Clinical Study Report Appendix 16.1.1

Drug Substance AZD2816

Study Code D7220C00001

Appendix 16.1.1
Protocol and Protocol Amendments

VERSION OF PROTOCOL OR PROTOCOL AMENDMENT

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Global Clinical Study Protocol	1.0	14 May 2021
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Clinical Study Protocol	
Study Intervention	AZD2816
Study Code	D7220C00001
Version	1
Date	14 May 2021

TITLE PAGE

A Phase II/III Partially Double-Blinded, Partially Randomised, Multinational, Active-Controlled Study in Both Previously Vaccinated and Unvaccinated Adults to Determine the Safety and Immunogenicity of AZD2816, a Vaccine for the Prevention of COVID-19 Caused by Variant Strains of SARS-CoV-2

Sponsor Name:	**AstraZeneca AB**
Legal Registered Address:	151 85 Södertälje, Sweden

Regulatory Agency Identifier Numbers:

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: D7220C00001

Study Intervention: AZD2816

Study Phase: II/III

Short Title: Phase II/III Study of AZD2816, a Vaccine for the Prevention of COVID-19 in Adults

Study Physician Name and Contact Information will be provided separately.

International Coordinating Investigator: Professor Andrew Pollard

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A phase II/III partially double-blinded, partially randomised, multinational, active-controlled study in both previously vaccinated and unvaccinated adults to determine the safety and immunogenicity of AZD2816, a vaccine for the prevention of COVID-19 caused by variant strains of SARS-CoV-2.

Short Title: Phase II/III study of AZD2816, a vaccine for the prevention of COVID-19 in adults.

Rationale: Recently, several variants of the SARS-CoV-2 virus with increased transmissibility have emerged, including B.1.1.7, first identified in the UK, P.1, first identified in Brazil, and B.1.351, first identified in South Africa. In an ongoing clinical trial of AZD1222 in South Africa, interim results failed to show protection against mild to moderate disease caused by the B.1.351 variant; protection against severe disease could not be determined as no severe cases were identified (Madhi et al 2021).

Based on available evidence about vaccine effectiveness and molecular epidemiology of emerging variants, B.1.351 is estimated to have a potential to escape vaccine-induced immunity. B.1.351 carries sequence mutations in common with other variants of concerns; immunity to B.1.351 therefore has the potential to provide some cross-immunity against other emerging strains. Development of candidate vaccines that include the B.1.351 S-protein variant is underway. AstraZeneca is developing AZD2816, a vaccine against the B.1.351 SARS-CoV-2 variant using the same ChAdOx1 platform and manufacturing processes used for AstraZeneca's currently available COVD-19 vaccine, AZD1222.

Objectives and Endpoints:

The purpose of this study is to demonstrate the safety and characterize the immunogenicity of AZD2816, AstraZeneca's candidate ChAdOx1 vector vaccine against SARS-CoV-2 variant strain B.1.351, when administered:

- As a single dose to SARS-CoV-2 seronegative individuals who previously received a primary 2-dose vaccination against SARS-CoV-2 with AZD1222 or an mRNA vaccine
- As a 2-dose primary series to SARS-CoV-2 seronegative individuals who are unvaccinated (ie, have neither been infected with SARS-CoV-2 nor been vaccinated against SARS-CoV-2).

The following table lists the primary and secondary endpoints:

Objectives	Endpoints
Safety Objectives	
- Primary	
Previously vaccinated seronegative participants	
To characterize the safety and tolerability of 1 dose of AZD2816 in seronegative participants previously vaccinated with 2 doses of AZD1222	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose
Unvaccinated seronegative participants	
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose
- Secondary	
Previously vaccinated seronegative participants	
To characterize the safety and tolerability of 1 dose of AZD1222 in seronegative participants previously vaccinated with 2 doses of AZD1222	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of 1 dose of AZD2816 in seronegative participants previously vaccinated with 2 doses of a SARS-CoV2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of 1 dose of AZD2816 in seronegative participants previously vaccinated with 2 doses of AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 dose of AZD2816 in seronegative participants previously vaccinated with 2 doses of a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 dose of AZD1222 in seronegative participants previously vaccinated with 2 doses of AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
Unvaccinated seronegative participants	
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD1222 with a	• Incidence of local and systemic solicited AEs for 7 days post-dose

4-week dosing interval in unvaccinated seronegative participants	• Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
Immunogenicity objectives	
- Primary (descriptive)	
Previously vaccinated seronegative participants	
To assess the humoral immune response against the B.1.351 and Wuhan-Hu-1 strains induced by 1 dose of AZD2816 in seronegative participants previously vaccinated with 2 doses of AZD1222	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To assess the humoral immune response against the B.1.351 and Wuhan-Hu-1 strains induced by 1 dose of AZD2816 in seronegative participants previously vaccinated with 2-doses of a SARS-CoV-2 mRNA vaccine	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
Unvaccinated seronegative participants	
To assess the humoral immune response against the B.1.351 and Wuhan-Hu-1 strains induced by a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in unvaccinated seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
- Secondary (descriptive)	
Previously vaccinated seronegative participants	
To describe the humoral immune response against the B.1.351 and Wuhan-Hu-1 variant strains induced by 1 dose of AZD1222 in seronegative participants previously vaccinated with 2 doses of AZD1222	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
Unvaccinated seronegative participants	

To describe the humoral immune response against the B.1.351 and Wuhan-Hu-1 variant strains induced by a 2-dose primary vaccination with AZD1222 with a 4-week interval in unvaccinated seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To describe the humoral immune response against the B.1.351 and Wuhan-Hu-1 variant strains induced by a 2-dose primary vaccination with AZD2816 with a 12-week interval in unvaccinated seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
- Secondary (comparative)	
Previously vaccinated seronegative participants receiving 1 dose versus unvaccinated seronegative participants receiving 2 doses	
To evaluate the immune responses against the B.1.3.51 variant strain and Wuhan-Hu-1 strain elicited by 1 dose of AZD2816 in seronegative participants previously vaccinated with 2 doses of AZD1222 relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rates of SARS-CoV-2 specific antibody binding titres and neutralization titres
To evaluate the immune responses against the B.1.351 variant strain and Wuhan-Hu-1 strain elicited by 1 dose of AZD2816 in seronegative participants previously vaccinated with 2 doses of a SARS-CoV-2 mRNA vaccine relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rates of SARS-CoV-2 specific antibody binding titres and neutralization titres
Previously vaccinated seronegative participants	
To evaluate the immune response against the B.1.351 variant strain and the Wuhan-Hu-1 strain elicited by 1 dose of AZD2816 as relative to the response with 1 dose of AZD1222 in seronegative participants previously vaccinated with 2 doses of AZD1222	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To evaluate the immune response against the B.1.351 and Wuhan-Hu-1 variant strain elicited by 1 dose of AZD2816 in seronegative participants previously vaccinated with a mRNA vaccine relative to the response with 1 dose of AZD1222 in seronegative participants previously vaccinated with 2 doses of AZD1222	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
Unvaccinated seronegative participants	
To evaluate the immune response against the B.1.351 and Wuhan-Hu-1 variant strain elicited by a primary 2-dose vaccination with AZD2816 with a 4-week dosing interval relative to the response elicited by a primary 2-dose vaccination with AZD1222 with a 4-	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio)

week interval in previously unvaccinated seronegative participants	• Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To evaluate the immune responses against the B.1.351 variant strain and the Wuhan-Hu-1 strain elicited by a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval relative to the response elicited by a 2-dose primary vaccination with AZD2816 with a 4-week interval in previously unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres

SAEs: serious adverse events; MAAEs: medically attended adverse events; AESIs: adverse events of special interest.

[a] At least a 4-fold increase in geometric mean titre from baseline

Overall Design: This is a phase II/III, multinational, partially randomized, partially double-blind, controlled study in both previously vaccinated and unvaccinated participants.

Disclosure Statement: This is a parallel-group preventive study with 6 treatment arms.

Number of Participants: Approximately 1650 SARS-CoV-2 nucleocapsid seronegative participants will be assigned to study intervention to support the primary and secondary objectives of this study. In addition, participants that are SARS-Cov-2 nucleocapsid seropositive at screening will be enrolled and assigned to study intervention for an exploratory analysis, with a cap of 10% of the seronegative population (ie, approximately 165 total participants).

Intervention Groups and Duration: Previously vaccinated individuals will receive 1 dose of AZD1222 or AZD2816 on Day 1. Previously unvaccinated participants will receive 2 doses of AZD1222 or AZD2816: one dose on Day 1 and one dose on either Day 29 or Day 85. Participants will be followed up for safety for 180 days after last study vaccine administration.

Data Monitoring Committee: A Data Safety Monitoring Board will provide oversight to ensure safe and ethical conduct of the study.

Statistical Methods:

Sample sizes of 300 seronegative participants per group (or 150 for the AZD2816 primary vaccination with a 12-week dosing interval group) are deemed appropriate based upon available immunogenicity data from previous clinical studies with AZD1222 for the primary and secondary objectives of this study.

The safety analysis set for adverse events consists of all participants who have received at least one dose of study intervention. The immunogenicity analysis set includes all participants in the safety analysis set who have no protocol deviations or intercurrent events judged to have the potential to interfere with the generation or interpretation of an immune response.

An interim analysis will be performed on data from 28 days after first dose to support assessment of 1 dose in both previously vaccinated and unvaccinated participants. A primary analysis will be performed on data from 28 days after the second dose of the 4-week dosing intervals to support assessment of these 2-dose primary vaccinations. A secondary analysis will be performed on data from 28 days after the second dose of the 12-week dosing interval to support assessment of this 2-dose primary vaccination. The final analysis will be performed on data from 6 months follow-up after participant's vaccination.

1.2 Schema

Figure 1 Study Design for Previously Vaccinated Seronegative/Seropositive Participants

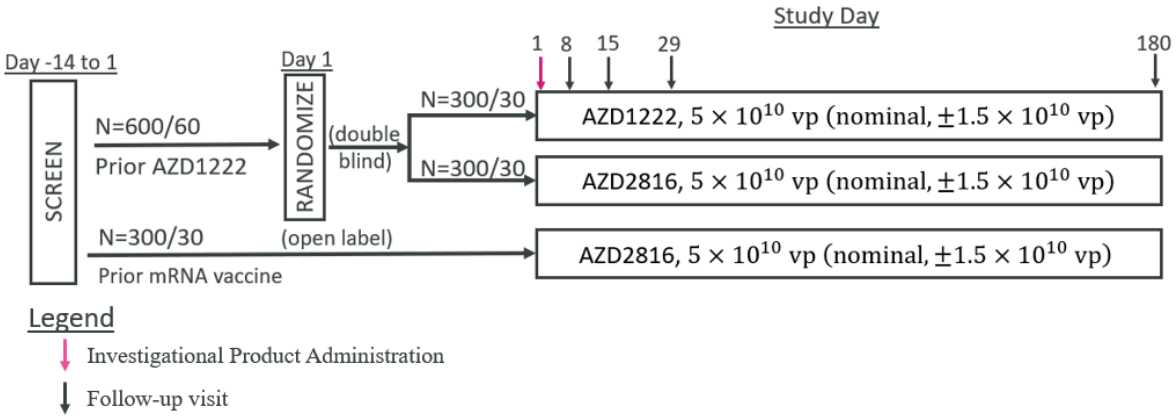
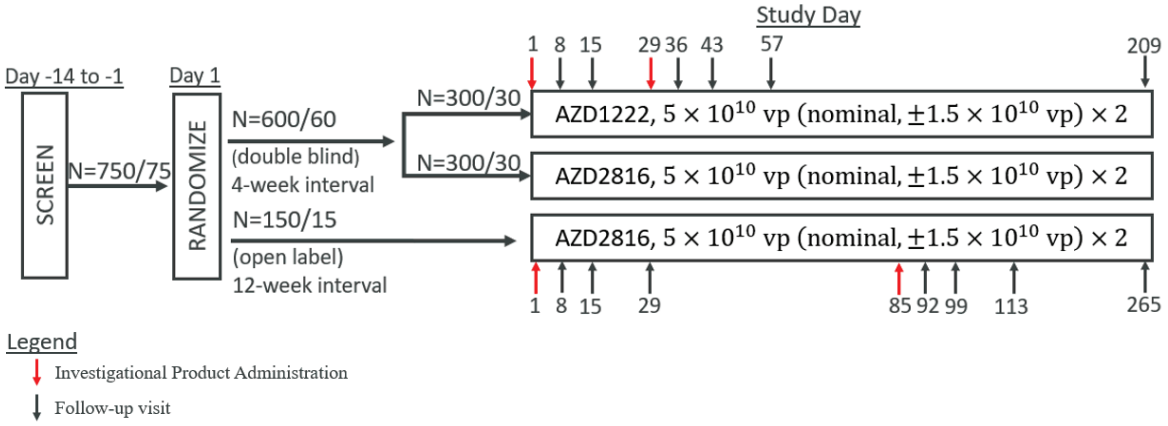


Figure 2 Study Design for Unvaccinated Seronegative/Seropositive Participants



Note: In addition to the approximately 1650 seronegative participants enrolled to support the primary/secondary objectives, seropositive participants will also be enrolled in the study to support exploratory objectives in this patient population, with a cap of 10% of the planned seronegative participants (ie, a maximum of 165 seropositive participants).

1.3 Schedule of Activities

Table 1 Schedule of Activities: Screening

Procedure	Day -14 to Day 1	See Section
Informed consent	X	5.1, Appendix A 3
Demography	X	-
Medical and surgical history	X	-
Prior and concomitant medications	X	6.5
Complete physical examination, including height and weight	X	8.2.1
Vital signs	X	8.2.2
Urine pregnancy test (for women of childbearing potential only)	X	8.2.3
Clinical safety laboratory assessments	X	8.2.3
Assessment of serious adverse events	X	8.3, Appendix B
Blood sample for SARS-CoV-2 antibody testing (lateral flow test)	X	8.5.2
Verify eligibility criteria	X	5.1, 5.2

Note: Screening activities can occur at same visit as initial vaccination with investigational product (ie, Visit 1 in Table 2, Table 3, and Table 4).

Table 2 Schedule of Activities: Treatment/Follow-up Period for Participants Previously Vaccinated with 2 Doses of AZD1222 or an mRNA Vaccine

Procedure	Treatment and Follow-up Period					Section
Day	**1**	**8**	**15**	**29**	**180**	
Window (days)	**-**	**±2**	**±2**	**±3**	**±14**	
Medical and surgical history	X	-	-	-	-	-
Urine pregnancy test (women of childbearing potential)	X	-	-	-	-	8.2.3
Concomitant medications/vaccinations	X	X	X	X	X	6.5
Verify eligibility criteria	X	-	-	-	-	5.1, 5.2
Monitoring of COVID-19	X	X	X	X	X	8.3.8
Vaccine administration (after screening activities, the activities listed above, and the pre-dose sampling activities listed below)	X	-	-	-	-	6.1.1
Immunological assessments						
Serum sample to assess SARS-CoV-2 serology/neutralising antibodies	X (pre-dose)	-	X	X	X	8.5.2
Serum sample to assess additional immunogenicity	X (pre-dose)	-	X	X	X	8.5.2
Blood sample to assess B-cell and T-cell responses in a sub-group of participants	X (pre-dose)	-	X	X	X	8.5.2.3
Blood sample for B-cell and T-cell response sequencing in a sub-group of participants	X (pre-dose)	-	X	X	X	8.5.2.3
Safety assessments						
Targeted physical examination	X	-	-	-	-	8.2.1
Vital signs	X	X	X	X	X	8.2.2
e-Diary provided with training	X	-	-	-	-	8.3.7
e-Diary collected	-	X	-	-	-	8.3.7
Unsolicited AEs	X (post-dose)	X	X	X	-	8.3
MAAEs, SAEs, and AESIs	Xa[b]	X	X	X	X	8.3.8, 8.3.8
Clinical safety laboratory assessments	X (pre-dose)	X	-	X	X	8.2.3

[a] Only SAEs pre-dose

AE: adverse event; AESI: adverse event of special interest; MAAE: medically-attended adverse event; SAE: serious adverse event

Table 3 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 4-Week Dosing Interval

Procedure	Treatment and Follow-up Period								Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	
Day	**1**	**8**	**15**	**29**	**V4+7**	**V4+14**	**V4+28**	**V4+180**	
Window (days)	**-**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
Medical and surgical history	X	-	-	-	-	-	-	-	-
Urine pregnancy test (women of childbearing potential)	X	-	-	X	-	-	-	-	8.2.3
Concomitant medications/vaccinations	X	X	X	X	X	X	X	X	6.5
Verify eligibility criteria	X	-	-	-	-	-	-	-	5.1, 5.2
Monitoring of COVID-19	X	X	X	X	X	X	X	X	8.3.8
Vaccine administration (after screening activities, the activities listed above, and the pre-dose sampling activities listed below)	X	-	-	X	-	-	-	-	6.1.1
Immunogenicity assessments									
Serum sample for SARS-CoV-2 serology/neutralising antibodies	X (pre-dose)	-	X	X (pre-dose)	-	X	X	X	8.5.2
Serum sample for additional immunogenicity	X (pre-dose)	-	X	X (pre-dose)	-	X	X	X	8.5.2
Blood sample to assess B-cell and T-cell responses in a sub-group of participants	X (pre-dose)	-	X	X (pre-dose)	-	-	X	X	8.5.2.3
Blood sample for B-cell and T-cell response sequencing in a sub-group of participants	X (pre-dose)	-	X	X (pre-dose)	-	-	X	X	8.5.2.3
Safety assessments									
Targeted physical examination	X	-	-	X	-	-	-	-	8.2.1
Vital signs	X	X	X	X	X	X	X	X	8.2.2
e-Diary provided with training	X	-	-	X	-	-	-		8.3.7

Table 3 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 4-Week Dosing Interval

Procedure	**Treatment and Follow-up Period**								**Section**
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	
Day	**1**	**8**	**15**	**29**	**V4+7**	**V4+14**	**V4+28**	**V4+180**	
Window (days)	**-**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
e-Diary collected	-	X	-	-	X	-	-		8.3.7
Unsolicited AEs	X (post-dose)	X	X	X	-	X	X	-	8.3
MAAEs, SAEs, and AESIs	X[a]	X	X	X	-	X	X	X	8.3.8
Clinical safety laboratory assessments	X (pre-dose)	X	-	X (pre-dose)	X	-	X	X	8.2.3

[a] Only SAEs pre-dose

AE: adverse event; AESI: adverse event of special interest; MAAE: medically-attended adverse event; SAE: serious adverse event

Table 4 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 12-Week Dosing Interval

Procedure	Treatment and Follow-up Period									Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	
Day	**1**	**8**	**15**	**29**	**85**	**V5+7**	**V5+14**	**V5+28**	**V5+180**	
Window (days)	**-**	**±2**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
Medical and surgical history	X	-	-	-	-	-	-	-	-	-
Urine pregnancy test (women of childbearing potential)	X	-	-	-	X	-	-	-	-	8.2.3
Concomitant medications/vaccinations	X	X	X	X	X	X	X	X	X	6.5
Verify eligibility criteria	X	-	-	-	-	-	-	-	-	5.1, 5.2
Monitoring of COVID-19	X	X	X	X	X	X	X	X	X	8.3.8
Vaccine administration (after screening activities, the activities listed above, and the pre-dose sampling activities listed below)	X	-	-	-	X	-	-	-	-	6.1.1
Immunogenicity assessments										
Serum sample to assess SARS-CoV-2 serology/neutralising antibodies	X (pre-dose)	-	X	X	X (pre-dose)	-	X	X	X	8.5.2
Serum sample to assess additional immunogenicity	X (pre-dose)	-	X	X	X (pre-dose)	-	X	X	X	8.5.2
Blood sample to assess B-cell and T-cell responses in a sub-group of participants	X (pre-dose)	-	X	X	X (pre-dose)	-	-	X	X	8.5.2.3
Blood sample for B-cell and T-cell response sequencing in a sub-group of participants	X (pre-dose)	-	X	X	X (pre-dose)	-	-	X	X	8.5.2.3
Safety assessments										
Targeted physical examination	X	-	-	-	X	-	-	-	-	8.2.1
Vital signs	X	X	X	X	X	X	X	X	X	8.2.2
e-Diary provided with training	X	-	-	-	X	-	-	-		8.3.7

Table 4 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 12-Week Dosing Interval

Procedure	Treatment and Follow-up Period									Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	
Day	**1**	**8**	**15**	**29**	**85**	**V5+7**	**V5+14**	**V5+28**	**V5+180**	
Window (days)	**-**	**±2**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
e-Diary collected	-	X	-	-	-	X	-	-	-	8.3.7
Unsolicited AEs	X (post-dose)	X	X	X	X	X	X	X	-	8.3
MAAEs, SAEs, and AESIs	X[a]	X	X	X	X	X	X	X	X	8.3.8, 8.3.8
Clinical safety laboratory assessments	X (pre-dose)	X	-	X	X (pre-dose)	X	-	X	X	8.2.3

[a] Only SAEs pre-dose

AE: adverse event; AESI: adverse event of special interest; MAAE: medically-attended adverse event; SAE: serious adverse event

2 INTRODUCTION

AZD2816 is being developed for the prevention of COVID-19. It is a modified version of the current AstraZeneca SARS-CoV-2 vaccine (referred to as AZD1222 in clinical documentation) that has been modified to also provide immunity against the newly emerging SARS-CoV-2 variant strain B.1.351. Like AZD1222, AZD2816 is a recombinant replication-defective chimpanzee adenovirus vector (ChAdOx1) expressing the SARS-CoV-2 S surface glycoprotein driven by the human cytomegalovirus major immediate early promoter that includes intron A with a human tissue plasminogen activator leader sequence at the N terminus. AZD2816 differs from AZD1222 in that the S glycoprotein gene sequence used is from the B.1.351 variant strain instead of the original Wuhan-Hu-1 variant.

2.1 Study Rationale

The aim of the study is to assess the safety and immunogenicity of AZD2816 for prevention of COVID-19 as both a primary 2-dose vaccination in previously unvaccinated participants and a 1-dose vaccination in participants previously vaccinated against the original Wuhan-Hu-1 strain of SARS-CoV-2. A safe and effective vaccine for COVID-19 prevention, including against the B.1.351 variant, 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, which was named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (Zhou et al 2020). The disease these patients contracted was subsequently named Coronavirus Disease 2019 (COVID-19). The World Health Organization declared the novel coronavirus a pandemic on 11 March 2020. The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has resulted in significant global morbidity and mortality as well as major disruption to healthcare systems. Measures to change the course of the pandemic have included the accelerated development vaccines against the original Wuhan-Hu-1 strain.

Coronaviruses are spherical, enveloped viruses with positive-sense single-stranded RNA genomes. SARS-CoV-2 belongs to the phylogenetic lineage B of the genus *Betacoronavirus*, and it is the seventh COVID virus known to cause human infections and the third known to cause severe disease after SARS-CoV and MERS-CoV. One fourth of the viral genome is responsible for coding structural proteins, such as the S glycoprotein, envelope, membrane, and nucleocapsid proteins. Envelope, membrane, and nucleocapsid proteins are mainly responsible for virion assembly while the S protein is involved in cellular receptor binding, mediating fusion of virus and cell membranes and virus entry into host cells during infection. The SARS-CoV-2 spike (S) glycoprotein is a type I trimeric, transmembrane protein that is located at the surface of the viral envelope forming spike-shaped protrusions. The S protein's

subunits are responsible for cellular receptor angiotensin-converting enzyme 2 binding via the receptor binding domain and subsequent fusion of virus and cell membranes, thereby mediating the entry of SARS-CoV-2 into the target cells. The S protein has an essential role in virus entry and determines tissue and cell tropism, as well as host range. The roles of the S-protein in receptor binding and membrane fusion have made it a desirable target for vaccine and antiviral development. The AstraZeneca vaccine AZD1222 expresses a codon-optimized coding sequence for S protein from the SARS-CoV-2 genome sequence accession MN908947 (ie, the Wuhan-Hu-1 isolate).

