rationale
8.1 Descriptive Efficacy Assessment	Removed 'throughout the study duration up to Day 365' from exploratory efficacy endpoints.	The analysis of exploratory efficacy will be based on different periods throughout the study.
8.3.8 Adverse Events of Special Interest	Expanded the AESI list and specified that AESIs will be reported to the Sponsor within one day of becoming aware of the event	To permit close monitoring and rapid communication of safety information, and further understanding of the AZD1222 safety profile
8.3.8.1 Potential Neurological AESIs	New section for evaluation of potential neurological AESIs	For additional safety monitoring
9.3 Populations for Analyses	Refined definition for analysis populations.	To fine tune the definition for analysis populations.
9.4.1 General Considerations	Changed analysis set for demography and baseline characteristics to "total vaccinated analysis set (TVS) and fully vaccinated analysis set (FVS) for efficacy" form safety analysis set.	To fine tune the definition for analysis populations.
9.4.2 Efficacy (Including Immunogenicity)	Added general information of analysis for efficacy including Immunogenicity.	To summarise analysis for efficacy including Immunogenicity.
9.4.2.1 Primary Endpoint(s)	Added "Fisher's exact test will not be presented for Subcohorts D1 and D2".	To clarify which cohorts will be used for analysis.
9.4.2.1 Primary Endpoint(s)	Removed description of participants to be excluded from analyses of immunogenicity.	This description is added to the newly defined analysis set and no longer required in this context.
9.4.2.2 Secondary Endpoint	Added secondary immunogenicity endpoints.	To align with protocol D8110C00001.
9.4.2.2 Secondary Endpoint	Added geometric mean fold rise (GMFR) for secondary immunogenicity endpoints.	To align with protocol D8110C00001.
9.4.2.2 Secondary Endpoint	Added the term of "receptor-binding domain (RBD)" for secondary immunogenicity objective and endpoint.	To align with protocol D8110C00001.
9.4.2.3 Exploratory Efficacy Analyses	Moved Section 9.4.4 to this new section and removed 'throughout the study duration up to Day 365' from exploratory efficacy endpoints. Also added information for analysis to be conducted post first dose of study intervention or occurring ≥ 15 days post second dose of study intervention	The analysis of exploratory efficacy is better fitted in this section, and analysis will be based on different periods throughout the study.
9.5 Subgroup Analyses	New section added for subgroup analyses.	To align with protocol D8110C00001.

Section # and Name	Description of Change	Brief Rationale
Appendix A5 Committee Structure	Added a description of the independent Neurological AESI Expert Committee	New committee to provide advice on selected neurological AESIs
Appendix D Toxicity Grading Scales for Solicited Adverse Events	Changed the temperature of mild fever in Table 9 to 37.9.	To align with protocol D8110C00001.
Appendix E Adverse Events of Special Interest	a) Expanded the AESI list and provided a description of the events b) Added new table listing potential immune-mediated conditions to provide more detail on this new AESI	To permit close monitoring and rapid communication of safety information and further understand the AZD1222 safety profile

Amendment 1: (13-August-2020)

Overall Rationale for the Amendment

The main changes are to change the vaccination regimen. The regimen of single intramuscular (IM) dose of either AZD1222 or placebo was removed and the regimen of 2 IM doses of either AZD1222 or placebo was only adopted. The cohorts with different age populations are Cohorts C and D, Subcohorts D1 and D2. Cohorts A and B, Subcohorts B1 and B2 were removed.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	The synopsis was updated to align with changes to the body of the protocol.	To ensure consistency between the protocol and the Synopsis.
1.2 Schema	The part of single dose was removed, and the number of participants was changed.	To change the study design.
1.3 Schedule of Activities	The table of "Schedule of Activities (Part I, Single Dose)" was removed.	To change the study design.
1.3 Schedule of Activities	The description of the way of eDiary provision was added in a footnote.	To clarify the way of providing eDiary.
2.2 Background	The description of other studies was updated according to the updated information in Investigator's Brochure.	To update the other studies information.
2.3.1 Risk Assessment	The description of other studies was updated according to the updated information in Investigator's Brochure.	To update the other studies information.