To date, 5 vaccines that rely upon the expression of the SARS CoV-2 S glycoprotein to stimulate/prime a protective immune response against the virus have demonstrated safety and efficacy in phase III clinical trials. Four of these, AZD1222 (also referred to as ChAdOx1 nCoV-19, a recombinant replication-defective chimpanzee adenoviral vectored), BNT162b2 (Pfizer-BioNTech, mRNA), mRNA-1273 (Moderna, mRNA), and Ad26.COV2-S (Janssen, adenovirus serotype 26 vectored) have received Emergency Use Authorization or Conditional Marketing Approval in the United States and/or the European Union, and elsewhere, and NVX-CoV2373 (Novavax; recombinant 86 protein) has also shown efficacy and is likely to be in use in the near future. These vaccines have been designed based upon the initial reported genetic sequence of the S protein from Wuhan in January 2020 (Lu et al 2020).

The immunogenicity and efficacy of AZD1222 has been shown in clinical trials (Ramasamy et al 2020, Voysey et al 2021a, Voysey et al 2021b). Immunogenicity data indicate that a single dose of AZD1222 elicits both humoral and cellular immunogenicity responses and that antibody responses are boosted after a second dose. In a pooled analysis of the 4 studies conducted in the United Kingdom, Brazil, and South Africa (DCO2 database lock 07 December 2020), the vaccine was highly immunogenic; seroresponse of S binding antibody was > 98% after a single dose of AZD1222. Seroresponse of live neutralising antibody was 82.4% after 1 dose, which rose to 99.4% after a second dose. Efficacy analyses of the pooled DCO2 data demonstrated effective protection of AZD1222 against COVID-19 with a vaccine efficacy of 66.73% (95.84% CI: 57.41%, 74.01%) ($p < 0.001$) from 15 days after the second dose in seronegative participants receiving 2 doses. The DCO2 data also demonstrated that the standard dose of AZD1222 (5×10^{10} viral particles) provides complete protection against COVID-19 hospital admission ≥ 22 days after the first dose in the seronegative analysis set (0 versus 14 cases in the control group, 2 of which were severe, including one with a fatal outcome). Vaccine efficacy was similar in participants with pre-existing comorbidities, being those at greatest risk of severe outcomes of COVID-19, compared to that in the general population. Recently available primary analysis data from a Phase III study performed in the United States and Latin America showed primary endpoint vaccine efficacy of 76% (95% CI: 67.60%, 82.22%; p-value < 0.001).

A sharp rise in COVID-19 cases was reported in late 2020, which was attributed to the emergence of new SARS-CoV-2 variant strains: B.1.1.7 in the United Kingdom, B.1.351 in South Africa, and P.1 in Brazil. These variant strains carry a number mutations in the S protein sequence: 9 amino acids in B.1.1.7, 10 amino acids in B.1.351, and 12 amino acids in P.1 compared with the Wuhan-Hu-1 sequence. These mutations may result in an increase of transmissibility and/or reduced vaccine effectiveness. Variant B.1.351 was first identified in South Africa in October 2020. Its attributes include approximately 50% increased transmission and moderate impact of neutralization by monoclonal antibody therapeutics, convalescent plasma and vaccine sera. In vitro neutralization assays suggest that the B.1.351 lineage viruses may be the most antigenically distinct from the original Wuhan-like strains (Zhou et al 2021). In addition, evidence suggests that AZD1222 may afford diminished protection against mild-moderate COVID-19 disease arising from the B.1.351 variant which is also antigenically the most different from the Wuhan-Hu-1 virus (Madhi et al 2021).

The development of candidate vaccines that would be effective against the B.1.351 variant strain is underway. AZD2816 is being developed as an updated ChADOx-nCOv19 vaccine designed to provide protective immunity against the newly arising B.1.351 variant strain, using the same ChAdOx1 platform and manufacturing processes used for AstraZeneca's currently approved COVID-19 vaccine, AZD1222.

The purpose of this Phase II/III, multinational, randomized, partially double-blind, active-controlled study is to demonstrate the safety and characterize the immunogenicity of AZD2816, AstraZeneca's candidate ChAdOx1 vector vaccine against B.1.351, when administered:

- As a single dose vaccination in SARS-CoV-2 seronegative individuals who have previously received a 2-dose primary vaccination series (AZD1222 or an mRNA vaccine) against SARS-CoV-2

- As a 2-dose primary vaccination to SARS-CoV-2 seronegative individuals who have not been vaccinated previously.

SARS-CoV-2 seropositive participants will be enrolled in separate cohorts to support a parallel exploratory analysis in these participants.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD1222 and AZD2816 is provided in the respective Investigator's Brochures.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of AZD2816 and AZD1222 can be found in the respective Investigators Brochures.

2.3.1 Risk Assessment

AZD2816 has been developed using the same vaccine vector, ChAdOx1, as AZD1222 and only differs in the sequence for SARS-CoV-2 S glycoprotein that is inserted in the vector. The anticipated safety profile of AZD2816 is the same as the observed safety profile of AZD1222. Risks associated with AZD2816 are thus the same as the risks associated with AZD1222, and no additional risks are anticipated due to the change in the targeted sequence.

A number of essentially mild and moderate adverse reactions to AZD1222 have been identified and resemble reactions frequently observed after many vaccines. Based on pooled clinical data from studies with AZD1222, the most commonly expected local solicited AEs for participants in this study are vaccination site pain and tenderness. The most commonly expected systemic solicited AEs are fatigue, headache, and malaise. The majority of reported events have been 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.

Post-authorisation hypersensitivity reactions, including anaphylaxis and angioedema, have occurred following administration of AZD1222 and are considered an identified risk.

A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with COVID-19 Vaccine during post-authorisation use. No events have been observed in the AZD1222 clinical development programme. Thrombosis in combination with thrombocytopenia is thus considered to be an important identified risk. This includes cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. Considering the frequency of this rare event and the size of this study, the risk for participants in this trial is considered to be low. The protocol includes exclusion criteria and instructions for heightened vigilance and thorough investigations for suspected cases to mitigate against further the risk for these rare event.

Important potential risks are 1) neurologic events and potential immune-mediated neurologic conditions and 2) vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease.

2.3.2 Benefit Assessment

All participants will receive active treatment: either AZD1222, which has been shown to be effective in providing protection against SARS-CoV-2, or AZD2816, which as a modified form of AZD1222 designed to be effective against the emergent B.1.351 variant strain and may also provide participants with protection. The information gained from this study will inform development decisions with regard to the efficacy of AZD2816 as both a primary 2-dose vaccination in participants that have not been previously vaccinated and a 1-dose booster vaccination in participants previously vaccinated against SARS-CoV-2.

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 and close monitoring of participants to minimize known and potential risks.

An independent Data Safety Monitoring Board will provide study oversight, evaluating cumulative safety and other clinical data at regular intervals.

Taking these measures into account, the potential risks identified in association with the administration of AZD2816 and AZD1222 are justified by the anticipated benefit that may be afforded to participants for the prevention of COVID-19.

3 OBJECTIVES AND ENDPOINTS

Table 5 describes the objectives and endpoints of this study. Co-primary objectives were chosen to characterise the safety and humoral immune response against selected strains of AZD2816 and AZD1222 when administered as either a primary vaccination series in previously unvaccinated participants or as a booster to participants who have been previously primed with 2 doses of AZD1222 or an approved mRNA COVID-19 vaccine. All primary and secondary objectives/endpoints are descriptive; there will be no hypothesis testing in this study. Estimates of neutralizing antibody geometric mean titre ratio and difference in seroresponse rates (and 95% confidence interval) will be generated as secondary analyses to support the assessment of relative immune responses between selected study groups.

Table 5 Study Objectives and Endpoints

Objectives	Endpoints
Safety Objectives	
- Primary	
Previously vaccinated seronegative participants	
To characterize the safety and tolerability of 1 dose of AZD2816 in seronegative participants previously vaccinated with 2 doses of AZD1222	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose
Unvaccinated seronegative participants	
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose
- Secondary	
Previously vaccinated seronegative participants	
To characterize the safety and tolerability of 1 dose of AZD1222 in seronegative participants previously vaccinated with 2 doses of AZD1222	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of 1 dose of AZD2816 in seronegative participants previously vaccinated with 2 doses of a SARS-CoV2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose

To characterize the extended safety of 1 dose of AZD2816 in seronegative participants previously vaccinated with 2 doses of AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 dose of AZD2816 in seronegative participants previously vaccinated with 2 doses of a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 dose of AZD1222 in seronegative participants previously vaccinated with 2 doses of AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
Unvaccinated seronegative participants	
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
Immunogenicity objectives	
- Primary (descriptive)	
Previously vaccinated seronegative participants	
To assess the humoral immune response against the B.1.351 and Wuhan-Hu-1 strains induced by 1 dose of AZD2816 in seronegative participants previously vaccinated with 2 doses of AZD1222	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To assess the humoral immune response against the B.1.351 and Wuhan-Hu-1 strains induced by 1 dose of AZD2816 in seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre)

previously vaccinated with 2-doses of a SARS-CoV-2 mRNA vaccine	• Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
Unvaccinated seronegative participants	
To assess the humoral immune response against the B.1.351 and Wuhan-Hu-1 strains induced by a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in unvaccinated seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
- Secondary (descriptive)	
Previously vaccinated seronegative participants	
To describe the humoral immune response against the B.1.351 and Wuhan-Hu-1 variant strains induced by 1 dose of AZD1222 in seronegative participants previously vaccinated with 2 doses of AZD1222	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
Unvaccinated seronegative participants	
To describe the humoral immune response against the B.1.351 and Wuhan-Hu-1 variant strains induced by a 2-dose primary vaccination with AZD1222 with a 4-week interval in unvaccinated seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To describe the humoral immune response against the B.1.351 and Wuhan-Hu-1 variant strains induced by a 2-dose primary vaccination with AZD2816 with a 12-week interval in unvaccinated seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
- Secondary (comparative)	
Previously vaccinated seronegative participants receiving 1 dose versus unvaccinated seronegative participants receiving 2 doses	
To evaluate the immune responses against the B.1.3.51 variant strain and Wuhan-Hu-1 strain elicited by 1 dose of AZD2816 in seronegative participants previously vaccinated with 2 doses of AZD1222 relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rates of SARS-CoV-2 specific antibody binding titres and neutralization titres
To evaluate the immune responses against the B.1.351 variant strain and Wuhan-Hu-1 strain elicited by 1 dose of AZD2816 in seronegative participants previously vaccinated with 2 doses of a SARS-CoV-2 mRNA vaccine relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rates of SARS-CoV-2 specific antibody binding titres and neutralization titres

Previously vaccinated seronegative participants	
To evaluate the immune response against the B.1.351 variant strain and the Wuhan-Hu-1 strain elicited by 1 dose of AZD2816 as relative to the response with 1 dose of AZD1222 in seronegative participants previously vaccinated with 2 doses of AZD1222	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To evaluate the immune response against the B.1.351 and Wuhan-Hu-1 variant strain elicited by 1 dose of AZD2816 in seronegative participants previously vaccinated with a mRNA vaccine relative to the response with 1 dose of AZD1222 in seronegative participants previously vaccinated with 2 doses of AZD1222	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
Unvaccinated seronegative participants	
To evaluate the immune response against the B.1.351 and Wuhan-Hu-1 variant strain elicited by a primary 2-dose vaccination with AZD2816 with a 4-week dosing interval relative to the response elicited by a primary 2-dose vaccination with AZD1222 with a 4-week interval in previously unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To evaluate the immune responses against the B.1.351 variant strain and the Wuhan-Hu-1 strain elicited by a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval relative to the response elicited by a 2-dose primary vaccination with AZD2816 with a 4-week interval in previously unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
Exploratory	
Previously vaccinated and unvaccinated participants (seronegative and seropositive at screening)	
To explore antibody response to selected SARS-CoV-2 variants of interest/variants of concern following 2-dose primary vaccination with AZD2816 or AZD1222 in a sub-group of seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding titres (geometric mean titre) for selected variants of concern/variants of interest • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding titres for selected variants of concern/variants of interest
To explore B-cell and T-cell responses following 2-dose primary vaccination with AZD2816 or AZD1222 in a sub-group of seronegative participants	• Intracellular cytokine staining and flow cytometry for T-cell responses over time • Quantification of (IFN-γ) ELISpot responses to SARS-CoV-2 B.1.351 or Wuhan-Hu-1 S protein from day of dosing baseline over time • Breadth and depth of peripheral blood B-cell and T-cell repertoire over time through immunosequencing
To monitor the incidence of SARS-CoV-2 infection following 1 dose of AZD2816 or 1 dose of AZD1222 in previously vaccinated seronegative participants	• The incidence of SARS-CoV-2 infection defined by the presence of nucleocapsid antibodies occurring post-dose of study intervention

To monitor the incidence of COVID-19 following 1 dose of AZD2816 or AZD 1222 in previously vaccinated seronegative participants	• Incidence of COVID-19, defined as SARS-CoV-2 RT-PCR-positive symptomatic illness.
To monitor the incidence of SARS-CoV-2 infection following vaccination with 2 doses of AZD2816 or 2 doses of AZD1222 in unvaccinated seronegative participants	• The incidence of SARS-CoV-2 infection defined by the presence of nucleocapsid antibodies occurring post-second dose of study intervention
To monitor the incidence of COVID-19 following 2 doses of AZD2816 or AZD 1222 in unvaccinated seronegative participants	• Incidence of COVID-19, defined as SARS-CoV-2 RT-PCR-positive symptomatic illness.
To explore the humoral immune response against the B.1.351 and Wuhan-Hu-1 variant strains induced by a 2-dose primary vaccination with AZD1222 or AZD2816 in sub-groups of seronegative and seropositive participants	• Magnitude of SARS-CoV-2 neutralization titres (geometric mean titre) as determined by a live virus neutralization assay • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres as determined by a live virus neutralization assay
To explore anti-vector responses to the ChAdOx-1 adenovirus vector following 2 doses of AZD2816 or AZD1222 in sub-groups of seronegative and seropositive participants	• Magnitude of ChAdOx1 nAb titres (geometric mean titre) • Seroresponse rate of ChAdOx1 neutralizing antibody titres • Pairwise correlations between anti-S, pseudo-neutralization, and ChAdOx1 neutralizing antibody titres, 1 month after both Dose 1 and Dose 2
To explore additional immune responses following 2 doses of AZD1222 or AZD2816 in sub-groups of seronegative and seropositive participants	• Other exploratory assays for humoral and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data

MAAEs: medically attended adverse events; SAEs: serious adverse events; AESIs: adverse events of special interest

[a] Seroresponse: An at least 4-fold increase in geometric mean titre from baseline.

4 DESIGN

4.1 Overall Design

This is a multi-country Phase II/III study to evaluate the safety and immunogenicity of AZD2816 as single-dose vaccination in previously vaccinated adult participants and as a 2-dose primary vaccination in previously unvaccinated adult participants.

A total of approximately 1650 SARS-CoV-2 nucleocapsid seronegative participants that have been screened and judged to be eligible for the study will be enrolled across these 2 patient populations with the goal of 900 previously vaccinated participants receiving single-dose vaccination and 750 unvaccinated participants receiving primary 2-dose vaccination. In addition, seropositive patients will be enrolled (with a cap of 10% of the seronegative population or 165 participants) to support exploratory analysis is these participants.

The enrollment and randomization strategy is intended to minimize group differences in terms of age, gender and the presence of comorbidities.

In both the single-dose treatment regimen and primary 2-dose vaccination treatment regimen, participants will receive study intervention consisting of intramuscular administration of either AZD1222 (5×10^{10} viral particles) or AZD2816 (5×10^{10} viral particles).

Approximately 600 seronegative participants previously vaccinated with AZD1222 will be randomised 1:1 to receive a single intramuscular dose of either AZD1222 or AZD2816 in a double-blinded fashion.

Approximately 300 seronegative participants previously vaccinated with an approved mRNA based vaccination will receive a single intramuscular open-label dose of AZD2816.

Approximately 750 seronegative, previously unvaccinated participants will be randomised 2:2:1 to receive a 2-dose primary vaccination of either 2 doses of AZD1222 or AZD2816 with a 4-week dosing interval in a double-blinded fashion or 2 doses of open-label AZD2816 with a 12-week dosing interval.

In addition, a smaller population seropositive participants (approximately 10% of the seroronegative population), will be randomised or assigned to treatment in a similar manner as above.

Immunogenicity (ie, anti-Wuhan-Hu-1 and anti-B.1.351 immune responses including S-binding antibody titres and neutralizing antibody levels [pseudoneutralization]) will be assessed in serum samples collected pre-dose on the day of each vaccination (baseline levels before vaccination), 14 and 28 days after each vaccination, and 180 days after the last vaccination.

All participants will be given an axillary thermometer, tape measure or ruler, and a proprietary e-diary application designed for use with a smart device with instructions for use. All participants will be asked to report on solicited signs and symptoms for 7 days following vaccination (Days 1-8 for all participants and Days 29-36 for the 4-week dosing interval and Days 85-92 for the 12-week dosing interval). An e-diary will be used to collect information on the timing and severity of the solicited signs and symptoms.

Follow-up visits will take place as per the schedule of assessment within respective windows. All participants will be assessed for local and systemic AE, physical examination, review of e-diaries at these time points as detailed in the schedule of assessment. Blood will also be taken for safety assessments and immunology purposes.

All study participants will be followed for safety for 180 days after administration of their last vaccination dose. In every participant, solicited local and systemic events will be reported for up to 7 days after each dose, all unsolicited AEs will be reported for up to 28 days after each

dose, and SAEs and AEs of special interest will be evaluated through study completion (up to 180 days after the last study vaccination).

An independent COVID-19 Vaccine Data Safety Monitoring Board will provide oversight, to ensure safe and ethical conduct of the study.

4.1.1 COVID-19 Assessments

Occurrence of COVID-19 in the trial will be reported as safety events, including monitoring of the potential risk of vaccine-induced enhanced disease as an AE of special interest (see Appendix E). COVID-19 will be diagnosed and treated as per standard medical practice. In addition, experimental treatments are permitted. Detailed information will be collected in a standard way and reported on a specific case report form.

4.1.2 Screening

All potential participants will be screened, which may take place at a visit up to 14 days prior to Day 1 or on Day 1 itself.

Informed consent will be obtained before screening/enrollment. If written consent is obtained, the screening procedures specified in the Schedule of Activities (Section 1.3) will be undertaken including a medical history, physical examination, height and weight, a SARS-CoV-2 screening test and clinical safety laboratory assessments. Baseline information collected in the previously vaccinated participants will include which vaccine was received, immunization dose interval, and time since last vaccination.

For women of childbearing potential, it will be recorded that they verbally confirmed use of one highly effective form of birth control for at least 28 days prior to the planned vaccination and a urine pregnancy test will be performed that must be negative for the participant to be enrolled. (Note: Women with urine test results that are positive or undetermined will not be enrolled and should be advised to seek medical attendance outside the context of the trial if pregnancy is suspected.)

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 enrollment or to withdraw a participant from the study will be at the discretion of the Investigator.

4.1.3 Vaccination Visit

Participants will be considered enrolled at the point of vaccination. Before vaccination, the eligibility of the participant will be reviewed. Body temperature will be observed and a medical history and physical examination will be undertaken before the first vaccination to determine need to postpone vaccination or screen fail the participant. A negative pregnancy

test (urine test) will need to be obtained from women of childbearing potential before vaccination. Baseline blood samples will be obtained before the first vaccination.

Participants will receive 1 dose of AZD2816 or AZD1222 at vaccination visits, administered by intramuscular injection. Previously immunized participants will have a single vaccination visit, Day 1. Participants that have not been previously vaccinated at baseline will have a second vaccination visit on Day 29 (4-week interval) or Day 85 (12-week interval).

All participants will be given an axillary thermometer, tape measure or ruler, and a proprietary e-diary application designed for use with a smart device with instructions for use. All participants will be asked to report on solicited signs and symptoms for 7 days following vaccination (Days 1 to 8 and Days 29 to 36 or Days 85 to 92 when applicable).

4.1.4 Follow-up visits

Follow-up visits will take place as specified in the Schedule of Activities (Section 1.3). All participants will be assessed for local and systemic AE, physical examination, review of the e-diary and blood tests at these time points as detailed in the Schedule of Activities. Blood will also be taken for safety and immunogenicity assessments.

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 the last study visit in order to collect information on any SAEs/AE of special interest.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Study Design and Participant Population

The participant population includes adults ≥18 years of age. Persons who are healthy or have medically stable underlying conditions will be eligible. Adults with medically-stable chronic diseases may participate if, according to the judgement of the investigator, hospitalization within the study period is not anticipated and the participant appears likely to be able to remain on study through the end of protocol-specified follow-up.

For the primary and secondary objectives, those enrolled in the study must test negative for SARS-CoV-2 nucleocapsid protein antibody during screening. Some seropositive participants (capped at 10% of the seronegative participant population) will be enrolled to support an exploratory analysis.

Those enrolled in the single-dose vaccination part of the study must have received 2 doses of AZD1222 (with a dosing interval of 4-12 weeks) or 2 doses of an mRNA COVID-19 vaccine (with a dosing interval of 3-12 weeks for the BNT162b2 mRNA vaccine [Pfizer-BioNTech] and 4-12 weeks for the mRNA-1273 vaccine [Moderna]) with the second doses administered at least 3 months prior to first study intervention administration.

Pregnant/breastfeeding women, persons with severe immunodeficiency or severe underlying disease will be excluded from participation in the study. Persons previously vaccinated with AZD1222 in the context of an AZD1222 vaccine trial are eligible for enrollment as previously vaccinated participants in the trial. Persons who have previously received any other investigational product for the prevention of COVID-19 will be excluded from participation in this study.

Participants with known risk factors for thrombosis and thrombocytopenia (excluding contraceptive hormonal therapy or replacement hormonal therapy) are excluded.

4.2.2 Rationale for Study Endpoints

There is no statistical hypothesis testing planned for this study. Descriptive statistics will support evaluation of safety, reactogenicity, and immunogenicity.

An interim analysis will occur when all vaccinated participants have completed their Day 29 visit.

The primary analysis will occur when all participants have completed their Day 29 visit AND all previously unvaccinated participants randomized to a 4-week dosing interval have completed their Day 57 visit (ie, 28 days after their second dose).

A secondary analysis will occur when all participants have completed their Day 29 visit AND all previously unvaccinated participants (including those randomized to either a 4-week or a 12-week dosing interval) have completed their Day 57/Day 113 visit (ie, 28 days after their second dose).

The final analysis will occur when data from all vaccinated participants are available through completion of the last study visit (180 days after the single dose for previously vaccinated participants/180 days after the second dose for unvaccinated participants).

The primary safety analysis includes:

- Incidence of local and systemic solicited AEs for 7 days following each vaccination will be summarized by day and overall.
- Incidence of unsolicited AEs for 28 days following each vaccination will be summarized by system organ class and preferred term, and by relationship to vaccination as assessed by the investigator.
- SAEs and AEs of special interest following the first vaccination and throughout the study duration will be summarized by system organ class and preferred term and by relationship to vaccination as assessed by the investigator.

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

The immunogenicity endpoints of interest in this study are:

- Geometric mean titre
- Seroresponse, defined as ≥ 4-fold increase in the geometric mean titre from baseline

Geometric mean titre ratios and differences in seroresponses with 95% confidence intervals will be presented to support selected comparisons of immunogenicity across groups of interest.

Immunogenicity against SARS-CoV-2 Wuhan-Hu-1 and B.1.351 strains will be characterized through the quantification of Spike-binding antibodies, pseudo-neutralization and, in a subset of participants, live neutralization. Exploratory analysis of immunogenicity against other strains and induction of other immune effectors including cell-mediated immunity will be conducted.

4.3 Justification for Dose

The AZD2816 nominal dose of 5×10^{10} viral particles is the same dose as the approved dose for AZD1222, which was based on the accumulated non-clinical data and clinical data from the AZD1222 clinical studies, as well as from other SARS-CoV-2 vaccines in development. Safety and immunogenicity data from an additional clinical study, MERS001(NCT03399578), using the same ChAdOx1 vector, also helped inform dose selection. MERS001 was the first clinical study of a ChAdOx1-vectored vaccine expressing the full-length S protein from a separate, but related, beta-coronavirus. ChAdOx1 MERS has been given to 31 participants to date at doses ranging from 5×10^{9} viral particles to 5×10^{10} viral particles. Despite higher reactogenicity observed at the 5×10^{10} viral particles, this dose was safe, with self-limiting AEs and no serious adverse reactions recorded. The 5×10^{10} viral particles was the most immunogenic, in terms of inducing neutralizing antibodies 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} viral particles dose was chosen for AZD1222.

Based on accumulating nonclinical and clinical data gathered for AZD1222, a 2-dose regimen was selected for vaccination of unvaccinated participants with AZD2816 (AZD1222

Investigators Brochure). A single dose vaccination has been selected for participants previously vaccinated in line with both FDA and EMA guidance (FDA 2021, EMA 2021).

4.4 End of Study Definition

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

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

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as a protocol waiver or exemption, is not permitted.

5.1 Inclusion Criteria

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

5.1.1 All Participants:

Age

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

COVID-19

For inclusion in the SARS-CoV-2 seronegative population supporting the primary and secondary objectives:

2 No history of laboratory-confirmed SARS-CoV-2 infection (ie, no positive nucleic acid amplification test and no positive antibody test).

3 Seronegative for SARS-CoV-2 at screening (lateral flow test to detect reactivity to the nucleoprotein).

Note, patients failing to meet criteria 2 and/or 3 may be included in the separate seropositive population supporting the seropositive exploratory objectives.

Type of Participant

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

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

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

6 Signed informed consent obtained before conducting any study-related procedures

Reproduction

7 Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
Female participants:

(a) Women of childbearing potential must:

- Have a negative pregnancy test on the day of screening and on days of vaccination
- 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 30 days following administration of the 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 6). Periodic abstinence, the rhythm method, and withdrawal are NOT acceptable methods of contraception.

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

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

    Until follicle-stimulating hormone is documented to be within menopausal range, the participant is to be considered of childbearing potential
  - For women aged ≥50 years, post-menopausal is defined as having a history of ≥12 months amenorrhea prior to randomization, without an alternative cause, following cessation of exogenous sex-hormonal treatment.

Table 6 Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
Intrauterine device Intrauterine hormone-releasing system[a] Bilateral tubal occlusion Vasectomized partner [b]	Combined (oestrogen- and progestogen-containing hormonal contraception Oral (combined pill) Intravaginal Transdermal (patch)

Table 6 Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
Sexual abstinence [c]	Progestogen-only hormonal contraception Oral Injectable Implantable

[a] This is also considered a hormonal method
[b] Provided that partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success
[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse from 28 days prior to Day 1 through 30 days following administration of the second dose of study intervention, and if it is the preferred and usual lifestyle of the participant

5.1.2 Previously COVID-19 Vaccinated Participants

8 Prior completion of a 2-dose primary homologous vaccination regimen against SARS-CoV-2 with either AZD1222 (2 standard doses as authorized vaccine or as investigational product in a clinical trial with a 4 to 12-week dosing interval) or with an mRNA vaccine approved for emergency or conditional use (eg, BNT162b2 vaccine [Pfizer-BioNTech] with a 3- to 12-week dosing interval or mRNA-1273 vaccine [Moderna] with a 4- to 12-week dosing interval). The second dose in all cases should have been administered at least 3 months prior to first administration of study intervention.

5.2 Exclusion Criteria

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

Medical Conditions

1 History of allergy to any component of AZD1222/AZD2816.

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

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

4 Any confirmed or suspected immunosuppressive or immunodeficient state, including asplenia or HIV/AIDS.

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

- Topical/inhaled steroids or short-term oral steroids (course lasting ≤ 14 days)

6 History of primary malignancy except for:

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

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

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

(d) Localized prostate cancer

7 History of thrombocytopenia and/or thrombosis, including participants who have experienced major venous and/or arterial thrombosis in combination with thrombocytopenia following vaccination with any COVID-19 vaccine

8 History of heparin-induced thrombocytopenia, congenital thrombophilia (ie, factor V Leiden, prothrombin G20210A, antithrombin III deficiency, protein C deficiency and protein S deficiency, factor XIII mutation, familial dysfibrinogenemia), auto-immune thrombophilia (antiphospholipid syndrome, anti-cardiolipin antibodies, anti-β_2-glycoprotein 1 antibodies), or paroxysmal nocturnal haemoglobinuria.

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

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

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

12 Any autoimmune conditions, except mild psoriasis and vitiligo

Note: The AEs of special interest as outlined in Appendix E (including Table 27) should be considered when evaluating a participant for exclusion criteria as the presence of these AEs of special interest, especially if untreated or uncontrolled, may be a safety risk to the participant, affect the ability of the participant to participate in the study, and/or impair interpretation of the study data. Investigators should review and consider the list of conditions in Appendix E. If any of these conditions are present in a participant, the Investigator is asked to utilize his/her clinical judgment in determining the participant's eligibility for the study. Should the participant have conditions as outlined in Appendix E and the participant is enrolled, the Investigator is asked to document notes on site regarding the final rationale for enrollment.

Prior/Concomitant Therapy

13 Receipt of or planned receipt of investigational products indicated for the treatment or prevention of SARS-CoV-2 or COVID-19 with the exception of prior vaccination with AZD1222 or an mRNA COVID-10 vaccine (2 doses of the same vaccine within an

approved dosing interval, see Section 5.1.2), which is allowed for participants in the previously vaccinated cohort
Note: For participants who develop COVID-19, receipt of licensed treatment options and/or participation in investigational treatment studies is permitted

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

15 Receipt of any influenza vaccine (licensed or investigational) within 7 days prior to and after administration of AZD1222/AZD2816.

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

Other Exclusions

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

18 Women who are currently pregnant (confirmed with positive pregnancy test), breastfeeding, having given birth less than 3 months before or planning pregnancy during the study.

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

20 Participants with a history of chronic alcohol or drug abuse or any condition associated with poor compliance.

21 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements or if vaccination would interfere with the participant's ongoing treatment.

22 Previous enrollment in the present study.

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 publishing requirements and to respond to

queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

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

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention, marketed product, or placebo intended to be administered to or medical device utilized by a study participant according to the study protocol. Study intervention is defined as AZD2816 or AZD1222 (Table 7).

6.1 Study Interventions Administered

6.1.1 Investigational Products

Table 7 Investigational Products

Intervention Name	AZD2816	AZD1222
Type	Vaccine	Vaccine
Dose Formulation	CCI [redacted]	CCI [redacted]
Unit Dose Strength	1×10^{11} viral particles/mL	1×10^{11} viral particles/mL
	$\geq 5 \times 10^{8}$ infectious units/mL	$\geq 5 \times 10^{8}$ infectious units/mL
Dosage Level	5×10^{10} viral particles (nominal, $\pm 1.5 \times 10^{10}$ viral particles)	5×10^{10} viral particles (nominal, $\pm 1.5 \times 10^{10}$ viral particles)
	$\geq 2.5 \times 10^{8}$ infectious units	$\geq 2.5 \times 10^{8}$ infectious units
Route	Intramuscular	Intramuscular
Use	Experimental	Experimental
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labelling	Will be provided in vials within a carton. Each carton and vial will be labelled as required per country requirement	Will be provided in vials within a carton. Each carton and vial will be labelled as required per country requirement
Current/Former Name	-	Previous clinical documentation: ChAdOx1 nCoV-19 Current tradename: Vaxzevria

IMP: investigational medicinal product; NIMP: non-investigational medical product; w/v: weight/volume.

AZD2816
AZD2816 will be supplied by the Sponsor as a vial solution for injection. It is a sterile, clear to slightly opaque solution, practically free from visible particles. Each vial of AZD2816 has a label-claim volume of 5 mL and can provide up to ten 0.5 mL doses.

AZD1222

AZD1222 will be supplied by the Sponsor as a vial solution for injection. It is a sterile, clear to slightly opaque solution, practically free from visible particles. Each vial of AZD1222 has a label-claim volume of 4 mL and can provide up to eight 0.5 mL doses.

Unopened vial must be stored at 2-8 ºC (36-46 ºF) for the duration of the assigned shelf-life and must not be frozen. Both investigational products must be kept in original packaging until use to prevent prolonged light exposure.

6.1.2 Dosing Instructions

Previously unvaccinated participants will receive 2 doses of either AZD1222 or AZD2816, with the first dose administered on Day 1 and the second dose on Day 29 (for a 4-week dosing interval) (Table 3) or Day 85 (for a 12-week dosing interval) (Table 4).

Previously vaccinated participants will receive 1 dose of either AZD1222 or AZD2816 (Table 2)

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

All study participants will be observed in the clinic for at least 15 minutes after vaccination. Allergic reactions to vaccines are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

6.2 Preparation/Handling/Storage/Accountability

The procedures for preparation, handling, storage, and accountability are identical for AZD2816 and AZD1222.

1 The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2 Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or

automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

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

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

6.2.1 Dose Preparation and Administration

Doses of AZD2816 and 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 AZD2816 or AZD1222 in a sterile syringe.

AZD2816 and AZD1222 do not contain preservatives. Each vial must be assigned a beyond-use-date of 6 hours at 2-30 °C (36-86 °F) from first needle puncture of the vial, after which any unused portion must be discarded.

Once an AZD2816 or AZD1222 dose is drawn into a syringe for administration, the dose must be administered within the beyond-use-date of the vial. If dose administration is not completed within the 6-hour vial beyond-use-date, a new dose must be prepared from a new vial.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization

The study contains 2 randomised cohorts and 1 non-randomised cohort:

- Participants that have previously been vaccinated with 2 doses of AZD1222 will be randomised 1:1 to 1 dose of AZD2816 or 1 dose of AZD1222.
- Participants that have been previously vaccinated with an mRNA COVID-19 vaccine will not be randomised; all will receive 1 dose of AZD2816.
- Vaccination naïve participants that will be randomised 2:2:1 to 2 doses of AZD2816 with a 4-week dosing interval, 2 doses of AZD1222 with a 4-week dosing interval, or 2 doses of AZD2816 with a 12-week dosing interval.

Separate populations of SARS-CoV-2 seronegative participants (supporting the primary and secondary objectives) and SARS-CoV-2 seropositive participants (supporting exploratory objectives) will be randomised/included in the above cohorts.

Randomization will be stratified based on age, gender, and presence of the following comorbidities that are known risk factors for severe illness from COVID-19 (based on the participant's past and current medical history):

- Obesity (BMI $\geq$ 30 kg/m^2 at baseline)
- Significant cardiovascular disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, or pulmonary hypertension)
- Chronic lung disease (eg, chronic obstructive pulmonary disease, idiopathic pulmonary disease, cystic fibrosis, or moderate to severe asthma)
- Diabetes (Type 1 or Type 2).

To maintain comparability between randomised groups (previously vaccinated with AZD1222 and previously unvaccinated participants) and the non-randomised group (previously vaccinated with mRNA participants), the randomisation stratification factors will be monitored during the enrolment period, and if required a recruitment cap on a particular level of a factor may be stipulated.

The randomised participants will be centrally assigned to randomized study intervention using an Interactive Response Technology (IRT)/Randomisation and Trial Supply Management. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information & directions for the Randomisation and Trial Supply Management will be provided to each site.

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

6.3.2 Blinding

Treatment will be double-blinded for previously AZD1222 vaccinated participants randomised to a single dose of either AZD2816 or AZD1222 and for previously unvaccinated participants randomised to either AZD2816 or AZD1222 given as 2 dose regimen with a 4-week dosing interval. Participants previously vaccinated with an mRNA COVID-19 vaccine will receive an open-label booster dose of AZD2816, and previously unvaccinated participants receiving a primary 2-dose vaccination of AZD2816 with a 12-week dosing interval in this study will also receive treatment in an open-label fashion.

For the double-blinded treatments, neither the participant nor any of the investigators or Sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the study intervention received. Since AZD2816 and AZD1222 are visually distinct prior to dose preparation (due to differences in container closure), investigational 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, AZD2816 and AZD1222 are not visually distinct from each other.

The IRT will provide the investigators with a dose tracking number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IRT user manual that will be provided to each study site.

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

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

6.3.3 Procedures for Unblinding

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

In the event that a study participant is contacted about receiving a licensed and/or authorized COVID-19 vaccine outside of this clinical study, unblinding instructions are being provided to the sites. If the participant is unblinded, the Sponsor needs to be notified within 24 hours, and this should be documented in the site source documents.

6.4 Study Intervention Compliance

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

6.5 Concomitant Therapy

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

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

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

6.5.1 Permitted Concomitant Medications

- Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance.
- Primary care providers, or where appropriate investigators, should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study.
- Participants who develop COVID-19 after receiving study intervention should be treated with licensed medications and interventions according to standard of care. All routine vaccinations other than influenza are permitted beginning > 30 days after last dose of study intervention. Licensed influenza vaccines are permitted 7 days before and 7 days after administration of study intervention.
- Topical/inhaled steroids or short-term oral steroids (course lasting ≤ 14 days) are permitted

6.5.2 Prohibited Concomitant Medications

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

- Primary or booster vaccinations, other than AZD2816 or AZD1222, for prevention of SARS-CoV-2 or COVID-19**.**

  Note: Participants choosing to receive a licenced and/or authorized COVID-19 vaccine should inform the Investigator so it can be properly documented. Participants, who receive a licenced and/or authorized COVID-19 vaccine outside the study, should be encouraged to continue study conduct to be followed for safety reporting and all assessments.

- Receipt of any vaccine (licensed or investigational) other than licensed influenza vaccines within 30 days prior to and after administration of study intervention. Thirty days after the second vaccination, other routine vaccinations are permitted as clinically indicated.
- Glucocorticoids at a dose ≥ 20 mg/day of prednisone or equivalent given daily or on alternate days for ≥ 14 consecutive days between randomization and the participant's scheduled final visit
- Other systemically administered drugs with significant immunosuppressive activity, such as azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy between randomization and the participant's scheduled final visit
- Immunoglobulins and/or any blood product.

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

6.6 Dose Modification

Study intervention will be administered as described in Section 6.1. Dose modification is not permitted.

6.7 Intervention After the End of the Study

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

An individual participant will not receive the first or second dose (if applicable) of study intervention if any of the following occur in the participant in question:

1 Withdrawal of consent after signing informed consent
2 Participant meets one or more of the exclusion criteria or fails to meet all inclusion criteria for study participation
3 Participant is pregnant or nursing
4 Any grade 3 or greater allergic reaction including anaphylaxis that is assessed as related to study intervention
5 Any SAE assessed as related to study intervention

6 Any AE that, in the judgment of the site investigator, is related to study intervention and may jeopardize the safety of the study participant

7 Receipt of a prohibited concomitant medication that may jeopardize the safety of the study participant or interpretation of the data

Each participant who has received at least 1 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.

In the event that a study participant receives a licensed and/or authorized COVID-19 vaccine during the study, AstraZeneca needs to be notified within 24 hours and this should be documented in the site source documents. Participants who have received study intervention, regardless of reason, will be followed for the full study period.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Sponsor Study Team. If the participant does not specifically request withdrawal of consent for use of samples, then the samples collected prior to the consent withdrawal will be destroyed once per protocol analysis is complete.

7.3 Lost to Follow-up

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

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

- The study site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Schedule of Activities (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 Schedule of Activities (Section 1.3) is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities.

8.1 Efficacy Assessments

Not applicable.

8.2 Safety Assessments

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

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

8.2.2 Vital Signs

Vital signs, including heart rate, pulse oximetry, blood pressure, and body temperature, will be performed as specified in the Schedule of Activities (Section 1.3). The participant should be resting prior to the collection of vital signs. On vaccination days, vital signs should be assessed prior to vaccine administration.

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

8.2.3 Clinical Laboratory Assessments

Blood samples for determination of clinical chemistry and haematology will be taken at the visits indicated in the Schedule of Activities (Section 1.3). Additional unscheduled safety samples may be collected if clinically indicated at the discretion of the investigator, with the date and time of collection recorded in the appropriate eCRF.

The standard clinical chemistry and haematology analysis will be performed at a local laboratory at or near to the investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The following laboratory variables will be measured:

Table 8 Laboratory Safety Variables

Blood	Serum/Plasma
Haemoglobin	Activated partial thromboplastin time
Leukocyte count	Prothrombin time
Leukocyte differential count (absolute count)	Fibrinogen
Platelet count	D-dimer

-	Creatinine
-	Bilirubin, total
-	Alkaline phosphatase
-	Aspartate aminotransferase
-	Alanine aminotransferase

In case a participant shows an aspartate aminotransferase **or** alanine aminotransferase ≥ 3 × upper limit of normal together with total bilirubin ≥ 2 × the upper limit of normal, please refer to Section 8.3.6

For women participants of childbearing potential, a urine sample for pregnancy testing will be collected according to the Schedule of Activities (Section 1.3). Urine pregnancy tests for β-human chorionic gonadotropin may be performed at the site using a licensed dipstick test.

8.3 Adverse Events and Serious Adverse Events

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

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

Solicited AEs are local or systemic predefined events for assessment of reactogenicity. Solicited AEs will be collected in a e-diary (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 the reporting of solicited AEs via e-diary unless otherwise noted..

All other AEs are considered to be unsolicited AEs (collected by ‘open question’ at study visits).

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

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

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

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

Solicited AEs will be recorded for 7 days after each dose of study intervention (ie, Day 1 through Day 8). If a solicited AE is not resolved within the e-diary reporting period, the event

will be reported as a non-solicited adverse event in the eCRF, with a start date of when started and the actual stop date.

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

Medically-attended AEs and AEs of special interest will be recorded from Day 1 through the last participant contact.

See the Schedule of Activities for the scheduled timepoints (Section 1.3).

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 Adverse Events and Serious Adverse Events

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. The Sponsor retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

AE variables

The following variables will be collected for each AE:

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

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

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge

- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

A revised toxicity grading scale from US FDA guidance for healthy volunteers enrolled in a preventive vaccine clinical study (FDA 2007) will be utilized for all unsolicited events with an assigned severity grading including Grade 5.

8.3.3 Causality Collection

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

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

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

8.3.4 Adverse Events Based on Signs and Symptoms

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

8.3.5 Adverse Events Based on Examinations and Tests

The results from the Clinical Study Protocol-mandated vital signs and laboratory safety assessments will be summarized in the Clinical Study Report.

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

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

8.3.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation. Any occurrences of aspartate aminotransferase or alanine aminotransferase ≥ 3 × the upper limit of normal together with total bilirubin ≥ 2 × upper limit of normal at any point during the study following the administration of study medication should be reported to the Sponsor as a potential Hy's Law SAE within 1 day with a serious criteria of 'Important medical event' and causality assessment 'yes/related'.

The study physician will contact the investigator to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.

8.3.7 Solicited Adverse Events

Local and systemic predefined solicited AEs for reactogenicity assessment (Table 9) will be collected in a Solicited AE e-Diary for 7 days following administration of each dose of study intervention via e-diary collection. If a solicited AE is not resolved within the e-diary reporting period, the event will be also reported as a non-solicited adverse event in the eCRF, with a start date of when started and the actual stop date.

Solicited AEs should not be reported as unsolicited AEs unless they fulfil the criteria for SAEs or medically-attended AEs(see Sections 8.3 and 8.3.8, respectively).

Table 9 Predefined Solicited Adverse Events for Reactogenicity Assessment

Local	Systemic
Pain at the site of the injection	Fever (> 100 °F/37.8 °C)
Redness/erythema at the site of the injection	Chills
Tenderness at the site of the injection	Muscle pains
Induration/swelling at the site of the injection	Fatigue (physical or mental tiredness/exhaustion)
-	Headache
-	Malaise (general feeling of discomfort or uneasiness)
-	Nausea
-	Vomiting

Solicited AE e-Diary

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

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

Severity Assessment of Solicited AEs

Severity will be assessed for solicited AEs by the participant (or, if applicable, their caregiver, surrogate, or legally authorized representative) according to toxicity grading scales modified and abridged from the US FDA guidance (FDA 2007) as defined in Appendix D. Because solicited AEs are expected to occur after vaccination, they will not be assessed for relationship to study intervention.

8.3.8 COVID-19 Assessment

This study will describe the incidence of COVID-19 adverse events reported from Day 1 to 180 days after the participant's last/only dose of vaccine.

COVID-19 is defined as SARS-CoV 2-RT-PCR positive symptomatic illness. At all clinic visits following the initial vaccination, participants will be asked if they have had a diagnosis of COVID-19 since their last clinic visit (see Schedule of Activities in Section 1.3). Medical records will be obtained for confirmation of a patient-reported diagnoses of COVID-19. Qualifying symptoms are fever, shortness of breath, difficulty breathing, chills, cough, fatigue, muscle/body aches, headache, new loss of taste or smell, sore throat, congestion, runny nose, nausea, vomiting, or diarrhoea. Events will be reported as AEs/SAEs.

If a participant presents at clinic visit with COVID symptoms, diagnosis will be confirmed using RT-PCR.

8.3.9 Medically-Attended Adverse Events

Medically-attended AEs will be collected according to the timepoints specified in the Schedule of Activities (Section 1.3).

Medically-attended AEs are defined as AEs leading to medically-attended visits that were not routine visits for physical examination or vaccination, such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. AEs, including abnormal vital signs, identified on a routine study visit or during the scheduled illness visits will not be considered medically-attended AEs.

8.3.10 Adverse Events of Special Interest

AEs of special interest will be collected according to the timepoints specified in the Schedule of Activities (Section 1.3).

AEs of special interest 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. AEs of special interest are based on Brighton Collaboration case definitions (SPEAC 2020), clinical experience, and scientific interest. A list of events is provided in Appendix E.

An AE of special interest can be serious or non-serious. All AEs of special interest will be recorded in the eCRF. If any AE of special interest occurs in the course of the study, investigators or other site personnel will inform the appropriate Sponsor representatives within 1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it. Serious AEs of special interest will be recorded and reported as per Section 8.3.11.

8.3.10.1 Vascular/Hematologic Adverse Events of Special Interest

The investigator should remain vigilant for the occurrence of thrombotic events with thrombocytopenia and/or bleeding. If a participant experiences new onset thromboembolic events with thrombocytopenia, there should be prompt evaluation with a thorough haematological investigation. COVID-19 testing, including PCR and serology (nucleoprotein antibodies), should also be performed. See Appendix F for further guidance on investigation and management of suspected events.