Section # and Name	Description of Change	Brief Rationale
3 OBJECTIVES AND ENDPOINTS	The description of objectives and endpoints for single dose was removed.	To change the study design.
3 OBJECTIVES AND ENDPOINTS	For primary immunogenicity endpoint, the description of the proportion of participants who have a post treatment seroresponse to Spike antigen of AZD1222 at Day 29 was removed.	To change the study design.
3 OBJECTIVES AND ENDPOINTS	For primary safety endpoint, the endpoint after single dose was removed.	To change the study design.
3 OBJECTIVES AND ENDPOINTS	The objective of "(2 dose schedules for Part II only) To assess the safety of a booster dose of AZD1222" was removed.	To change the study design.
3 OBJECTIVES AND ENDPOINTS	For the primary safety endpoint for 28 days following throughout vaccination, the occurrence of SAEs and AESIs was added.	To change the study design.
3 OBJECTIVES AND ENDPOINTS	For secondary immunogenicity endpoint, the description of the proportion of participants who have a post treatment seroresponse to AZD1222 as measured by SARS-CoV-2 nAb at Day 29 was removed.	To change the study design.
3 OBJECTIVES AND ENDPOINTS	The description of exploratory objectives and endpoints was changed.	To change the study design.
4.1 Overall Design	The number of participants with single dose and the method of randomization were removed.	To change the study design.
4.1 Overall Design	"128 eligible participants" was changed to "256 eligible participants".	To change the study design.
4.1.2 Vaccination Visit	The method of randomization of participants with single dose was removed.	To change the study design.
4.1.2 Vaccination Visit	Thermometer given to participants was change from "oral thermometer" to "axillary thermometer".	To change the device.
4.1.3 Subsequent Visits	The transition from double blind to open-label and the timing of unblind were changed.	To change the study design.
4.1.3 Subsequent Visits	The timing when participants in placebo group may receive licensed vaccine was mentioned.	To change the study design.
4.4 End of Study Definition	The description of "(which will differ for participants randomised to AZD1222 and to placebo)" was removed.	To change the study design.
5.2 Exclusion Criteria	The timing when participants in placebo group may receive licensed vaccine was mentioned.	To change the study design.

Section # and Name	Description of Change	Brief Rationale
6.3.2 Blinding	The transition from double blind to open-label and the timing of unblind were changed.	To change the study design.
6.3.2 Blinding	The timing when participants in placebo group may receive licensed vaccine was mentioned.	To change the study design.
6.5.2 Prohibited Concomitant Medications	The timing when participants in placebo group may receive licensed vaccine was mentioned.	To change the study design.
7.1 Discontinuation of Study Intervention	The description of (which is a shorter period for those randomised to placebo)" was removed.	To change the study design.
8 STUDY ASSESSMENTS AND PROCEDURES	The amount of blood collection of single dose was removed.	To change the study design.
8.1 Descriptive Efficacy Assessments	The description of exploratory objectives and endpoints was changed.	To change the study design.
8.3.7 Solicited Adverse Events	Thermometer given to participants was change from "oral thermometer" to "axillary thermometer".	To change the device.
9.1 Statistical Hypotheses	The primary immunogenicity endpoint at Day 29 was removed.	To change the study design.
9.2 Sample Size Determination	The number of participants in Cohorts C and D was changed from 64 to 128. The number of participants with AZD1222 was changed from 48 to 96, and participants with placebo was changed from 16 to 32 within each cohort. In addition, the sample size determination of these participants was updated.	To change the study design.
9.4.1 General Considerations	The timing of database lock for single dose was removed and the transition from double blind to open-label was changed.	To change the study design.
9.4.2.1 Primary Endpoint(s)	For primary immunogenicity endpoint, the description of the proportion of participants who have a post treatment seroresponse to Spike antigen of AZD1222 at Day 29 was removed.	To change the study design.
9.4.2.2 Secondary Endpoint	For secondary immunogenicity endpoint, the description of the proportion of participants who have a post treatment seroresponse to AZD1222 as measured by SARS-CoV-2 nAb at Day 29 was removed.	To change the study design.

Section # and Name	Description of Change	Brief Rationale
9.4.3.1 Primary Endpoints	For the primary safety endpoint for 28 days following vaccination, the occurrence of SAEs and AESIs was added.	To change the study design.
9.4.4 Exploratory Efficacy Analyses	The description of exploratory endpoints was changed.	To change the study design.

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