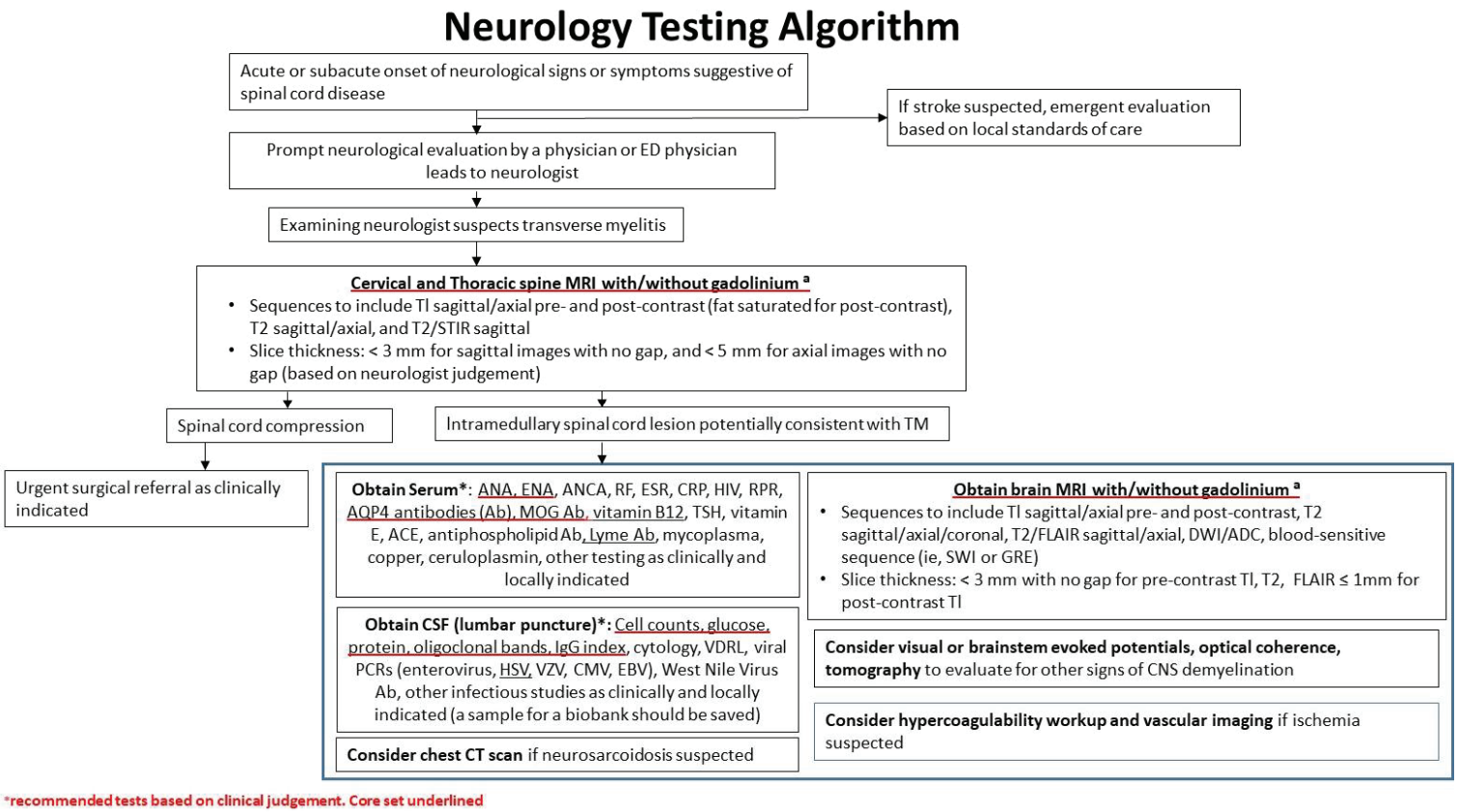
In the event of such a case of thrombosis and in accordance with local laws and ethical procedures, one blood sample may be taken from the participant and whole genome sequencing performed in order to enable investigations into the possible role of genetic polymorphisms as risk factors for these events.

8.3.10.2 Potential Neurological Adverse Events of Special Interest

If a participant experiences new onset (acute or subacute) motor and sensory disturbances (eg, weakness, numbness, paraesthesia, 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, including referral to a neurology specialist for further evaluation and testing, as clinically indicated. Testing can include evaluation for peripheral demyelinating conditions (eg, electromyography). In cases of concern for spinal cord disease, see Figure 3 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 AEs of special interest occurring in the AZD1222 clinical development program (see Appendix A 5).

Figure 3 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.

8.3.11 Reporting of Serious Adverse Events

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

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

The designated Sponsor representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform Sponsor representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but no later than 24 hours of when he or she becomes aware.

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 Sponsor representative.

If the Electronic Data Capture system is not available, then the investigator or other study site staff reports an SAE to the appropriate Sponsor representative by telephone or other method and the event is entered into the Electronic Data Capture system when available.

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

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

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

8.3.12 Pregnancy

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

8.3.12.1 Maternal Exposure

Female participants who are pregnant or have a confirmed positive pregnancy test at screening or Day 1 will be excluded from the study (see Section 5.2). Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and

spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the participant was discontinued from the study.

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

The designated Sponsor representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.11) and **within 30 days** for all other pregnancies that are not associated with an SAEs.

The same timelines apply when outcome information is available.

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

8.3.13 Medication Error

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

The designated Sponsor representative works with the investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) **or 5** (other serious initial and follow up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.11) and **within 30 days** for all other medication errors.

The definition of a Medication Error can be found in Appendix B 3.

8.4 Overdose

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

There is no specific treatment for an overdose with AZD2816 or AZD1222. If overdose occurs, the participant should be treated supportively with appropriate monitoring as necessary.

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

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

The designated Sponsor representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.11) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

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

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

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

8.5.1 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5.2 Immunogenicity Assessments

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

8.5.2.1 SARS-CoV-2 Serology Assessments

Serum samples will be collected to assess SARS-CoV-2 antigen-specific antibody levels from all participants according to the Schedule of Activities (Section 1.3). Authorized laboratories will assess serologic responses to AZD1222 and AZD2816 using validated (or qualified, where appropriate) assays. Serologic assessment to the S protein from different SARS-CoV-2 variants (which include Wuhan-Hu-1, B.1.351, B.1.1.7, and P.1) will be assessed quantitatively using a validated multiplexed ECL based immunoassay. Additionally, seroresponse will be assessed for each antigen over time. The rate of SARS-CoV-2 infection in participants receiving AZD2816 versus AZD1222 will be determined by seroconversion in a SARS-CoV-2 nucleocapsid antigen in a multiplexed electrochemiluminescence-based assay performed at an authorized laboratory. Additional exploratory assessments may be performed to measure binding antibodies to SARS-CoV-2 variants of interest (which may include B.1.429, B.1.525, B.1.526, P.2, P.3, B.1.617, and the Q677H mutation observed in multiple variants).

8.5.2.2 CCI

CCI

[redacted]

8.5.2.3 CCI

CCI

[redacted]

8.5.2.4 CCI

CCI

[redacted]

8.5.3 Pharmacodynamics

Pharmacodynamics are not evaluated in this study.

8.6 Human Biological Sample Biomarkers

Already collected samples may be analysed for biomarkers thought to play a role in COVID-19 severity or outcomes based upon emerging immunogenicity and pharmacodynamic analysis from this or other studies involving the study interventions. These analyses include but are not limited to serum or plasma cytokines, quantification of RNA, micro-RNA, and/or non-coding RNA using quantitative reverse transcriptase polymerase chain reaction (RT-PCR), microarray, sequencing, or other technologies in blood, or peripheral blood mononuclear cells to evaluate their association with AZD1222/2816 and observed clinical responses to these study interventions.

8.7 Optional Genomics Initiative Sample

Not applicable.

8.8 Medical Resource Utilization and Health Economics

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

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

There is no statistical hypothesis testing planned for this study. Descriptive analyses will support evaluation of safety, reactogenicity and immunogenicity.

9.2 Sample Size Determination

Primary Objective: Characterise Immunogenicity (Precision)

Historical data were available for the immunogenicity responses to AZD1222 from the pooled COV001/002/003/005 studies. Table 10 presents the log transformed immunogenicity responses (ie, geometric mean titres) by assay for participants that received 2 standard doses

of AZD1222. These results indicate that the pseudo-neutralising antibodies exhibited the largest variation (standard deviation of 1.20 and 1.10 for the 4-week and 12-week dosing intervals respectively), while live-neutralising antibodies had the lowest (standard deviation of 0.72 for the 4-week dosing interval).

Table 10 Historic Immunogenicity Responses by Dosing Interval (Geometric Mean Antibody Titres, Standard Dose Immunogenicity Analysis Set)

	Post-1st Dose			Post-2nd dose with a 4-week dosing interval[a]			Post-2nd dose with a 12-week dosing interval[b]		
Assay	**N**	**Mean**	**Std Dev**	**N**	**Mean**	**Std Dev**	**N**	**Mean**	**Std Dev**
Pseudo	476	4.3	1.34	166	5.3	1.20	113	5.4	1.10
Live	51	4.9	1.15	42	6.2	0.72	0	-	-
S protein	1139	9.1	1.14	293	10.1	0.96	302	10.7	0.83

[a] Estimates from pooled COV001/002/003/005 study data from participants with 2- to 6-week dosing interval
[b] Estimates from pooled COV001/002/003/005 study data from participants with 10- to 14-week dosing interval

Table 11 presents the seroresponse (ie, > 4 fold increase from baseline) by assay. These results indicate that the pseudo-neutralising antibodies exhibited the lowest proportion of seroresponse (59.7% and 85.5% for the 4-week and 12-week dosing intervals respectively), while both live-neutralising and spike-binding seroresponse rates exceeded 95%.

Table 11 Historic Seroresponse Rates by Dosing Interval (>4-fold Increase from Baseline, Standard Dose Immunogenicity Analysis Set)

	Post-1st Dose		Post-2nd dose with a 4-week dosing interval[a]		Post-2nd dose with a 12-dose week interval[b]	
Assay	**N**	**Proportion**	**N**	**Proportion**	**N**	**Proportion**
Pseudo	499	32%	382	59.7%	117	85.5%
Live	96	75%	95	96.8%	-	-
Spike	940	96.6%	636	95.9%	304	99.3%

[a] Estimates from pooled COV001/002/003/005 study data from participants with 2- to 6-week dosing interval
[b] Estimates from pooled COV001/002/003/005 study data from participants with 10- to 14-week dosing interval

Under the assumption that the immunogenicity responses (ie, geometric mean antibody titres) associated with AZD2816 will be similar to the responses associated with AZD1222 in participants that received 2 standard doses in the pooled COV001/002/003/005 studies, in which standard deviations ranged from 0.72 to 1.2 (Table 10), 150 participants will provide a 95% confidence interval half-width between 0.115 and 0.192 (see Table 12). Similarly, 300 participants will provide a 95% confidence interval half-width between 0.081 and 0.136.

Table 12 Estimated Half-width of the 95% Confidence Intervals for Immunogenicity Responses (Geometric Mean Titres) Based on Historic Immunogenicity Assay Variances and the Proposed Sample Sizes

Standard Deviation	Number of participants	Estimated half-width of the 95% confidence interval (natural log scale)
0.72	150	0.115
	300	0.081
0.83	150	0.133
	300	0.094
0.96	150	0.154
	300	0.109
1.1	150	0.176
	300	0.124
1.2	150	0.192
	300	0.136

Under the assumption that the seroresponse rates associated with AZD2816 will be similar to the response rates in adults that received 2 standard doses of AZD1222 in the pooled COV001/002/003/005 studies (Table 11), 150 participants will provide a 95% confidence interval half-width between 1.33% and 7.85%, and 300 participants will provide a 95% confidence interval half-width between 0.94% and 5.55% (Table 13).

Table 13 Estimated Half-Width of the 95% Confidence Interval for the Seroresponses Rates based on Historic Seroconversion Rates and Proposed Sample Sizes

Observed seroconversion rate	Number of participants	Estimated half-width of the 95% confidence interval (natural log scale)
59.7%	150	7.85%
	300	5.55%
85.5%	150	5.63%
	300	3.98%
95.9%	150	3.17%
	300	2.24%
96.8%	150	2.82%
	300	1.99%
99.3%	150	1.33%
	300	0.94%

For a fixed sample size, the precision with which the 95% confidence interval of the binary seroresponse rate can be estimated is a function of the response rate. Table 13 provides the lower bounds of the 95% confidence interval for selected response proportions for alternate sample sizes. For a given response rate, we can be 95% confident that the true seroresponse rate is at least as large as the lower bound of the confidence interval.

Primary Objective: Safety

Table 14 indicates the probability of observing 1 or more safety events, such as solicited injection site or systemic reactogenicity events or an unsolicited non-serious AE of a particular type for participants in each treatment arm. With the sample size of 300 participants, at least 1 participant with an AE of incidence rate of 1% can be detected with probability of about 95%.

Table 14 Probability of detecting 1 or more safety events (N = 300)

Event Frequency	Probability (> 1 event)
≥ 10% (Very Common)	> 99%
≥ 1% (Common)	95%
≥ 0.1% (Uncommon)	26%
≥ 0.01% (Rare)	3%

Secondary Objective: Compare Immunogenicity

Although this study will describe and compare the immune responses between AZD2816 and AZD1222 for selected group pairs, no-formal non-inferiority margin for either the geometric mean titre ratio or the difference in seroresponse is prospectively defined.

Under the assumption that there is no difference between treatment arms of interest (ie, a ratio of 1, difference on the log scale of 0), the power conferred by 150 and 300 participants respectively for the comparison of geometric mean titre ratio using a noninferiority margin of 1.5 (equivalent to a difference on the log scale of 0.405) is presented in Table 15.

Table 15 Power for Non-inferiority Using 1.5 as the Upper Bound of the Geometric Mean Titre Ratio

Sides	Null difference	Assumed mean treatment difference	Assumed standard deviation	N of participants in comparator group	N of participants in reference group	Alpha	Power
Upper	ln1.5 = 0.405	0	0.72	150	300	0.05	> 0.999
				300	300		> 0.999
			0.83	150	300		0.999
				300	300		> 0.999
			0.96	150	300		0.995
				300	300		> 0.999
			1.10	150	300		0.979
				300	300		0.998
			1.20	150	300		0.958
				300	300		0.994

Similarly, if there is no difference between treatment arms of interest (ie, a ratio of 1) in the proportion of seroresponders, 300 participants provides 80% power for to establish non-inferiority to within margin of -10% if the seroresponse rate is > 75%. The observed pseudo-neutralising response rates (> 4 fold increase from baseline) from the COV001/002/003/005 studies for AZD1222 were 59.7% and 85.5% for the 4-week and 12-week dosing interval respectively (Table 11). A population of 300 participants provides 70% power to detect non-inferiority (using a non-inferiority margin of -10%) if the observed response rate is 59.7% (Table 16).

Table 16 Power for Non-inferiority Using -10% as the Upper Bound of the Difference in Seroresponse Rate

Sides	Null proportion difference	Assumed proportion of seroresponders in both groups	Assumed difference in proportion of seroresponders	N in comparator group	N in reference group	Alpha	Power
Lower	-0.1	0.597	0	150	300	0.05	0.665
				300	300		0.805
		0.855		150	300		0.904
				300	300		0.963
		0.959		150	300		0.999
				300	300		> 0.999
		0.968		150	300		> 0.999
				300	300		> 0.999
		0.993		150	300		> 0.999
				300	300		> 0.999

9.3 Populations for Analyses

The following populations are defined:

Table 17 Populations for Analysis

Population	Description
All participants analysis set	All participants screened for the study, to be used for reporting disposition and screening failures.
Seronegative full analysis set	All randomized seronegative participants who received at least 1 dose of study intervention, irrespective of their protocol adherence and continued participation in the study. Participants will be analysed according to their randomized treatment irrespective of whether or not they have prematurely discontinued, according to the intent-to-treat principle. Participants who withdraw consent to participate in the study will be included up to the date of their study withdrawal.
Safety analysis set	The safety analysis set consists of all participants (seropositive and seronegative at screening) who have received at least 1 dose of study intervention. Erroneously-treated participants (eg, those randomized to one treatment but actually received another treatment) are accounted for in this analysis set by assigning them to the treatment they actually received. A participant who has on one or several occasions received active study intervention is classified as active for all summaries, including summaries by dose. This will be the primary analysis set for all safety analyses.

Table 17 Populations for Analysis

Population	Description
Seronegative immunogenicity analysis set	The immunogenicity analysis population will include all seronegative participants in the safety analysis set who have no protocol deviations or intercurrent events judged to have the potential to interfere with the generation or interpretation of an immune response. Examples of such protocol violations will be documented in the Statistical Analysis Plan. This will be the primary analysis set for all immunogenicity analyses.

Participants that are SARS-CoV-2 seropositive at screening will be included in seropositive analysis sets analogous to the above seronegative analysis sets. Further definition is provided in the Statistical Analysis Plan.

9.4 Statistical Analyses

This section provides a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints. A more technical and detailed description of the statistical analyses will be described in the Statistical Analysis Plan, and an approved version will be finalized prior to the interim analyses.

An interim analysis will occur when all participants have completed their Day 29 visit (ie, 28 days after first dose for all participants). It is estimated that this early analysis has the potential to provide clear signals about whether AZD2816 provides a strong neutralizing response against the B.1.351 strain while retaining immunogenicity against the Wuhan strain, and thereby influence programmatic decisions early. Sample size re-estimation may be performed at the interim analysis, full details of the methods and procedures are presented in the statistical analysis plan.

The primary analysis will occur when all participants have completed their Day 29 visit AND safety and immunogenicity data from all previously unvaccinated participants randomized to a 4-week dosing interval are available through completion of their visit 28 days after the second priming dose.

A secondary analysis will occur when all participants have completed their Day 29 visit AND safety and immunogenicity data from all previously unvaccinated participants (including those randomized to a 12-week dosing interval) are available through completion of the visit 28 days after the second priming dose.

The final analysis will occur when data from all vaccinated participants is available through completion of the last study visit (180 days after the single dose for previously vaccinated participants / 180 days after the second dose for unvaccinated participants).

To maintain trial integrity sponsor roles with direct input into participant management and safety monitoring will not have access to unblinded participant level data or associated outputs from the interim analyses until end of study.

Further details on the tools and processes to maintain the blind will be presented in the Study Integrity Plan.

9.4.1 General Considerations

An interim analysis will occur when all participants have completed their Day 29 visit (ie, 28 days after first dose for all participants). It is estimated that this early analysis has the potential to provide clear signals about whether AZD2816 provides a strong neutralizing response against the B.1.351 strain while retaining immunogenicity against the Wuhan strain, and thereby influence programmatic decisions early. Sample size re-estimation may be performed at the interim analysis, full details of the methods and procedures are presented in the statistical analysis plan.

The primary analysis will occur when all participants have completed their Day 29 visit and safety and immunogenicity data from all unvaccinated participants randomized to a 4-week dosing interval are available through completion of their visit 28 days after the second priming dose.

A secondary analysis will occur when all participants have completed their Day 29 visit and safety and immunogenicity data from all unvaccinated participants (including those randomized to a 12-week dosing interval) are available through completion of the visit 28 days after the second dose.

The final analysis will occur when data from all vaccinated participants is available through completion of the last study visit (180 days after the single dose for previously vaccinated participants / 180 days after the second dose for unvaccinated participants).

To maintain trial integrity sponsor roles with direct input into participant management and safety monitoring will not have access to unblinded participant level data or associated outputs from the interim analyses until end of study.

Further details on the tools and processes to maintain the blind will be presented in the Study Integrity Plan.

9.4.2 Safety

9.4.2.1 Primary Endpoints

Overview

Descriptive analyses will support evaluation of safety, reactogenicity and immunogenicity. The primary safety analysis includes:

- Incidence of local and systemic solicited AEs for 7 days following each vaccination will be summarised by day and overall.
- Incidence of unsolicited AEs for 28 days following each vaccination will be summarised by system organ class and preferred term, and by relationship to vaccination as assessed by the investigator.
- MAAEs, SAEs, and AESIs following the first vaccination and throughout the study duration will be summarised by system organ class and preferred term and by relationship to vaccination as assessed by the investigator.
- The change from baseline for safety laboratory measures at 7 and 28 days after vaccination.

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

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

A listing will cover details for each individual AE. Full details of all AE analyses will be provided in the Statistical Analysis Plan, including intercurrent events for safety due to potential unblinding of participants for administration of licensed and/or approved SARS-CoV-2 or COVID-19 vaccine.

At the time of the interim analysis, group assignment will not be presented when safety event data has the potential to unblind participant's study group attribution.

9.4.2.2 Other Safety Endpoints

Vital Signs

Vital sign measurements will be performed as specified in the Schedule of Activities (Section 1.3). The set of assessments will include pulse oximetry, blood pressure, and body temperature.

Details of all vital sign analyses will be provided in the Statistical Analysis Plan, which will include descriptive statistics presented for observed values for all vital sign parameters.

COVID-19

This study will describe the incidence of COVID-19 adverse events from the first dose of the vaccine to study end (180 days post-vaccination). Descriptive statistics will be produced based on the safety analysis set. Full details will be documented in the statistical analysis plan.

9.4.3 Immunogenicity

9.4.3.1 Immunogenicity Endpoints

The immunogenicity endpoints of interest in this study are:

- Geometric mean antibody titre.
- Seroresponse, defined as ≥ 4-fold increase in the geometric mean antibody titre from baseline

Both the geometric mean antibody titre and seroresponse of participants will be summarized descriptively by strain, treatment arm, and timepoint for the immunogenicity population.

9.4.3.1.1 Estimand framework for immunogenicity descriptions and comparisons

Target populations:

1) Previously unvaccinated participants

    a. Seronegative Analysis Set: and with no evidence of prior or current infection

2) Participants who previously received SARS-CoV-2 vaccination with either AZD1222 or a licensed mRNA vaccine according to the authorized dose and dosing regimen at least 3 months prior to first study intervention (see Section 5.1.2).

Outcome variable: neutralizing antibody and binding titres to SARS-CoV-2 at 28 days after each treatment administration (1 treatment administration for the previously vaccinated population and 2 planned treatment administrations for the unvaccinated population).

Treatment conditions:

Previously unvaccinated population

- 2 doses of AZD1222 given on Day 1 and on Day 29 (4-week interval)
- 2 doses of AZD2816 given on Day 1 and on Day 29 (4-week dosing interval)
- 2 doses of AZD2816 given on Day 1 and on Day 85 (12-week dosing interval)

Previously vaccinated population

- 1 dose of AZD1222 given on Day 1.
- 1 dose of AZD2816 given on Day 1.

Intercurrent events: the following intercurrent events could impact the antibody levels achieved:

- missing the second vaccination (for the unvaccinated population)
- receiving of immune-modifying drugs or vaccines
- subsequent infection with SARS-CoV-2.

All immunogenicity descriptions and comparisons will use the principal stratum strategy, ie, all analyses will exclude participants who experience any of the intercurrent events above

Population-level summary:

Descriptive Analyses (see Table 19 and Table 20)

- geometric means of the antibody titres
- seroresponse proportions

Comparative Analyses (see Table 21 and Table 22)

- ratio of geometric means of the antibody titres.
- difference in seroresponse proportion

Planned Descriptive Analyses:

Table 19 and Table 20 present planned descriptive immunogenicity analyses for the unvaccinated and previously vaccinated populations respectively (each one exploring an individual treatment arm at a specific timepoint against a particular strain).

The tables show that without introduction of further variants, there are 24 planned descriptive analyses for the unvaccinated population and 16 planned descriptive analyses for the previously immunised population (index). Within each table there is an analysis key which describes the population (see Table 18). The descriptive analyses presented in Tables 19 and 20 will be repeated for the subset of participants who are seropositive at screening.

Table 18 Description of the Analysis Keys for Tables 19 and 20

Population	Analysis Key	Example
Previously unvaccinated	Primary series dosing interval: P4 (4-week dosing interval) or P12 (12-week dosing interval) Treatment received: 1222 (2 doses of AZD1222) or 2816 (2 doses of AZD2816) Strain: W (Wuhan-Hu-1) or V (Variant B.1.351) Analysis Timepoint: 1 (28 days post-dose 1) 2 (28 days post-dose 2)	[P4:1222:W:1] = Immunogenicity following primary vaccination with a 4-week dosing interval of 2 doses of AZD1222 against Wuhan-Hu-1 28 days post-dose 1
Previously vaccinated	Pre-study primary vaccination: P1222 (2 doses of AZD1222) or PmRNA (2 doses of an mRNA vaccine) Treatment received: B1222 (1 booster dose of AZD1222) or B2816 (1 booster dose of AZD2816) Strain: W (Wuhan-Hu-1) or V (Variant B.1.351)	[P1222:B1222:V] = Immunogenicity in participants who were previously vaccinated with 2 doses of AZD1222 as primary vaccination series and received a single boost dose of AZD1222 against the B.1.351 variant

Table 19 Immunogenicity Descriptive Analysis for Previously Unvaccinated Treatment Groups (with Separate Seronegative and Seropositive Analyses)

Objective	Treatment	Dosing interval	Strain	Timepoint	Endpoint	Index	Analysis Key
To describe the humoral immune response against the B.1.351 and Wuhan-Hu-1 variant strains induced by a 2-dose primary vaccination with AZD1222 with a 4-week interval in unvaccinated participants	AZD1222	4 weeks	Wuhan-Hu-1	28 days after 1st dose	GMT	1	[P4:1222:W:1]
					Seroresponse	2	
				28 days after 2nd dose	GMT	3	[P4:1222:W:2]
					Seroresponse	4	
			B.1.351	28 days after 1st dose	GMT	5	[P4:1222:V:1]
					Seroresponse	6	
				28 days after 2nd dose	GMT	7	[P4:1222:V:2]
					Seroresponse	8	
To assess the humoral immune response against the B.1.351 and Wuhan-Hu-1 strains induced by a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in unvaccinated participants	AZD2816	4 weeks	Wuhan-Hu-1	28 days after 1st dose	GMT	9	[P4:2816:W:1]
					Seroresponse	10	
				28 days after 2nd dose	GMT	11	[P4:2816:W:2]
					Seroresponse	12	
			B.1.351	28 days after 1st dose	GMT	13	[P4:2816:V:1]
					Seroresponse	14	
				28 days after 2nd dose	GMT	15	[P4:2816:V:2]
					Seroresponse	16	
To describe the humoral immune response against the B.1.351 and Wuhan-Hu-1 variant strains induced by a 2-dose primary vaccination with AZD2816 with a 12-week interval in unvaccinated participants	AZD2816	12 weeks	Wuhan-Hu-1	28 days after 1st dose	GMT	17	[P12:2816:W:1]
					Seroresponse	18	
				28 days after 2nd dose	GMT	19	[P12:2816:W:2]
					Seroresponse	20	
			B.1.351	28 days after 1st dose	GMT	21	[P12:2816:V:1]
					Seroresponse	22	
				28 days after 2nd dose	GMT	23	[P12:2816:V:2]
					Seroresponse	24	

GMT: Geometric mean titre

Table 20 Immunogenicity Descriptive Analysis for Previously Vaccinated Treatment Groups (with Separate Seronegative and Seropositive Analyses)

Objective	Primary vaccination	Booster Treatment	Strain	Timepoint	Endpoint	Index	Analysis Key
To assess the humoral immune response against the B.1.351 and Wuhan-Hu-1 strains induced by 1 dose of AZD1222 in participants previously vaccinated with 2 doses of AZD1222	AZD1222	AZD1222	Wuhan-Hu-1	28 days after booster dose	GMT	1	[P1222:B1222:W]
					Seroresponse	2	
			B.1.351	28 days after booster dose	GMT	3	[P1222:B1222:V]
					Seroresponse	4	
To assess the humoral immune response against the B.1.351 and Wuhan-Hu-1 strains induced by 1 dose of AZD2816 in participants previously vaccinated with 2-doses of AZD1222		AZD2816	Wuhan-Hu-1	28 days after booster dose	GMT	5	[P1222:B2816:W]
					Seroresponse	6	
			B.1.351	28 days after booster dose	GMT	7	[P1222:B2816:V]
					Seroresponse	8	
To assess the humoral immune response against the B.1.351 and Wuhan-Hu-1 strains induced by 1 dose of AZD2816 in participants previously vaccinated with 2-doses of a SARS-CoV-2 mRNA vaccine	mRNA	AZD2816	Wuhan-Hu-1	28 days after booster dose	GMT	9	[PmRNA:B2816:W]
					Seroresponse	10	
			B.1.351	28 days after booster dose	GMT	11	[PmRNA:B2816:V]
					Seroresponse	12	

GMT: Geometric mean titre

In addition to descriptive immunogenicity assessments for all treatment arms, geometric mean titre ratios and differences in seroresponse will be evaluated for the pairs of groups as detailed in Table 21 and Table 22. For each pair, the two-sided 95% confidence intervals for the ratio of the geometric mean titre and difference in seroresponse will be calculated. The geometric mean titre ratio assume a normal distribution for the natural log of the concentration. All confidence intervals will be unadjusted for multiple analyses and are provided solely as a guide to clinical and scientific judgment. It is acknowledged that the chance of falsely concluding that one or more differences in immunogenicity outcomes exist will be greater than the nominal two-sided 0.05 level used for each individual comparison.

Table 21 Immunogenicity Comparisons for Previously Unvaccinated Groups

Objective	$\frac{[\mathbf{GMT}_{\mathbf{comparator}}]}{[\mathbf{GMT}_{\mathbf{reference}}]}$	$\Delta = [\mathbf{Seroresponse}_{\mathbf{comparator}}] - [\mathbf{Seroresponse}_{\mathbf{reference}}]$
To evaluate the immune response against the B.1.351 and Wuhan-Hu-1 variant strain elicited by a primary 2-dose vaccination with AZD2816 with a 4-week dosing interval relative to the response elicited by a primary 2-dose vaccination with AZD1222 with a 4-week interval in previously unvaccinated seronegative participants	$\frac{[\mathrm{P4:2816:V:2}]}{[\mathrm{P4:1222:W:2}]}$	$[\mathrm{P4:2816:V:2}] - [\mathrm{P4:1222:W:2}]$
	$\frac{[P4:2816:V:1]}{[P4:1222:W:1]}$	$[\mathrm{P4:2816:V:1}] - [\mathrm{P4:1222:W:1}]$
	$\frac{[\mathrm{P4:2816:W:2}]}{[\mathrm{P4:1222:W:2}]}$	$[\mathrm{P4:2816:W:2}] - [\mathrm{P4:1222:W:2}]$
	$\frac{[\mathrm{P4:2816:W:1}]}{[P4:1222:W:1]}$	$[\mathrm{P4:2816:W:1}] - [\mathrm{P4:1222:W:1}]$
	$\frac{[\mathrm{P4:2816:V:2}]}{[\mathrm{P4:1222:V:2}]}$	$[\mathrm{P4:2816:V:2}] - [\mathrm{P4:1222:V:2}]$
	$\frac{[P4:2816:V:1]}{[P4:1222:V:1]}$	$[\mathrm{P4:2816:V:1}] - [\mathrm{P4:1222:V:1}]$
To evaluate the immune responses against the B.1.351 variant strain and the Wuhan-Hu-1 strain elicited by a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval relative to the response elicited by a 2-dose primary vaccination with AZD2816 with a 4-week interval in previously unvaccinated seronegative participants	$\frac{[\mathrm{P12:2816:W:2}]}{[\mathrm{P4:2816:W:2}]}$	$[\mathrm{P12:2816:W:2}] - [\mathrm{P4:2816:W:2}]$
	$\frac{[P12:2816:W:1]}{[P4:2816:W:1]}$	$[\mathrm{P12:2816:W:1}] - [\mathrm{P4:2816:W:1}]$
	$\frac{[P12:2816:V:2]}{[\mathrm{P4:2816:V:2}]}$	$[\mathrm{P12:2816:V:2}] - [\mathrm{P4:2816:V:2}]$
	$\frac{[P4:2816:V:2]}{[\mathrm{P4:2816:V:2}]}$	$[\mathrm{P12:2816:V:1}] - [\mathrm{P4:2816:V:1}]$
	$\frac{[P12:2816:V:1]}{[P4:1222:V:1]}$	$[\mathrm{P12:2816:V:1}] - [\mathrm{P4:1222:V:1}]$

Table 22 Immunogenicity Comparisons for Previously Vaccinated Groups

Objective	$\frac{[\mathbf{GMT}_{\mathbf{comparator}}]}{[\mathbf{GMT}_{\mathbf{reference}}]}$	$\Delta = [\mathbf{Seroresponse}_{\mathbf{comparator}}] - [\mathbf{Seroresponse}_{\mathbf{reference}}]$
To evaluate the immune responses against the B.1.3.51 variant strain and Wuhan-Hu-1 strain elicited by 1 dose of AZD2816 in seronegative participants previously vaccinated with 2 doses of AZD1222 relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in seronegative unvaccinated participants	$\frac{[\mathrm{P1222:B2816:V}]}{[\mathrm{P4:1222:W}]}$	$[\mathrm{P1222:B2816:V}] - [\mathrm{P4:1222:W}]$
	$\frac{[\mathrm{P1222:B2816:W}]}{[\mathrm{P4:1222:W}]}$	$[\mathrm{P1222:B2816:W}] - [\mathrm{P4:1222:W}]$
To evaluate the immune responses against the B.1.351 variant strain and Wuhan-Hu-1 strain elicited by 1 dose of AZD2816 in seronegative participants previously vaccinated with 2 doses of a SARS-CoV-2 mRNA vaccine relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in seronegative unvaccinated participants	$\frac{[\mathrm{PmRNA:B2816:V}]}{[\mathrm{P4:1222:W}]}$	$[\mathrm{PmRNA:B2816:V}] - [\mathrm{P4:1222:W}]$
	$\frac{[\mathrm{PmRNA:B2816:W}]}{[\mathrm{P4:1222:W}]}$	$[\mathrm{PmRNA:B2816:W}] - [\mathrm{P4:1222:W}]$
To evaluate the immune response against the B.1.351 and Wuhan-Hu-1 variant strain elicited by 1 dose of AZD2816 in seronegative participants previously vaccinated with a mRNA vaccine relative to the response with 1 dose of AZD1222 in seronegative participants previously vaccinated with 2 doses of AZD1222	$\frac{[\mathrm{PmRNA:B2816:V}]}{[\mathrm{P1222:B1222:W}]}$	$[\mathrm{PmRNA:B2816:V}] - [\mathrm{P1222:B1222:W}]$
	$\frac{[\mathrm{PmRNA:B2816:W}]}{[\mathrm{P1222:B1222:W}]}$	$[\mathrm{PmRNA:B2816:W}] - [\mathrm{P1222:B1222:W}]$
	$\frac{[\mathrm{PmRNA:B2816:V}]}{[\mathrm{P1222:B1222:V}]}$	$[\mathrm{PmRNA:B2816:V}] - [\mathrm{P1222:B1222:V}]$
To evaluate the immune responses against the B.1.351 variant strain and the Wuhan-Hu-1 strain elicited by 1 dose of AZD2816 relative to the response with 1 dose of AZD1222 in seronegative participants previously vaccinated with 2 doses of AZD1222	$\frac{[\mathrm{P1222:B2816:V}]}{[\mathrm{P1222:B1222:W}]}$	$[\mathrm{P1222:B2816:V}] - [\mathrm{P1222:B1222:W}]$
	$\frac{[\mathrm{P1222:B2816:W}]}{[\mathrm{P1222:B1222:W}]}$	$[\mathrm{P1222:B2816:W}] - [\mathrm{P1222:B1222:W}]$
	$\frac{[\mathrm{P1222:B2816:V}]}{[\mathrm{P1222:B1222:V}]}$	$[\mathrm{P1222:B2816:V}] - [\mathrm{P1222:B1222:V}]$

9.4.4 Data Safety Monitoring Board

An independent COVID-19 Vaccine Data Safety Monitoring Board will provide oversight, to ensure safe and ethical conduct of the study. During the study, the benefit/risk assessment will be continuously monitored by the Board to ensure that the balance remains favourable. Further details, composition, and operation of the COVID-19 Vaccine Data Safety Monitoring Board will be described in a separate charter. For further details, see Appendix A 5.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Not applicable.

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

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

Regulatory Reporting Requirements for SAEs

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

A 2 Financial Disclosure

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

A 3 Informed Consent Process

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

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

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

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

A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

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

A 5 Committee Structure

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

A COVID-19 Vaccine Data Safety Monitoring Board comprised of independent experts will be convened to provide oversight and to ensure safe and ethical conduct of the study. The COVID 19 Vaccine Data Safety Monitoring Board will have the responsibility of evaluating cumulative safety and other clinical study data at regular intervals and making appropriate recommendations based on the available data. During the study, the benefit/risk assessment will be continuously monitored by the COVID-19 Vaccine Data Safety Monitoring Board to ensure that the balance remains favourable. Full details of the COVID-19 Vaccine Data Safety Monitoring Board composition and operations can be found in the COVID-19 Vaccine Data Safety Monitoring Board Charter.

An independent Neurological AESI Expert Committee will be available to review and provide on request about the diagnosis and causality assessment of selected neurological AEs of special interest occurring in the study. Details on the composition and operation of this committee are described in the Neurological AESI Expert Committee Charter.

A 6 Dissemination of Clinical Study Data

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

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

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

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A 9 Study and Site Start and Closure

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

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or ICH/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 IRB/IECs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of 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 SAEs and non-SAEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

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

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

AEs for **malignant tumours** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-SAE**. 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 hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life Threatening

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

Hospitalization

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

Important Medical Event or Medical Treatment

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

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

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

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

Intensity Rating Scale

A revised toxicity grading scale found in the US FDA guidance for healthy volunteers enrolled in a preventive vaccine clinical study (FDA 2007) will be utilized for all events with an assigned severity grading including Grade 5.

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

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

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 investigational product.

- 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 investigational product?
- Consistency with known investigational product profile. Was the AE consistent with the previous knowledge of the suspect investigational product (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 investigational product?
- 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 investigational product was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

- Is this a recognized feature of overdose of the investigational medicinal product?
- 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 3 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 investigational product, but rather a human or process related failure while the investigational product 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 investigational product
- 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:

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

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

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

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

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

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

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

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

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

C 2 Withdrawal of Informed Consent for Donated Biological Samples

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

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

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

The investigator:

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

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

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

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

Appendix D 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 23: Clinical Abnormalities, Local Reactions to Injectable Product
- Table 24: Clinical Abnormalities, Vital Signs
- Table 25: Clinical Abnormalities, Systemic (General or Illness)

Table 23 Tables for Clinical Abnormalities: Local Reactions to Injectable Product

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

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

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

ER: emergency room.

Table 24 Tables for Clinical Abnormalities: Vital Signs

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

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

Table 25 Tables for Clinical Abnormalities: Systemic (General or Illness)

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

Appendix E Adverse Events of Special Interest

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

Table 26 Adverse Events of Special Interest

Category	Medical Concept
Neurologic	Generalized convulsion: episodes of neuronal hyperactivity most commonly resulting in sudden, involuntary muscular contractions. They may also manifest as sensory disturbances, autonomic dysfunction and behavioural abnormalities, and impairment or loss of consciousness.
	Guillain-Barré syndrome: a peripheral nerve demyelinating disease, which can present as temporary ascending paralysis.
	Acute disseminated encephalomyelitis: defined as a uniphasic syndrome of brain inflammation and demyelination occurring in temporal association with an antecedent immunologic challenge, such as infection or an immunization. ADEM most commonly occurs in the paediatric population.
	Other neurologic events: include new onset event (acute or subacute) motor and sensory disturbances (eg, weakness, numbness, paraesthesia, hypoesthesia, hyperesthesia, dysesthesias), bowel/bladder dysfunction, gait impairment, or visual disturbance, or any event of myelitis, encephalomyelitis, myelitis transverse, or other sudden neurological deficit.
Vascular	Thrombotic, thromboembolic, and neurovascular events: events that can manifest as transient or permanent vision problems, dizziness, trouble understanding, facial droop, slurred speech, unilateral weakness, deep vein thrombosis with swollen, warm or painful leg, pulmonary embolism with shortness of breath, chest pain or irregular heart rate.
Hematologic	Thrombocytopenia: a disorder in which there is an abnormally low platelet count; a normal platelet count ranges from 150 000 to 450 000 platelets per µL.
Immunologic	Vasculitides: a group of related disorders characterized by inflammation of blood vessels (vasculitis) leading to tissue or end-organ injury.
	Anaphylaxis: an acute hypersensitivity reaction with multi-organ-system involvement that can present as, or rapidly progress to, a severe life-threatening reaction requiring immediate medical attention.
	Vaccine-associated enhanced respiratory disease: pathogenicity has been linked to a vaccine immune response characterized by induction of non-neutralizing antibodies, and a T-cell response of the Th2 type with hypereosinophilia (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: 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 27.

Table 27 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

Table 27 List of Potential Immune-mediated Medical Conditions

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, Bechet's syndrome, leukocytoclastic vasculitis

Table 27 List of Potential Immune-mediated Medical Conditions

Category	Condition
Other	Antiphospholipid syndrome
	Autoimmune haemolytic anaemia
	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 anaemia
	Raynaud's phenomenon
	Sarcoidosis
	Sjögren's syndrome
	Stevens-Johnson syndrome
	Uveitis

Appendix F Actions Required in Cases of any Thrombotic Events With Thrombocytopenia and/or Bleeding

F 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of thrombotic events with thrombocytopenia and/or bleeding. It is not intended to be a comprehensive guide to the management of all venous thromboembolic events.

During the course of the study, the investigator will remain vigilant for occurrence of thrombotic events with thrombocytopenia and/or bleeding. Appropriate investigations (eg, imaging) to diagnose these events should be made on a case-by-case basis. The investigator is responsible for determining whether a participant meets criteria for thrombotic events with thrombocytopenia and/or bleeding at any point during the study.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting criteria for thrombotic events with thrombocytopenia and/or bleeding. The Study Physician contacts the investigator to provide guidance, discuss, and agree an approach for the participant's follow-up and the continuous review of data. Guidance from the International Society of Thrombosis and Haemostasis for management of thrombocytopenic thromboembolism occurring after vaccination can be found at www.isth.org. Notably, participants should only be treated with heparin if a test for heparin-induced thrombocytopenia antibodies is negative. An alternative explanation for thrombocytopenia should be considered (eg, alcohol use, liver cirrhosis, concomitant medications, exposure to toxic chemicals, viral infections).

The investigator is responsible for recording data pertaining to thrombotic events with thrombocytopenia and/or bleeding and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

F 2 Tests that Should Be Considered if Thrombotic Events With Thrombocytopenia and/or Bleeding Are Suspected

The following tests should be considered, but not limited to:

1. Measurement of platelet levels, prothrombin time, activated partial thromboplastin time, D-dimer levels, and fibrinogen levels

2. Complete blood count, reticulocyte count, blood film, haptoglobins

3. Anti-platelet factor 4 antibodies

4. Anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies, rheumatoid factor, human leucocyte antigen B27, ADAMTS13 activity, anti-cardiolipin antibodies IgG + IgM, and anti-B2GPI antibodies IgG + IgM

5. Complement (eg, C3, C4, complement complex C5b-9, C5a), autoantibodies (eg, antinuclear IgG, anti-double stranded DNA IgG, anti-Smith IgG, anti-SSA IgG, anti-SSB IgG, anti-Jo1 IgG, anti-MPO IgG, anti-PR3 IgG, anti-glomerular basement membrane IgG)

6. Factor V Leiden, Factor II (prothrombin) variant

7. Platelet activation markers and functional assays (eg: sCD40L, soluble glycoproteins, degranulation markers [PF4, vWF, P-selectin, annexin V]), anti-PF4-plasma-serotonin release assay (if anti-PF4 ELISA positive)

8. Inflammatory markers: TNFa, IL-1, IL-4, IL-6, IL-10, IL-13

9. Cell adhesion molecules: VCAM, ICAM, E-selectin

10. Adenovirus serology

11. Additional viral serology: Cytomegalovirus (IgG and IgM), Ebstein-Barr virus (IgG and IgM), HIV, Parvo virus B19

12. COVID-19 testing, including PCR and serology

13. Calculation of an International Society of Thrombosis and Haemostatis score for Disseminated Intravascular Coagulation (derived from platelet levels, fibrinogen, and D-Dimer)

Appendix G Abbreviations

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ChAdOx1 MERS	Chimpanzee adenovirus Ox1 with MERS Spike antigen
ChAdOx1 nCoV-19	AZD1222 when initially developed by the University of Oxford
COVID-19	Coronavirus disease 2019
eCRF	electronic case report form
e-Diary	electronic diary
GMT	Geometric mean titre
ICF	Informed consent form
ICH/GCP	International Council for Harmonisation/Good Clinical Practice
IRB/IEC	Institutional Review Board/ Independent Ethics Committee
IRT	Interactive Response Technology
MAAEs	Medically attended adverse events
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
S	Spike
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome-coronavirus-2

Appendix H Protocol Amendment History

Not applicable.

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Clinical Study Protocol	
Study Intervention	AZD2816
Study Code	D7220C00001
Version	Amendment 1
Date	2 June 2021

TITLE PAGE

A Phase II/III Partially Double-Blinded, Randomised, Multinational, Active-Controlled Study in Both Previously Vaccinated and Unvaccinated Adults to Determine the Safety and Immunogenicity of AZD2816, a Vaccine for the Prevention of COVID-19 Caused by Variant Strains of SARS-CoV-2

Sponsor Name:	**AstraZeneca AB**
Legal Registered Address:	151 85 Södertälje, Sweden
Regulatory Agency Identifier Numbers:	EudraCT: 2021-002530-17

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: D7220C00001

Amendment Number: 1

Study Intervention: AZD2816

Study Phase: II/III

Short Title: Phase II/III Study of AZD2816, a Vaccine for the Prevention of COVID-19 in Adults

Study Physician Name and Contact Information will be provided separately.

International Coordinating Investigator: Andrew J Pollard, FRCPCH PhD FMedSci
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PROTOCOL AMENDMENT SUMMARY OF CHANGES

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Version 1	14 May 2021

Amendment 1: 2 June 2021

Version 1 of the protocol was amended prior to the commencement of the study (ie, prior to approval of the protocol by an ethics committee) based on feedback from internal and regulatory authority reviews. The most substantial changes were as follows:

- addition of 2 treatment arms: 1) AZD1222 as a single booster vaccination in participants previously vaccinated with an mRNA COVID-19 vaccine and 2) heterologous vaccination with AZD1222 plus AZD2816 in previously unvaccinated participants
- further definition of analysis sets
- addition of thrombotic events with thrombocytopenia as a discontinuation criteria

In addition, corrections and revisions to text to improve readability were made.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A phase II/III partially double-blinded, randomised, multinational, active-controlled study in both previously vaccinated and unvaccinated adults to determine the safety and immunogenicity of AZD2816, a vaccine for the prevention of COVID-19 caused by variant strains of SARS-CoV-2.

Short Title: Phase II/III study of AZD2816, a vaccine for the prevention of COVID-19 in adults.

Rationale: Recently, several variants of the SARS-CoV-2 virus with increased transmissibility have emerged, including B.1.1.7, first identified in the UK, P.1, first identified in Brazil, and B.1.351, first identified in South Africa. In an ongoing clinical trial of AZD1222 in South Africa, interim results failed to show protection against mild to moderate disease caused by the B.1.351 variant; protection against severe disease could not be determined as no severe cases were identified (Madhi et al 2021).

Based on available evidence about vaccine effectiveness and molecular epidemiology of emerging variants, B.1.351 is estimated to have a potential to escape vaccine-induced immunity. B.1.351 carries sequence mutations in common with other variants of concerns; immunity to B.1.351 therefore has the potential to provide some cross-immunity against other emerging strains. Development of candidate vaccines that include the B.1.351 S-protein variant is underway. AstraZeneca is developing AZD2816, a vaccine against the B.1.351 SARS-CoV-2 variant using the same ChAdOx1 platform and manufacturing processes used for AstraZeneca's currently available COVD-19 vaccine, AZD1222.

Objectives and Endpoints:

The purpose of this study is to demonstrate the safety and characterize the immunogenicity of AZD2816, AstraZeneca's candidate ChAdOx1 vector vaccine against SARS-CoV-2 variant strain B.1.351, when administered:

- As a single dose to SARS-CoV-2 seronegative individuals who previously received a 2-dose primary vaccination against SARS-CoV-2 with AZD1222 or an mRNA COVID-19 vaccine
- As a 2-dose primary homologous vaccination to SARS-CoV-2 seronegative individuals who are unvaccinated
- As the second dose of 2-dose primary heterologous vaccination (with AZD1222 as first dose) to SARS-CoV-2 seronegative individuals who are unvaccinated.

The following table lists the primary and secondary endpoints:

Objectives	Endpoints
Safety Objectives	
- Primary	
Previously vaccinated seronegative participants	
To characterize the safety and tolerability of 1 dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose
Unvaccinated seronegative participants	
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose
- Secondary	
Previously vaccinated seronegative participants	
To characterize the safety and tolerability of 1 dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of 1 dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of 1 dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of 1 dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination

To characterize the extended safety of 1 dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
Unvaccinated seronegative participants	
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of a heterologous 2-dose primary vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of a 2-dose primary heterologous vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
Immunogenicity objectives	
- Primary (descriptive)	
Previously vaccinated seronegative participants	
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by 1 dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre)

1 dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
Unvaccinated seronegative participants	
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in unvaccinated seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
- Secondary (descriptive)	
Previously vaccinated seronegative participants	
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by 1 dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by 1 dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
Unvaccinated seronegative participants	
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by a 2-dose primary vaccination with AZD1222 with a 4-week interval in unvaccinated seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by a heterologous 2-dose primary vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in unvaccinated seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by a 2-dose primary vaccination with AZD2816 with a 12-week interval in unvaccinated seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
- Secondary (comparative)	
Previously vaccinated seronegative participants receiving 1 dose versus unvaccinated seronegative participants receiving 2 doses	
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD2816 in seronegative participants previously vaccinated with AZD1222 relative to the response elicited by a 2-dose primary vaccination with	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rates of SARS-CoV-2 specific antibody binding titres and neutralization titres

AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rates of SARS-CoV-2 specific antibody binding titres and neutralization titres
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD1222 in seronegative participants previously vaccinated with AZD1222 relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rates of SARS-CoV-2 specific antibody binding titres and neutralization titres
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rates of SARS-CoV-2 specific antibody binding titres and neutralization titres
Previously vaccinated seronegative participants	
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD2816 relative to the response with 1 dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD2816 in seronegative participants previously vaccinated with an mRNA vaccine relative to the response with 1 dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD1222 relative to 1 dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rates of SARS-CoV-2 specific antibody binding titres and neutralization titres
Unvaccinated seronegative participants	
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 variant strain elicited by a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval relative to the response elicited by a 2-dose primary vaccination with	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres

AZD1222 with a 4-week interval in previously unvaccinated seronegative participants	
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 variant strain elicited by a 2-dose primary heterologous vaccination with AZD1222/AZD2816 with a 4-week dosing interval relative to the response elicited by a 2-dose primary homologous vaccination with AZD1222 with a 4-week interval in previously unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To evaluate the immune responses against the B.1.351 variant strain and the Wuhan-Hu-1 strain elicited by a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval relative to the response elicited by a 2-dose primary vaccination with AZD2816 with a 4-week interval in previously unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres

SAEs: serious adverse events; MAAEs: medically attended adverse events; AESIs: adverse events of special interest.

[a] At least a 4-fold increase in geometric mean titre from baseline

Overall Design: This is a phase II/III, multinational, randomised, partially double-blind, controlled study in both previously vaccinated and unvaccinated participants.

Disclosure Statement: This is a parallel-group preventive study with 8 treatment arms.

Number of Participants: Approximately 2250 SARS-CoV-2 nucleocapsid seronegative participants will be assigned to study intervention to support the primary and secondary objectives of this study. In addition, participants that are SARS-Cov-2 nucleocapsid seropositive at screening will be enrolled and assigned to study intervention for an exploratory analysis, with a cap of 10% of the seronegative population (ie, approximately 225 total participants).

Intervention Groups and Duration: Previously vaccinated individuals will receive 1 dose of AZD1222 or AZD2816 on Day 1. Previously unvaccinated participants will receive one of the following 2-dose vaccinations:

- 1 dose of AZD2816 on Day 1 and on Day 29
- 1 dose of AZD1222 on Day1 and on Day 29
- 1 dose of AZD1222 on Day 1 and 1 dose of AZD2816 on Day 29
- 1 dose of AZD2816 on Day 1 and on Day 85.

Participants will be followed up for safety for 180 days after last study vaccine administration.

Data Monitoring Committee: A Data Safety Monitoring Board will provide oversight to ensure safe and ethical conduct of the study.

Statistical Methods:

Sample sizes of 300 seronegative participants per group (or 150 for the AZD2816 primary vaccination with a 12-week dosing interval group) are deemed appropriate based upon available immunogenicity data from previous clinical studies with AZD1222 for the primary and secondary objectives of this study.

The safety analysis set for adverse events consists of all participants who have received at least one dose of study intervention. The immunogenicity analysis set includes all participants in the safety analysis set who have no protocol deviations or intercurrent events judged to have the potential to interfere with the generation or interpretation of an immune response.

An interim analysis will be performed when all previously vaccinated participants have completed their Day 29 visit. A primary analysis will be performed on data from 28 days after the second dose of the 4-week dosing intervals to support assessment of these 2-dose primary vaccinations. A secondary analysis will be performed on data from 28 days after the second dose of the 12-week dosing interval to support assessment of this 2-dose primary vaccination. The final analysis will be performed on data from 6 months follow-up after participant's vaccination.

1.2 Schema

Figure 1 Study Design for Previously Vaccinated Seronegative/Seropositive Participants

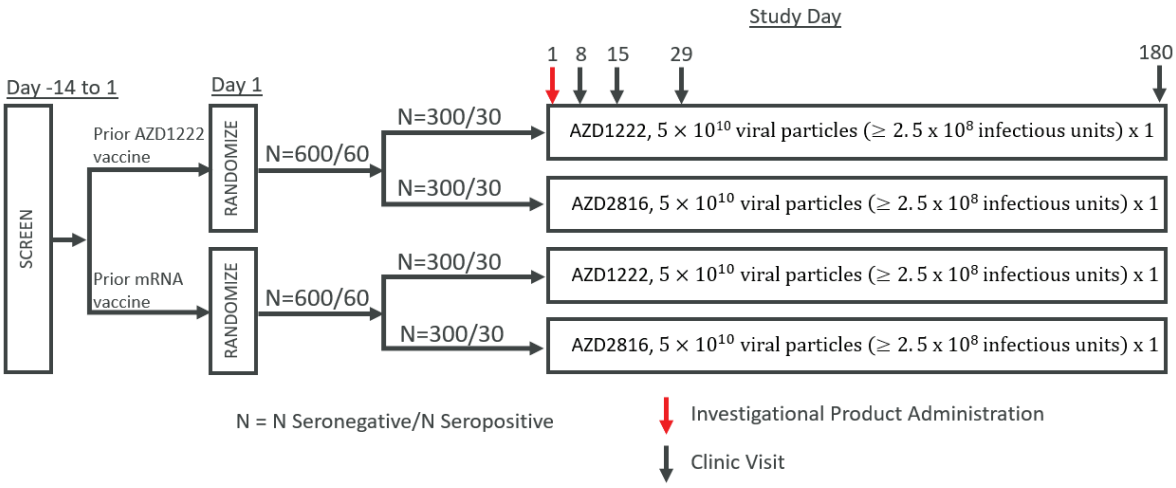
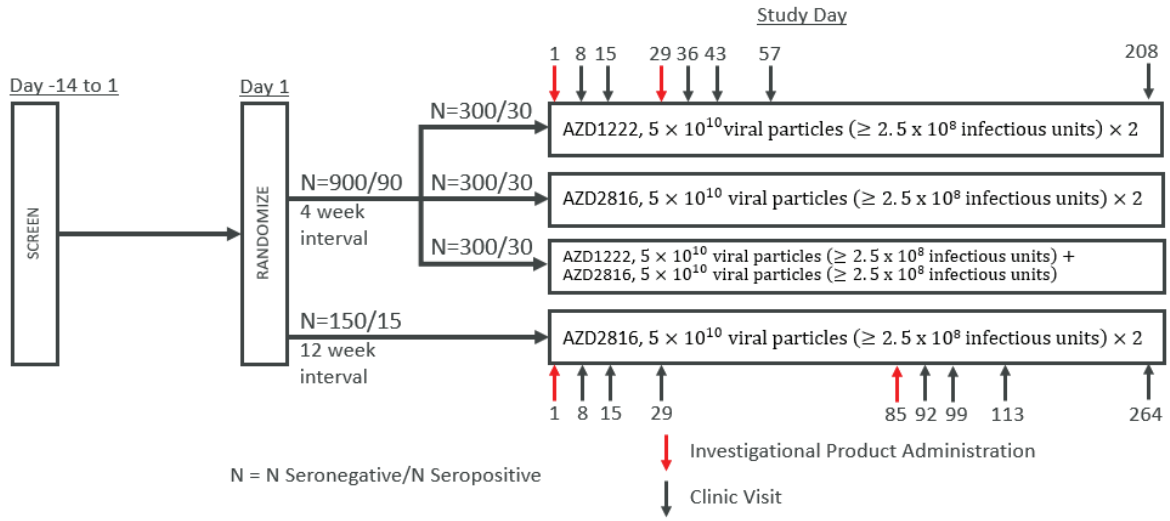


Figure 2 Study Design for Unvaccinated Seronegative/Seropositive Participants



Note: In addition to the approximately 2250 seronegative participants enrolled to support the primary/secondary objectives, seropositive participants will also be enrolled in the study to support exploratory objectives in this population, with a cap of 10% of the planned seronegative participants (ie, a maximum of 225 seropositive participants, bringing total enrollment to 2475).

1.3 Schedule of Activities

Table 1 Schedule of Activities: Screening

Procedure	Day -14 to Day 1	See Section
Informed consent	X	5.1, Appendix A 3
Demography	X	-
Medical and surgical history	X	-
Prior and concomitant medications	X	6.5
Complete physical examination, including height and weight	X	8.2.1
Vital signs	X	8.2.2
Urine pregnancy test (for women of childbearing potential only)	X	8.2.3
Clinical safety laboratory assessments	X	8.2.3
Assessment of serious adverse events	X	8.3, Appendix B
Blood sample for SARS-CoV-2 antibody testing (lateral flow test)	X	8.5.2
Verify eligibility criteria	X	5.1, 5.2

Note: Screening activities can occur at same visit as initial vaccination with investigational product (ie, Visit 1 in Table 2, Table 3, and Table 4).

Table 2 Schedule of Activities: Treatment/Follow-up Period for Participants Previously Vaccinated with 2 Doses of AZD1222 or an mRNA Vaccine

Procedure	Treatment and Follow-up Period					Section
Day	**1**	**8**	**15**	**29**	**180**	
Window (days)	**-**	**±2**	**±2**	**±3**	**±14**	
Medical and surgical history	X	-	-	-	-	-
Urine pregnancy test (women of childbearing potential)	X	-	-	-	-	8.2.3
Concomitant medications/vaccinations	X	X	X	X	X	6.5
Verify eligibility criteria	X	-	-	-	-	5.1, 5.2
Monitoring of COVID-19	X	X	X	X	X	8.3.8
Vaccine administration (after screening activities, the activities listed above, and the pre-dose sampling activities listed below)	X	-	-	-	-	6.1.1
Immunological assessments						
Serum sample to assess SARS-CoV-2 serology/neutralising antibodies	X (pre-dose)	-	X	X	X	8.5.2
Serum sample to assess additional immunogenicity	X (pre-dose)	-	X	X	X	8.5.2
Blood sample to assess B-cell and T-cell responses in a sub-group of participants	X (pre-dose)	-	X	X	X	8.5.2.3
Blood sample for B-cell and T-cell response sequencing in a sub-group of participants	X (pre-dose)	-	X	X	X	8.5.2.3
Safety assessments						
Targeted physical examination	X	-	-	-	-	8.2.1
Vital signs	X	X	X	X	X	8.2.2
e-Diary provided with training	X	-	-	-	-	8.3.7
e-Diary collected	-	X	-	-	-	8.3.7
Unsolicited AEs	X (post-dose)	X	X	X	-	8.3
MAAEs, SAEs, and AESIs	X[a]	X	X	X	X	8.3.8, 8.3.8
Clinical safety laboratory assessments	X (pre-dose)	X	-	X	X	8.2.3

[a] Only SAEs pre-dose

AE: adverse event; AESI: adverse event of special interest; MAAE: medically-attended adverse event; SAE: serious adverse event

Table 3 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 4-Week Dosing Interval

Procedure	Treatment and Follow-up Period								Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	
Day	**1**	**8**	**15**	**29**	**V4+7**	**V4+14**	**V4+28**	**V4+180**	
Window (days)	**-**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
Medical and surgical history	X	-	-	-	-	-	-	-	-
Urine pregnancy test (women of childbearing potential)	X	-	-	X	-	-	-	-	8.2.3
Concomitant medications/vaccinations	X	X	X	X	X	X	X	X	6.5
Verify eligibility criteria	X	-	-	-	-	-	-	-	5.1, 5.2
Monitoring of COVID-19	X	X	X	X	X	X	X	X	8.3.8
Vaccine administration (after screening activities, the activities listed above, and the pre-dose sampling activities listed below)	X	-	-	X	-	-	-	-	6.1.1
Immunogenicity assessments									
Serum sample for SARS-CoV-2 serology/neutralising antibodies	X (pre-dose)	-	X	X (pre-dose)	-	X	X	X	8.5.2
Serum sample for additional immunogenicity	X (pre-dose)	-	X	X (pre-dose)	-	X	X	X	8.5.2
Blood sample to assess B-cell and T-cell responses in a sub-group of participants	X (pre-dose)	-	X	X (pre-dose)	-	-	X	X	8.5.2.3
Blood sample for B-cell and T-cell response sequencing in a sub-group of participants	X (pre-dose)	-	X	X (pre-dose)	-	-	X	X	8.5.2.3
Safety assessments									
Targeted physical examination	X	-	-	X	-	-	-	-	8.2.1
Vital signs	X	X	X	X	X	X	X	X	8.2.2
e-Diary provided with training	X	-	-	X	-	-	-		8.3.7

Table 3 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 4-Week Dosing Interval

Procedure	**Treatment and Follow-up Period**								**Section**
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	
Day	**1**	**8**	**15**	**29**	**V4+7**	**V4+14**	**V4+28**	**V4+180**	
Window (days)	**-**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
e-Diary collected	-	X	-	-	X	-	-		8.3.7
Unsolicited AEs	X (post-dose)	X	X	X	-	X	X	-	8.3
MAAEs, SAEs, and AESIs	X[a]	X	X	X	-	X	X	X	8.3.8
Clinical safety laboratory assessments	X (pre-dose)	X	-	X (pre-dose)	X	-	X	X	8.2.3

[a] Only SAEs pre-dose

AE: adverse event; AESI: adverse event of special interest; MAAE: medically-attended adverse event; SAE: serious adverse event

Table 4 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 12-Week Dosing Interval

Procedure	Treatment and Follow-up Period									Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	
Day	**1**	**8**	**15**	**29**	**85**	**V5+7**	**V5+14**	**V5+28**	**V5+180**	
Window (days)	**-**	**±2**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
Medical and surgical history	X	-	-	-	-	-	-	-	-	-
Urine pregnancy test (women of childbearing potential)	X	-	-	-	X	-	-	-	-	8.2.3
Concomitant medications/vaccinations	X	X	X	X	X	X	X	X	X	6.5
Verify eligibility criteria	X	-	-	-	-	-	-	-	-	5.1, 5.2
Monitoring of COVID-19	X	X	X	X	X	X	X	X	X	8.3.8
Vaccine administration (after screening activities, the activities listed above, and the pre-dose sampling activities listed below)	X	-	-	-	X	-	-	-	-	6.1.1
Immunogenicity assessments										
Serum sample to assess SARS-CoV-2 serology/neutralising antibodies	X (pre-dose)	-	X	X	X (pre-dose)	-	X	X	X	8.5.2
Serum sample to assess additional immunogenicity	X (pre-dose)	-	X	X	X (pre-dose)	-	X	X	X	8.5.2
Blood sample to assess B-cell and T-cell responses in a sub-group of participants	X (pre-dose)	-	X	X	X (pre-dose)	-	-	X	X	8.5.2.3
Blood sample for B-cell and T-cell response sequencing in a sub-group of participants	X (pre-dose)	-	X	X	X (pre-dose)	-	-	X	X	8.5.2.3
Safety assessments										
Targeted physical examination	X	-	-	-	X	-	-	-	-	8.2.1
Vital signs	X	X	X	X	X	X	X	X	X	8.2.2
e-Diary provided with training	X	-	-	-	X	-	-	-		8.3.7

Table 4 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 12-Week Dosing Interval

Procedure	Treatment and Follow-up Period									Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	
Day	**1**	**8**	**15**	**29**	**85**	**V5+7**	**V5+14**	**V5+28**	**V5+180**	
Window (days)	**-**	**±2**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
e-Diary collected	-	X	-	-	-	X	-	-	-	8.3.7
Unsolicited AEs	X (post-dose)	X	X	X	X	X	X	X	-	8.3
MAAEs, SAEs, and AESIs	X[a]	X	X	X	X	X	X	X	X	8.3.8, 8.3.8
Clinical safety laboratory assessments	X (pre-dose)	X	-	X	X (pre-dose)	X	-	X	X	8.2.3

[a] Only SAEs pre-dose

AE: adverse event; AESI: adverse event of special interest; MAAE: medically-attended adverse event; SAE: serious adverse event

2 INTRODUCTION

AZD2816 is being developed for the prevention of COVID-19. It is a modified version of the current AstraZeneca SARS-CoV-2 vaccine (referred to as AZD1222 in clinical documentation) that has been modified to also provide immunity against the newly emerging SARS-CoV-2 variant strain B.1.351. Like AZD1222, AZD2816 is a recombinant replication-defective chimpanzee adenovirus vector (ChAdOx1) expressing the SARS-CoV-2 S surface glycoprotein driven by the human cytomegalovirus major immediate early promoter that includes intron A with a human tissue plasminogen activator leader sequence at the N terminus. AZD2816 differs from AZD1222 in that the S glycoprotein gene sequence used is from the B.1.351 variant strain instead of the original Wuhan-Hu-1 variant.

2.1 Study Rationale

The aim of the study is to assess the safety and immunogenicity of AZD2816 for prevention of COVID-19 as both a 2-dose primary vaccination in previously unvaccinated participants and a 1-dose booster vaccination in participants previously vaccinated against the original Wuhan-Hu-1 strain of SARS-CoV-2. A safe and effective vaccine for COVID-19 prevention, including against the B.1.351 variant, would have significant global public health impact.

The study will also investigate the safety and immunogenicity of 1) a heterologous 2-dose vaccination with AZD1222 as first dose and AZD2816 as the second dose and 2) a single dose of AZD1222 as a booster vaccination in participants that have been previously vaccinated with an mRNA COVID-19 vaccine.

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, which was named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (Zhou et al 2020). The disease these patients contracted was subsequently named Coronavirus Disease 2019 (COVID-19). The World Health Organization declared the novel coronavirus a pandemic on 11 March 2020. The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has resulted in significant global morbidity and mortality as well as major disruption to healthcare systems. Measures to change the course of the pandemic have included the accelerated development vaccines against the original Wuhan-Hu-1 strain.

Coronaviruses are spherical, enveloped viruses with positive-sense single-stranded RNA genomes. SARS-CoV-2 belongs to the phylogenetic lineage B of the genus *Betacoronavirus*, and it is the seventh corona virus known to cause human infections and the third known to cause severe disease after SARS-CoV and MERS-CoV. One fourth of the viral genome is responsible for coding structural proteins, such as the S glycoprotein, envelope, membrane,

and nucleocapsid proteins. Envelope, membrane, and nucleocapsid proteins are mainly responsible for virion assembly while the S protein is involved in cellular receptor binding, mediating fusion of virus and cell membranes and virus entry into host cells during infection. The SARS-CoV-2 spike (S) glycoprotein is a type I trimeric, transmembrane protein that is located at the surface of the viral envelope forming spike-shaped protrusions. The S protein's subunits are responsible for cellular receptor angiotensin-converting enzyme 2 binding via the receptor binding domain and subsequent fusion of virus and cell membranes, thereby mediating the entry of SARS-CoV-2 into the target cells. The S protein has an essential role in virus entry and determines tissue and cell tropism, as well as host range. The roles of the S-protein in receptor binding and membrane fusion have made it a desirable target for vaccine and antiviral development. The AstraZeneca vaccine AZD1222 expresses a codon-optimized coding sequence for S protein from the SARS-CoV-2 genome sequence accession MN908947 (ie, the Wuhan-Hu-1 isolate).

To date, 5 vaccines that rely upon the expression of the SARS CoV-2 S glycoprotein to stimulate/prime a protective immune response against the virus have demonstrated safety and efficacy in phase III clinical trials. Four of these, AZD1222 (also referred to as ChAdOx1 nCoV-19, a recombinant replication-defective chimpanzee adenoviral vectored), BNT162b2 (Pfizer-BioNTech, mRNA), mRNA-1273 (Moderna, mRNA), and Ad26.COV2-S (Janssen, adenovirus serotype 26 vectored) have received Emergency Use Authorization or Conditional Marketing Approval in the United States and/or the European Union, and elsewhere, and NVX-CoV2373 (Novavax; recombinant 86 protein) has also shown efficacy and is likely to be in use in the near future. These vaccines have been designed based upon the initial reported genetic sequence of the S protein from Wuhan in January 2020 (Lu et al 2020).

The immunogenicity and efficacy of AZD1222 has been shown in clinical trials (Ramasamy et al 2020, Voysey et al 2021a, Voysey et al 2021b). Immunogenicity data indicate that a single dose of AZD1222 elicits both humoral and cellular immunogenicity responses and that antibody responses are boosted after a second dose. In a pooled analysis of the 4 studies conducted in the United Kingdom, Brazil, and South Africa (DCO2 database lock 07 December 2020), the vaccine was highly immunogenic; seroresponse of S binding antibody was > 98% after a single dose of AZD1222. Seroresponse of live neutralising antibody was 82.4% after 1 dose, which rose to 99.4% after a second dose. Efficacy analyses of the pooled DCO2 data demonstrated effective protection of AZD1222 against COVID-19 with a vaccine efficacy of 66.73% (95.84% CI: 57.41%, 74.01%) ($p < 0.001$) from 15 days after the second dose in seronegative participants receiving 2 doses. The DCO2 data also demonstrated that the standard dose of AZD1222 (5×10^{10} viral particles) provides complete protection against COVID-19 hospital admission ≥ 22 days after the first dose in the seronegative analysis set (0 versus 14 cases in the control group, 2 of which were severe, including one with a fatal outcome). Vaccine efficacy was similar in participants with pre-existing comorbidities, being those at greatest risk of severe outcomes of COVID-19, compared to that in the general

population. Recently available primary analysis data from a Phase III study performed in the United States and Latin America showed primary endpoint vaccine efficacy of 76% (95% CI: 67.60%, 82.22%; p-value < 0.001).

A sharp rise in COVID-19 cases was reported in late 2020, which was attributed to the emergence of new SARS-CoV-2 variant strains: B.1.1.7 in the United Kingdom, B.1.351 in South Africa, and P.1 in Brazil. These variant strains carry a number mutations in the S protein sequence: 9 amino acids in B.1.1.7, 10 amino acids in B.1.351, and 12 amino acids in P.1 compared with the Wuhan-Hu-1 sequence. These mutations may result in an increase of transmissibility and/or reduced vaccine effectiveness. Variant B.1.351 was first identified in South Africa in October 2020. Its attributes include approximately 50% increased transmission and moderate impact of neutralization by monoclonal antibody therapeutics, convalescent plasma and vaccine sera. In vitro neutralization assays suggest that the B.1.351 lineage viruses may be the most antigenically distinct from the original Wuhan-like strains (Zhou et al 2021). In addition, evidence suggests that AZD1222 may afford diminished protection against mild-moderate COVID-19 disease arising from the B.1.351 variant which is also antigenically the most different from the Wuhan-Hu-1 virus (Madhi et al 2021).

The development of candidate vaccines that would be effective against the B.1.351 variant strain is underway. AZD2816 is being developed as an updated ChADOx-nCOv19 vaccine designed to provide protective immunity against the newly arising B.1.351 variant strain, using the same ChAdOx1 platform and manufacturing processes used for AstraZeneca's currently approved COVID-19 vaccine, AZD1222. The purpose of this Phase II/III, multinational, randomised, partially double-blind, active-controlled study is to demonstrate the safety and characterize the immunogenicity of AZD2816, AstraZeneca's candidate ChAdOx1 vector vaccine against B.1.351, when administered:

- As a single booster dose to SARS-CoV-2 seronegative individuals who have previously received a 2-dose primary vaccination series (AZD1222 or an mRNA vaccine) against SARS-CoV-2
- As a 2-dose homologous primary vaccination to SARS-CoV-2 seronegative individuals who have not been vaccinated previously.

The immunogenicity of a 2-dose primary heterologous vaccination (with AZD1222 as first dose and AZD2816 as second dose) to SARS-CoV-2 seronegative individuals who are unvaccinated and a single booster dose of AZD1222 to SARS-CoV-2 seronegative individuals who have previously received a 2-dose primary mRNA vaccination series will also be investigated.

SARS-CoV-2 seropositive participants will be enrolled in separate cohorts to support a parallel exploratory analysis in these participants.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD1222 and AZD2816 is provided in the respective Investigator's Brochures.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of AZD2816 and AZD1222 can be found in the respective Investigator's Brochures.

2.3.1 Risk Assessment

AZD2816 has been developed using the same vaccine vector, ChAdOx1, as AZD1222 and only differs in the sequence for SARS-CoV-2 S glycoprotein that is inserted in the vector. The anticipated safety profile of AZD2816 is the same as the observed safety profile of AZD1222. Risks associated with AZD2816 are thus the same as the risks associated with AZD1222, and no additional risks are anticipated due to the change in the targeted sequence.

A number of essentially mild and moderate adverse reactions to AZD1222 have been identified and resemble reactions frequently observed after many vaccines. Based on pooled clinical data from studies with AZD1222, the most commonly expected local solicited AEs for participants in this study are vaccination site pain and tenderness. The most commonly expected systemic solicited AEs are fatigue, headache, and malaise. The majority of reported events have been 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.

Post-authorisation hypersensitivity reactions, including anaphylaxis and angioedema, have occurred following administration of AZD1222 and are considered an identified risk.

A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with COVID-19 Vaccine (ie, AZD1222) during post-authorisation use. No events have been observed in the AZD1222 clinical development programme. Thrombosis in combination with thrombocytopenia is thus considered to be an important identified risk. This includes cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. Considering the frequency of this rare event and the size of this study, the risk for participants in this trial is considered to be low. The protocol includes exclusion criteria and instructions for heightened vigilance and thorough investigations for suspected cases to mitigate against further the risk for these rare event.

Important potential risks are 1) neurologic events and potential immune-mediated neurologic conditions and 2) vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease.

2.3.2 Benefit Assessment

All participants will receive active treatment: either AZD1222, which has been shown to be effective in providing protection against SARS-CoV-2, or AZD2816, which as a modified form of AZD1222 designed to be effective against the emergent B.1.351 variant strain and may also provide participants with protection. The information gained from this study will inform development decisions with regard to the efficacy of AZD2816 as both a primary 2-dose vaccination in participants that have not been previously vaccinated and a 1-dose booster vaccination in participants previously vaccinated against SARS-CoV-2.

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 and close monitoring of participants to minimize known and potential risks.

An independent Data Safety Monitoring Board will provide study oversight, evaluating cumulative safety and other clinical data at regular intervals.

Taking these measures into account, the potential risks identified in association with the administration of AZD2816 and AZD1222 are justified by the anticipated benefit that may be afforded to participants for the prevention of COVID-19.

3 OBJECTIVES AND ENDPOINTS

Table 5 describes the objectives and endpoints of this study. Co-primary objectives were chosen to characterise the safety and humoral immune response of AZD2816 and AZD1222 against selected strains when administered as a primary 2-dose homologous vaccination series or a primary 2-dose heterologous vaccination series in previously unvaccinated participants or as a single booster vaccination to participants who have been previously vaccinated with 2 doses of AZD1222 or an approved mRNA COVID-19 vaccine. All primary and secondary objectives/endpoints are descriptive; there will be no hypothesis testing in this study. Estimates of neutralizing antibody geometric mean titre ratio and difference in seroresponse rates (and 95% confidence interval) will be generated as secondary analyses to support the assessment of relative immune responses between selected study groups.

Table 5 Study Objectives and Endpoints

Objectives	Endpoints
Safety Objectives	
- Primary	
Previously vaccinated seronegative participants	
To characterize the safety and tolerability of 1 dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose
Unvaccinated seronegative participants	
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose
- Secondary	
Previously vaccinated seronegative participants	
To characterize the safety and tolerability of 1 dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of 1 dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose

To characterize the safety and tolerability of 1 dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of 1 dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
Unvaccinated seronegative participants	
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of a heterologous primary vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety and tolerability of a heterologous primary vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination

To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
Immunogenicity objectives	
- Primary (descriptive)	
Previously vaccinated seronegative participants	
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by 1 dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by 1 dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
Unvaccinated seronegative participants	
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in unvaccinated seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
- Secondary (descriptive)	
Previously vaccinated seronegative participants	
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by 1 dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by 1 dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
Unvaccinated seronegative participants	
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by a 2-dose primary vaccination with AZD1222 with a 4-week interval in unvaccinated seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres

To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by a heterologous dose primary vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in unvaccinated seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by a 2-dose primary vaccination with AZD2816 with a 12-week interval in unvaccinated seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
- **Secondary (comparative)**	
Previously vaccinated seronegative participants receiving 1 dose versus unvaccinated seronegative participants receiving 2 doses	
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD2816 in seronegative participants previously vaccinated with AZD1222 relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rates of SARS-CoV-2 specific antibody binding titres and neutralization titres
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rates of SARS-CoV-2 specific antibody binding titres and neutralization titres
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD1222 in seronegative participants previously vaccinated with AZD1222 relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rates of SARS-CoV-2 specific antibody binding titres and neutralization titres
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rates of SARS-CoV-2 specific antibody binding titres and neutralization titres
Previously vaccinated seronegative participants	
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD2816 relative to the response with 1 dose of	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio)

AZD1222 in seronegative participants previously vaccinated with AZD1222	• Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD2816 in seronegative participants previously vaccinated with an mRNA vaccine relative to the response with 1 dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD1222 relative to 1 dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rates of SARS-CoV-2 specific antibody binding titres and neutralization titres
Unvaccinated seronegative participants	
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by a primary 2-dose vaccination with AZD2816 with a 4-week dosing interval relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week interval in previously unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by a heterologous dose primary vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week interval in previously unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval relative to the response elicited by a 2-dose primary vaccination with AZD2816 with a 4-week interval in previously unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
Exploratory	
Previously vaccinated and unvaccinated participants (seronegative and seropositive at screening)	
To explore antibody response to selected SARS-CoV-2 variants of interest/variants of concern following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in a sub-group of seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding titres (geometric mean titre) for selected variants of concern/variants of interest • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding titres for selected variants of concern/variants of interest

To explore B-cell and T-cell responses following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in a sub-group of seronegative participants	• Intracellular cytokine staining and flow cytometry for T-cell responses over time • Quantification of (IFN-γ) ELISpot responses to SARS-CoV-2 B.1.351 or Wuhan-Hu-1 S protein from day of dosing baseline over time • Breadth and depth of peripheral blood B-cell and T-cell repertoire over time through immunosequencing
To monitor the incidence of SARS-CoV-2 infection following 1 dose of AZD2816 or 1 dose of AZD1222 in previously vaccinated seronegative participants	• The incidence of SARS-CoV-2 infection defined by the presence of nucleocapsid antibodies occurring post-dose of study intervention
To monitor the incidence of COVID-19 following 1 dose of AZD2816 or AZD1222 in previously vaccinated seronegative participants	• Incidence of COVID-19, defined as SARS-CoV-2 RT-PCR-positive symptomatic illness.
To monitor the incidence of SARS-CoV-2 infection following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in unvaccinated seronegative participants	• The incidence of SARS-CoV-2 infection defined by the presence of nucleocapsid antibodies occurring post-second dose of study intervention
To monitor the incidence of COVID-19 following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in unvaccinated seronegative participants	• Incidence of COVID-19, defined as SARS-CoV-2 RT-PCR-positive symptomatic illness.
To explore the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in sub-groups of seronegative and seropositive participants	• Magnitude of SARS-CoV-2 neutralization titres (geometric mean titre) as determined by a live virus neutralization assay • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres as determined by a live virus neutralization assay
To explore anti-vector responses to the ChAdOx-1 adenovirus vector following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in sub-groups of seronegative and seropositive participants	• Magnitude of ChAdOx1 nAb titres (geometric mean titre) • Seroresponse rate of ChAdOx1 neutralizing antibody titres • Pairwise correlations between anti-S, pseudo-neutralization, and ChAdOx1 neutralizing antibody titres, 1 month after both Dose 1 and Dose 2
To explore additional immune responses following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in sub-groups of seronegative and seropositive participants	• Other exploratory assays for humoral and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data

MAAEs: medically attended adverse events; SAEs: serious adverse events; AESIs: adverse events of special interest

[a] Seroresponse: An at least 4-fold increase in geometric mean titre from baseline.

4 DESIGN

4.1 Overall Design

This is a multi-country Phase II/III study to evaluate the safety and immunogenicity of AZD2816 as single-dose vaccination in previously vaccinated adult participants and as a 2-dose primary vaccination in previously unvaccinated adult participants.

A total of approximately 2250 SARS-CoV-2 nucleocapsid seronegative participants that have been screened and judged to be eligible for the study will be enrolled across these 2 populations with the goal of 1200 previously vaccinated participants receiving single-dose vaccination and 1050 unvaccinated participants receiving 2-dose primary vaccination. In addition, seropositive participants will be enrolled (with a cap of 10% of the seronegative population or 225 participants) to support exploratory analysis is these participants.

The enrollment and randomization strategy is intended to minimize group differences in terms of age, gender and the presence of comorbidities.

In both the single-dose booster treatment regimen and the 2-dose primary vaccination treatment regimen, participants will receive study intervention consisting of intramuscular administration of either AZD1222 (5×10^{10} viral particles) or AZD2816 (5×10^{10} viral particles).

Approximately 600 seronegative participants previously vaccinated with AZD1222 will be randomised 1:1 to receive a single intramuscular dose of either AZD1222 or AZD2816 in a double-blinded fashion.

Approximately 600 seronegative participants previously vaccinated with an approved mRNA based vaccination will be randomised 1:1 to receive a single intramuscular dose of AZD2816 or AZD1222 in a double-blinded fashion.

Approximately 1050 seronegative, previously unvaccinated participants will be randomised 2:2:2:1 to receive a 2-dose primary vaccination of the following:

- 2 doses of AZD1222 with a 4-week dosing interval
- 2 doses of AZD2816 with a 4-week dosing interval
- 1 dose of AZD1222 followed by 1 dose of AZD2816 with a 4-week dosing interval
- 2 doses of AZD2816 with a 12-week dosing interval.

The 3 treatments with a 4-week dosing interval will be double-blinded while the treatment with the 12-week interval will be open-label due to the difference in dosing interval.

In addition, a smaller population seropositive participants (approximately 10% of the seronegative population), will be randomised to treatment in a similar manner as above.

Immunogenicity (ie, anti-Wuhan-Hu-1 and anti-B.1.351 immune responses including S-binding antibody titres and neutralizing antibody levels [pseudo-neutralization]) will be assessed in serum samples collected pre-dose on the day of each vaccination (baseline levels before vaccination), 14 and 28 days after each vaccination, and 180 days after the last vaccination.

All participants will be given a thermometer, tape measure or ruler, and a proprietary e-diary application designed for use with a smart device with instructions for use. All participants will be asked to report on solicited signs and symptoms for 7 days following vaccination (Days 1-8 for all participants and Days 29-36 for the 4-week dosing interval and Days 85-92 for the 12-week dosing interval). An e-diary will be used to collect information on the timing and severity of the solicited signs and symptoms.

Follow-up visits will take place as per the schedule of assessment within respective windows. All participants will be assessed for local and systemic AE, physical examination, review of e-diaries at these time points as detailed in the schedule of assessment. Blood will also be taken for safety assessments and immunology purposes.

All study participants will be followed for safety for 180 days after administration of their last vaccination dose. In every participant, solicited local and systemic events will be reported for up to 7 days after each dose, all unsolicited AEs will be reported for up to 28 days after each dose, and SAEs and AEs of special interest will be evaluated through study completion (up to 180 days after the last study vaccination).

An independent COVID-19 Vaccine Data Safety Monitoring Board will provide oversight, to ensure safe and ethical conduct of the study.

4.1.1 COVID-19 Assessments

Occurrence of COVID-19 in the trial will be reported as safety events, including monitoring of the potential risk of vaccine-induced enhanced disease as an AE of special interest (see Appendix E). COVID-19 will be diagnosed and treated as per standard medical practice. In addition, experimental treatments are permitted. Detailed information will be collected in a standard way and reported on a specific case report form.

4.1.2 Screening

All potential participants will be screened, which may take place at a visit up to 14 days prior to Day 1 or on Day 1 itself.

Informed consent will be obtained before screening/enrollment. If written consent is obtained, the screening procedures specified in the Schedule of Activities (Section 1.3) will be undertaken including a medical history, physical examination, height and weight, a SARS-CoV-2 screening test and clinical safety laboratory assessments. Baseline information collected in the previously vaccinated participants will include which vaccine was received, immunization dose interval, and time since last vaccination.

For women of childbearing potential, it will be recorded that they verbally confirmed use of one highly effective form of birth control for at least 28 days prior to the planned vaccination and a urine pregnancy test will be performed that must be negative for the participant to be enrolled. (Note: Women with urine test results that are positive or undetermined will not be enrolled and should be advised to seek medical attendance outside the context of the trial if pregnancy is suspected.)

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 enrollment or to withdraw a participant from the study will be at the discretion of the Investigator.

4.1.3 Vaccination Visit

Participants will be considered enrolled at the point of vaccination. Before vaccination, the eligibility of the participant will be reviewed. Body temperature will be observed and a medical history and physical examination will be undertaken before the first vaccination to determine need to postpone vaccination or screen fail the participant. A negative pregnancy test (urine test) will need to be obtained from women of childbearing potential before vaccination. Baseline blood samples will be obtained before the first vaccination.

Participants will receive 1 dose of AZD2816 or AZD1222 at vaccination visits, administered by intramuscular injection. Previously immunized participants will have a single vaccination visit, Day 1. Participants that have not been previously vaccinated at baseline will have a second vaccination visit on Day 29 (4-week interval) or Day 85 (12-week interval).

All participants will be given a thermometer, tape measure or ruler, and a proprietary e-diary application designed for use with a smart device with instructions for use. All participants will be asked to report on solicited signs and symptoms for 7 days following vaccination (Days 1 to 8 and Days 29 to 36 or Days 85 to 92 when applicable).

4.1.4 Follow-up visits

Follow-up visits will take place as specified in the Schedule of Activities (Section 1.3). All participants will be assessed for local and systemic AE, physical examination, review of the

e-diary and blood tests at these time points as detailed in the Schedule of Activities. Blood will also be taken for safety and immunogenicity assessments.

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 the last study visit in order to collect information on any SAEs/AE of special interest.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Study Design and Participant Population

The participant population includes adults ≥ 18 years of age. Persons who are healthy or have medically stable underlying conditions will be eligible. Adults with medically-stable chronic diseases may participate if, according to the judgement of the investigator, hospitalization within the study period is not anticipated and the participant appears likely to be able to remain on study through the end of protocol-specified follow-up.

For the primary and secondary objectives, those enrolled in the study must test negative for SARS-CoV-2 nucleocapsid protein antibody during screening. Some seropositive participants (capped at 10% of the seronegative participant population) will be enrolled to support an exploratory analysis.

Those enrolled in the single-dose vaccination part of the study must have received 2 doses of AZD1222 (with a dosing interval of 4-12 weeks) or 2 doses of an mRNA COVID-19 vaccine (with a dosing interval of 3-12 weeks for the BNT162b2 mRNA vaccine [Pfizer-BioNTech] and 4-12 weeks for the mRNA-1273 vaccine [Moderna]) with the second doses administered at least 3 months prior to first study intervention administration.

Pregnant/breastfeeding women, persons with severe immunodeficiency or severe underlying disease will be excluded from participation in the study. Persons previously vaccinated with AZD1222 in the context of an AZD1222 vaccine trial are eligible for enrollment as previously vaccinated participants in the trial. Persons who have previously received any other investigational product for the prevention of COVID-19 will be excluded from participation in this study.

Participants with known risk factors for thrombosis and thrombocytopenia (excluding contraceptive hormonal therapy or replacement hormonal therapy) are excluded.

4.2.2 Rationale for Study Endpoints

There is no statistical hypothesis testing planned for this study. Descriptive statistics will support evaluation of safety, reactogenicity, and immunogenicity.

An interim analysis will occur when all previously vaccinated participants have completed their Day 29 visit. A second interim analysis may be conducted when previously unvaccinated participants have completed their Day 29 visit.

The primary analysis will occur when all participants have completed their Day 29 visit AND all previously unvaccinated participants randomised to a 4-week dosing interval have completed their Day 57 visit (ie, 28 days after their second dose).

A secondary analysis will occur when all participants have completed their Day 29 visit AND all previously unvaccinated participants (including those randomised to either a 4-week or a 12-week dosing interval) have completed their Day 57/Day 113 visit (ie, 28 days after their second dose).

The final analysis will occur when data from all vaccinated participants are available through completion of the last study visit (180 days after the single dose for previously vaccinated participants/180 days after the second dose for unvaccinated participants).

The primary safety analysis includes:

- Incidence of local and systemic solicited AEs for 7 days following each vaccination will be summarized by day and overall.
- Incidence of unsolicited AEs for 28 days following each vaccination will be summarized by system organ class and preferred term, and by relationship to vaccination as assessed by the investigator.
- SAEs and AEs of special interest following the first vaccination and throughout the study duration will be summarized by system organ class and preferred term and by relationship to vaccination as assessed by the investigator.

Solicited AEs will be collected for 7 days after each dose of study intervention, a period that has proven adequate to describe reactogenicity events in previous vaccine studies. For all participants, AEs will be collected through 28 days after each dose of study intervention. SAEs, medically-attended AEs, and AEs of special interest and will be collected from Day 1 through end of the study. AEs of special interest include terms identified by the Brighton Collaboration involving events associated with vaccination in general .

The immunogenicity endpoints of interest in this study are:

- Geometric mean titre
- Seroresponse, defined as ≥ 4-fold increase in the geometric mean titre from baseline

Geometric mean titre ratios and differences in seroresponses with 95% confidence intervals will be presented to support selected comparisons of immunogenicity across groups of interest.

Immunogenicity against SARS-CoV-2 Wuhan-Hu-1 and B.1.351 strains will be characterized through the quantification of Spike-binding antibodies, pseudo-neutralization and, in a subset of participants, live neutralization. Exploratory analysis of immunogenicity against other strains and induction of other immune effectors including cell-mediated immunity will be conducted.

4.3 Justification for Dose

The AZD2816 nominal dose of 5×10^{10} viral particles is the same dose as the approved dose for AZD1222, which was based on the accumulated non-clinical data and clinical data from the AZD1222 clinical studies, as well as from other SARS-CoV-2 vaccines in development. Safety and immunogenicity data from an additional clinical study, MERS001(NCT03399578), using the same ChAdOx1 vector, also helped inform dose selection. MERS001 was the first clinical study of a ChAdOx1-vectored vaccine expressing the full-length S protein from a separate, but related, beta-coronavirus. ChAdOx1 MERS has been given to 31 participants to date at doses ranging from 5×10^{9} viral particles to 5×10^{10} viral particles. Despite higher reactogenicity observed at the 5×10^{10} viral particles, this dose was safe, with self-limiting AEs and no serious adverse reactions recorded. The 5×10^{10} viral particles was the most immunogenic, in terms of inducing neutralizing antibodies 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} viral particles dose was chosen for AZD1222.

Based on accumulating nonclinical and clinical data gathered for AZD1222, a 2-dose regimen was selected for vaccination of unvaccinated participants with AZD2816 (AZD1222 Investigators Brochure). A single dose vaccination has been selected for participants previously vaccinated in line with both FDA and EMA guidance (FDA 2021, EMA 2021).

4.4 End of Study Definition

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

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

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as a protocol waiver or exemption, is not permitted.

5.1 Inclusion Criteria

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

5.1.1 All Participants:

Age

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

COVID-19

For inclusion in the SARS-CoV-2 seronegative population supporting the primary and secondary objectives:

2 No history of laboratory-confirmed SARS-CoV-2 infection (ie, no positive nucleic acid amplification test and no positive antibody test).

3 Seronegative for SARS-CoV-2 at screening (lateral flow test to detect reactivity to the nucleoprotein).

Note, patients failing to meet criteria 2 and/or 3 may be included in the separate seropositive population supporting the seropositive exploratory objectives.

Type of Participant

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

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

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

6 Signed informed consent obtained before conducting any study-related procedures

Reproduction

7 Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
Female participants:

(a) Women of childbearing potential must:

- Have a negative pregnancy test on the day of screening and on days of vaccination
- 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 30 days following administration of the 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 6). Periodic abstinence, the rhythm method, and withdrawal are NOT acceptable methods of contraception.

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

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

    Until follicle-stimulating hormone is documented to be within menopausal range, the participant is to be considered of childbearing potential
  - For women aged ≥50 years, post-menopausal is defined as having a history of ≥12 months amenorrhea prior to randomization, without an alternative cause, following cessation of exogenous sex-hormonal treatment.

Table 6 Highly Effective Methods of Contraception

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

[a] This is also considered a hormonal method
[b] Provided that partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success
[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse from 28 days prior to Day 1 through 30 days following administration of the second dose of study intervention, and if it is the preferred and usual lifestyle of the participant

5.1.2 Previously COVID-19 Vaccinated Participants

8 Prior completion of a 2-dose primary homologous vaccination regimen against SARS-CoV-2 with either AZD1222 (2 standard doses as authorized vaccine or as investigational product in a clinical trial with a 4- to 12-week dosing interval) or with an mRNA vaccine approved for emergency or conditional use (eg, BNT162b2 vaccine [Pfizer-BioNTech] with a 3- to 12-week dosing interval or mRNA-1273 vaccine [Moderna] with a 4- to 12-week dosing interval). The second dose in all cases should have been administered at least 3 months prior to first administration of study intervention.

5.2 Exclusion Criteria

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

Medical Conditions

1 History of allergy to any component of AZD1222/AZD2816.

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

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

4 Any confirmed or suspected immunosuppressive or immunodeficient state, including asplenia or HIV/AIDS.

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

- Topical/inhaled steroids or short-term oral steroids (course lasting ≤ 14 days)

6 History of primary malignancy except for:

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

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

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

(d) Localized prostate cancer

7 History of thrombocytopenia and/or thrombosis, including participants who have experienced major venous and/or arterial thrombosis in combination with thrombocytopenia following vaccination with any COVID-19 vaccine

8 History of heparin-induced thrombocytopenia, congenital thrombophilia (ie, factor V Leiden, prothrombin G20210A, antithrombin III deficiency, protein C deficiency and

protein S deficiency, factor XIII mutation, familial dysfibrinogenemia), auto-immune thrombophilia (antiphospholipid syndrome, anti-cardiolipin antibodies, anti-β_2-glycoprotein 1 antibodies), or paroxysmal nocturnal haemoglobinuria.

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

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

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

12 Any autoimmune conditions, except mild psoriasis and vitiligo

Note: The AEs of special interest as outlined in Appendix E (including Table 27) should be considered when evaluating a participant for exclusion criteria as the presence of these AEs of special interest, especially if untreated or uncontrolled, may be a safety risk to the participant, affect the ability of the participant to participate in the study, and/or impair interpretation of the study data. Investigators should review and consider the list of conditions in Appendix E. If any of these conditions are present in a participant, the Investigator is asked to utilize his/her clinical judgment in determining the participant's eligibility for the study. Should the participant have conditions as outlined in Appendix E and the participant is enrolled, the Investigator is asked to document notes on site regarding the final rationale for enrollment.

Prior/Concomitant Therapy

13 Receipt of or planned receipt of investigational products indicated for the treatment or prevention of SARS-CoV-2 or COVID-19 with the exception of prior vaccination with AZD1222 or an mRNA COVID-10 vaccine (2 doses of the same vaccine within an approved dosing interval, see Section 5.1.2), which is allowed for participants in the previously vaccinated cohort
Note: For participants who develop COVID-19, receipt of licensed treatment options and/or participation in investigational treatment studies is permitted

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

15 Receipt of any influenza vaccine (licensed or investigational) within 7 days prior to and after administration of AZD1222/AZD2816.

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

Other Exclusions

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

18 Women who are currently pregnant (confirmed with positive pregnancy test), breastfeeding, having given birth less than 3 months before or planning pregnancy during the study.

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

20 Participants with a history of chronic alcohol or drug abuse or any condition associated with poor compliance.

21 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements or if vaccination would interfere with the participant's ongoing treatment.

22 Previous enrollment in the present study.

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 assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

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

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention, marketed product, or placebo intended to be administered to or medical device utilized by a study participant according to the study protocol. Study intervention is defined as AZD2816 or AZD1222 (Table 7).

6.1 Study Interventions Administered

6.1.1 Investigational Products

Table 7 Investigational Products

Intervention Name	AZD2816	AZD1222
Type	Vaccine	Vaccine
Dose Formulation	CCI [redacted]	CCI [redacted]
Unit Dose Strength	1×10^{11} viral particles/mL	1×10^{11} viral particles/mL
	$\geq 5 \times 10^{8}$ infectious units/mL	$\geq 5 \times 10^{8}$ infectious units/mL
Dosage Level	5×10^{10} viral particles (nominal, $\pm 1.5 \times 10^{10}$ viral particles)	5×10^{10} viral particles (nominal, $\pm 1.5 \times 10^{10}$ viral particles)
	$\geq 2.5 \times 10^{8}$ infectious units	$\geq 2.5 \times 10^{8}$ infectious units
Route	Intramuscular	Intramuscular
Use	Experimental	Experimental
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labelling	Will be provided in vials within a carton. Each carton and vial will be labelled as required per country requirement	Will be provided in vials within a carton. Each carton and vial will be labelled as required per country requirement
Current/Former Name	-	Previous clinical documentation: ChAdOx1 nCoV-19 Current tradename: Vaxzevria

IMP: investigational medicinal product; NIMP: non-investigational medical product; w/v: weight/volume.

AZD2816

AZD2816 will be supplied by the Sponsor as a vial solution for injection. It is a sterile, clear to slightly opaque solution, practically free from visible particles. Each vial of AZD2816 has a label-claim volume of 5 mL and can provide up to ten 0.5 mL doses.

AZD1222

AZD1222 will be supplied by the Sponsor as a vial solution for injection. It is a sterile, clear to slightly opaque solution, practically free from visible particles. Each vial of AZD1222 has a label-claim volume of 4 mL and can provide up to eight 0.5 mL doses.

Unopened vials of AZD2816 and AZD1222 must be stored at 2-8 ºC (36-46 ºF) for the duration of the assigned shelf-life and must not be frozen. Both investigational products must be kept in original packaging until use to prevent prolonged light exposure.

6.1.2 Dosing Instructions

Previously unvaccinated participants will receive 2 doses of either AZD1222, AZD2816, or AZD1222 plus AZD2816, with the first dose administered on Day 1 and the second dose on Day 29 (for a 4-week dosing interval) (Table 3) or Day 85 (for a 12-week dosing interval) (Table 4).

Previously vaccinated participants will receive 1 dose of either AZD1222 or AZD2816 (Table 2).

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

All study participants will be observed in the clinic for at least 15 minutes after vaccination. Allergic reactions to vaccines are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

6.2 Preparation/Handling/Storage/Accountability

The procedures for preparation, handling, storage, and accountability are identical for AZD2816 and AZD1222.

1 The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2 Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
3 The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4 Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual or specified handling instructions.

6.2.1 Dose Preparation and Administration

Doses of AZD2816 and 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 AZD2816 or AZD1222 in a sterile syringe.

AZD2816 and AZD1222 do not contain preservatives. Each vial must be assigned a beyond-use-date of 6 hours at 2-30 °C (36-86 °F) from first needle puncture of the vial, after which any unused portion must be discarded.

Once an AZD2816 or AZD1222 dose is drawn into a syringe for administration, the dose must be administered within the beyond-use-date of the vial. If dose administration is not completed within the 6-hour vial beyond-use-date, a new dose must be prepared from a new vial.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization

The study contains 3 cohorts that are randomised to a total of 8 treatments:

- Participants that have previously been vaccinated with 2 doses of AZD1222 will be randomised 1:1 to 1 dose of AZD2816 or 1 dose of AZD1222.
- Participants that have been previously vaccinated with an mRNA COVID-19 vaccine will be randomised 1:1 to 1 dose of AZD2816 or AZD2816.
- Vaccination naïve participants that will be randomised 2:2:2:1 to 2 doses of AZD2816 with a 4-week dosing interval, 2 doses of AZD1222 with a 4-week dosing interval, 1 dose of AZD1222 followed by 1 dose of AZD216 with a 4-week dosing interval, or 2 doses of AZD2816 with a 12-week dosing interval.

Separate populations of SARS-CoV-2 seronegative participants (supporting the primary and secondary objectives) and SARS-CoV-2 seropositive participants (supporting exploratory objectives) will be randomised/included in the above cohorts.

Randomization will be stratified based on age (less than 65, 65 and above), gender, and presence of at least one of the following comorbidities that are known risk factors for severe illness from COVID-19 (based on the participant's past and current medical history):

- Obesity (BMI $\geq$ 30 kg/m^2 at baseline)
- Significant cardiovascular disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, or pulmonary hypertension)
- Chronic lung disease (eg, chronic obstructive pulmonary disease, idiopathic pulmonary disease, cystic fibrosis, or moderate to severe asthma)
- Diabetes (Type 1 or Type 2).

The randomised participants will be centrally assigned to randomised study intervention using an Interactive Response Technology (IRT)/Randomisation and Trial Supply Management. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information & directions for the Randomisation and Trial Supply Management will be provided to each site.

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

6.3.2 Blinding

Treatment will be double-blinded for previously vaccinated participants randomised to a single dose of either AZD2816 or AZD1222. Treatment will also be double-blind for previously unvaccinated participants randomised to 2 dose vaccinations with a 4-week dosing interval (ie, homologous AZD2816 or AZD1222 vaccination or heterologous AZD1222/AZD2816 vaccination). Previously unvaccinated participants randomised to a homologous AZD2816 vaccination with a 12-week dosing interval will receive treatment in an open-label fashion due to the different dosing interval.

For the double-blinded treatments, neither the participant nor any of the investigators or Sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the study intervention received. Since AZD2816 and AZD1222 are visually distinct prior to dose preparation (due to differences in container closure), all investigational 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, AZD2816 and AZD1222 are not visually distinct from each other.

The IRT will provide the investigators with a dose tracking number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IRT user manual that will be provided to each study site.

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

The Sponsor retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational medicinal product and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken

for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

6.3.3 Procedures for Unblinding

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

In the event that a study participant is contacted about receiving a licensed and/or authorized COVID-19 vaccine outside of this clinical study, unblinding instructions are being provided to the sites. If the participant is unblinded, the Sponsor needs to be notified within 24 hours, and this should be documented in the site source documents.

6.4 Study Intervention Compliance

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

6.5 Concomitant Therapy

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

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

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

6.5.1 Permitted Concomitant Medications

- Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance.

- Primary care providers, or where appropriate investigators, should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study.
- Participants who develop COVID-19 after receiving study intervention should be treated with licensed medications and interventions according to standard of care. All routine vaccinations other than influenza are permitted beginning > 30 days after last dose of study intervention. Licensed influenza vaccines are permitted 7 days before and 7 days after administration of study intervention.
- Topical/inhaled steroids or short-term oral steroids (course lasting ≤ 14 days) are permitted

6.5.2 Prohibited Concomitant Medications

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

- Primary or booster vaccinations, other than AZD2816 or AZD1222, for prevention of SARS-CoV-2 or COVID-19**.**

  Note: Participants choosing to receive a licenced and/or authorized COVID-19 vaccine should inform the Investigator so it can be properly documented. Participants, who receive a licenced and/or authorized COVID-19 vaccine outside the study, should be encouraged to continue study conduct to be followed for safety reporting and all assessments.
- Receipt of any vaccine (licensed or investigational) other than licensed influenza vaccines within 30 days prior to and after administration of study intervention. Thirty days after the second vaccination, other routine vaccinations are permitted as clinically indicated.
- Glucocorticoids at a dose ≥ 20 mg/day of prednisone or equivalent given daily or on alternate days for ≥ 14 consecutive days between randomization and the participant's scheduled final visit
- Other systemically administered drugs with significant immunosuppressive activity, such as azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy between randomization and the participant's scheduled final visit
- Immunoglobulins and/or any blood product.

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

6.6 Dose Modification

Study intervention will be administered as described in Section 6.1. Dose modification is not permitted.

6.7 Intervention After the End of the Study

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

An individual participant will not receive the first or second dose (if applicable) of study intervention if any of the following occur in the participant in question:

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

Each participant who has received at least 1 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.

In the event that a study participant receives a licensed and/or authorized COVID-19 vaccine during the study, AstraZeneca needs to be notified within 24 hours and this should be documented in the site source documents. Participants who have received study intervention, regardless of reason, will be followed for the full study period.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Sponsor Study Team. If the participant does not specifically request withdrawal of consent for use of samples, then the samples collected prior to the consent withdrawal will be destroyed once per protocol analysis is complete.

7.3 Lost to Follow-up

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

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

- The study site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Schedule of Activities (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 Schedule of Activities (Section 1.3) is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities.

8.1 Efficacy Assessments

Not applicable.

8.2 Safety Assessments

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

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

8.2.2 Vital Signs

Vital signs, including heart rate, pulse oximetry, blood pressure, and body temperature, will be performed as specified in the Schedule of Activities (Section 1.3). The participant should be resting prior to the collection of vital signs. On vaccination days, vital signs should be assessed prior to vaccine administration.

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

8.2.3 Clinical Laboratory Assessments

Blood samples for determination of clinical chemistry and haematology will be taken at the visits indicated in the Schedule of Activities (Section 1.3). Additional unscheduled safety samples may be collected if clinically indicated at the discretion of the investigator, with the date and time of collection recorded in the appropriate eCRF.

The standard clinical chemistry and haematology analysis will be performed at a local laboratory at or near to the investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The following laboratory variables will be measured:

Table 8 Laboratory Safety Variables

Blood	Serum/Plasma
Haemoglobin	Activated partial thromboplastin time
Leukocyte count	Prothrombin time
Leukocyte differential count (absolute count)	Fibrinogen
Platelet count	D-dimer
-	Creatinine
-	Bilirubin, total
-	Alkaline phosphatase
-	Aspartate aminotransferase
-	Alanine aminotransferase

In case a participant shows an aspartate aminotransferase **or** alanine aminotransferase ≥ 3 × upper limit of normal together with total bilirubin ≥ 2 × the upper limit of normal, please refer to Section 8.3.6

For women participants of childbearing potential, a urine sample for pregnancy testing will be collected according to the Schedule of Activities (Section 1.3). Urine pregnancy tests for β-human chorionic gonadotropin may be performed at the site using a licensed dipstick test.

8.3 Adverse Events and Serious Adverse Events

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

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

Solicited AEs are local or systemic predefined events for assessment of reactogenicity. Solicited AEs will be collected in a e-diary (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 the reporting of solicited AEs via e-diary unless otherwise noted..

All other AEs are considered to be unsolicited AEs (collected by 'open question' at study visits).

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

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

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

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

Solicited AEs will be recorded for 7 days after each dose of study intervention (ie, Day 1 through Day 8). If a solicited AE is not resolved within the e-diary reporting period, the event will be reported as a non-solicited adverse event in the eCRF, with a start date of when started and the actual stop date.

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

Medically-attended AEs and AEs of special interest will be recorded from Day 1 through the last participant contact.

See the Schedule of Activities for the scheduled timepoints (Section 1.3).

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 Adverse Events and Serious Adverse Events

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. The Sponsor retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

AE variables

The following variables will be collected for each AE:

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

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

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

A revised toxicity grading scale from US FDA guidance for healthy volunteers enrolled in a preventive vaccine clinical study (FDA 2007) will be utilized for all unsolicited events with an assigned severity grading including Grade 5.

8.3.3 Causality Collection

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

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

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

8.3.4 Adverse Events Based on Signs and Symptoms

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

8.3.5 Adverse Events Based on Examinations and Tests

The results from the Clinical Study Protocol-mandated vital signs and laboratory safety assessments will be summarized in the Clinical Study Report.

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

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

8.3.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation. Any occurrences of aspartate aminotransferase or alanine aminotransferase $\geq 3 \times$ the upper limit of normal together with total bilirubin $\geq 2 \times$ upper limit of normal at any point during the study following the administration of study medication should be reported to the Sponsor as a potential Hy's Law SAE within 1 day with a serious criteria of 'Important medical event' and causality assessment 'yes/related'.

The study physician will contact the investigator to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.

8.3.7 Solicited Adverse Events

Local and systemic predefined solicited AEs for reactogenicity assessment (Table 9) will be collected in a Solicited AE e-Diary for 7 days following administration of each dose of study intervention via e-diary collection. If a solicited AE is not resolved within the e-diary reporting period, the event will be also reported as a non-solicited adverse event in the eCRF, with a start date of when started and the actual stop date.

Solicited AEs should not be reported as unsolicited AEs unless they fulfil the criteria for SAEs or medically-attended AEs(see Sections 8.3 and 8.3.8, respectively).

Table 9 Predefined Solicited Adverse Events for Reactogenicity Assessment

Local	Systemic
Pain at the site of the injection	Fever (> 100 °F/37.8 °C)
Redness/erythema at the site of the injection	Chills
Tenderness at the site of the injection	Muscle pains
Induration/swelling at the site of the injection	Fatigue (physical or mental tiredness/exhaustion)
-	Headache
-	Malaise (general feeling of discomfort or uneasiness)
-	Nausea
-	Vomiting

Solicited AE e-Diary

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

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

Severity Assessment of Solicited AEs

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

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

8.3.8 COVID-19 Assessment

This study will describe the incidence of COVID-19 adverse events reported from Day 1 to 180 days after the participant's last/only dose of vaccine.

COVID-19 is defined as SARS-CoV 2-RT-PCR positive symptomatic illness. At all clinic visits following the initial vaccination, participants will be asked if they have had a diagnosis of COVID-19 since their last clinic visit (see Schedule of Activities in Section 1.3). Medical records will be obtained for confirmation of a participant-reported diagnoses of COVID-19. Qualifying symptoms are fever, shortness of breath, difficulty breathing, chills, cough, fatigue, muscle/body aches, headache, new loss of taste or smell, sore throat, congestion, runny nose, nausea, vomiting, or diarrhoea. Events will be reported as AEs/SAEs.

If a participant presents at clinic visit with COVID symptoms, diagnosis will be confirmed using RT-PCR.

8.3.9 Medically-Attended Adverse Events

Medically-attended AEs will be collected according to the timepoints specified in the Schedule of Activities (Section 1.3).

Medically-attended AEs are defined as AEs leading to medically-attended visits that were not routine visits for physical examination or vaccination, such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. AEs, including abnormal vital signs, identified on a routine study visit or during the scheduled illness visits will not be considered medically-attended AEs.

8.3.10 Adverse Events of Special Interest

AEs of special interest will be collected according to the timepoints specified in the Schedule of Activities (Section 1.3).

AEs of special interest 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. AEs of special interest are based on Brighton Collaboration case definitions (SPEAC 2020), clinical experience, and scientific interest. A list of events is provided in Appendix E.

An AE of special interest can be serious or non-serious. All AEs of special interest will be recorded in the eCRF. If any AE of special interest occurs in the course of the study, investigators or other site personnel will inform the appropriate Sponsor representatives within

1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it. Serious AEs of special interest will be recorded and reported as per Section 8.3.11.

8.3.10.1 Vascular/Hematologic Adverse Events of Special Interest

Both thrombotic, thromboembolic, and neurovascular events and thrombocytopenia events are considered to be adverse events of special interest. The investigator should remain vigilant for the occurrence of thrombotic events with thrombocytopenia and/or bleeding. If a participant experiences new onset thromboembolic events with thrombocytopenia, there should be prompt evaluation with a thorough haematological investigation. COVID-19 testing, including PCR and serology (nucleoprotein antibodies), should also be performed. See Appendix F for further guidance on investigation and management of suspected events.

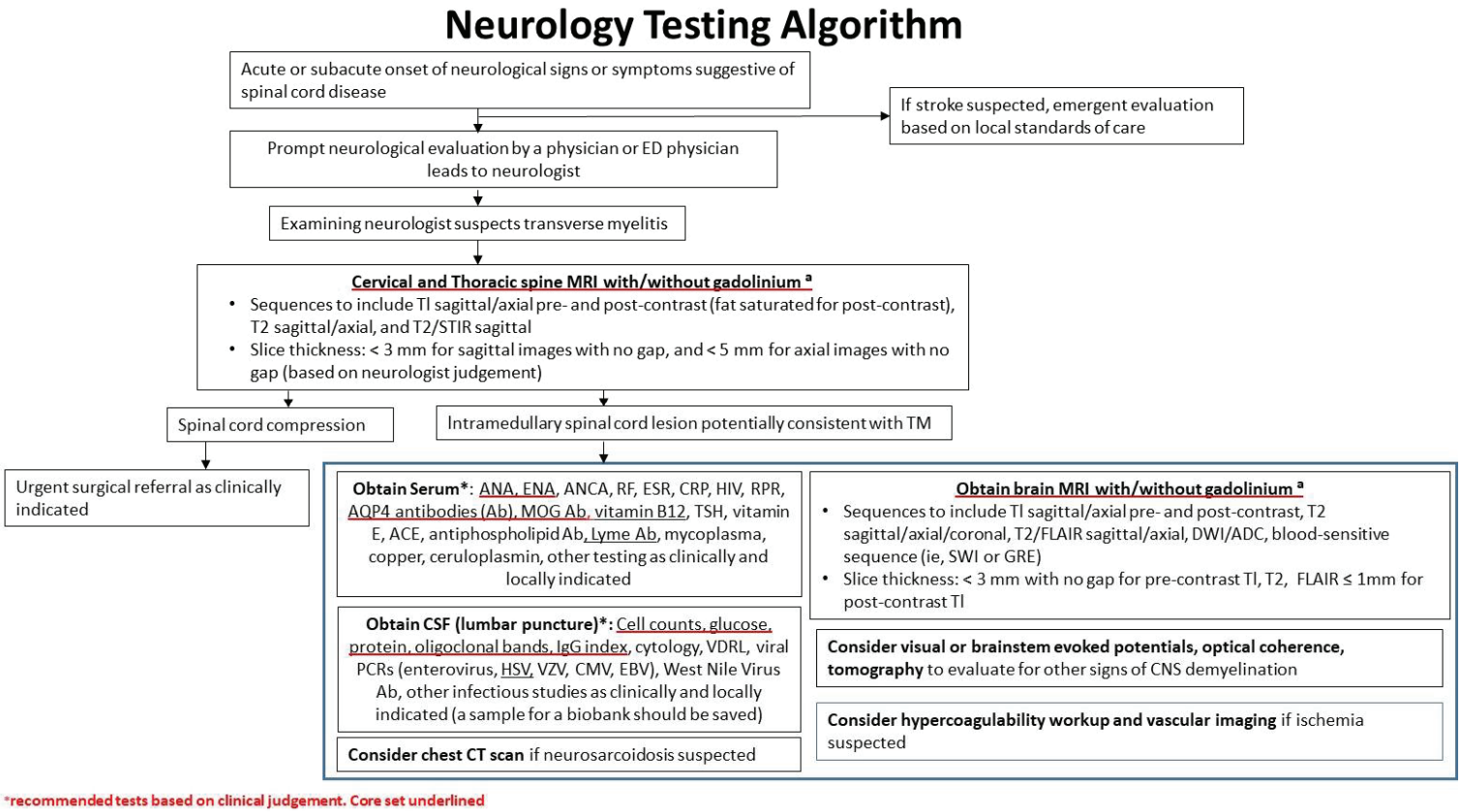
In the event of such a case of thrombosis and in accordance with local laws and ethical procedures, one blood sample may be taken from the participant and whole genome sequencing performed in order to enable investigations into the possible role of genetic polymorphisms as risk factors for these events.

8.3.10.2 Potential Neurological Adverse Events of Special Interest

If a participant experiences new onset (acute or subacute) motor and sensory disturbances (eg, weakness, numbness, paraesthesia, 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, including referral to a neurology specialist for further evaluation and testing, as clinically indicated. Testing can include evaluation for peripheral demyelinating conditions (eg, electromyography). In cases of concern for spinal cord disease, see Figure 3 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 AEs of special interest occurring in the AZD1222 clinical development program (see Appendix A 5).

Figure 3 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.

8.3.11 Reporting of Serious Adverse Events

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

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

The designated Sponsor representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform Sponsor representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but no later than 24 hours of when he or she becomes aware.

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 Sponsor representative.

If the Electronic Data Capture system is not available, then the investigator or other study site staff reports an SAE to the appropriate Sponsor representative by telephone or other method and the event is entered into the Electronic Data Capture system when available.

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

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

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

8.3.12 Pregnancy

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

8.3.12.1 Maternal Exposure

Female participants who are pregnant or have a confirmed positive pregnancy test at screening or Day 1 will be excluded from the study (see Section 5.2). Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and

spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the participant was discontinued from the study.

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

The designated Sponsor representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.11) and **within 30 days** for all other pregnancies that are not associated with an SAEs.

The same timelines apply when outcome information is available.

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

8.3.13 Medication Error

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

The designated Sponsor representative works with the investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) **or 5** (other serious initial and follow up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.11) and **within 30 days** for all other medication errors.

The definition of a Medication Error can be found in Appendix B 3.

8.4 Overdose

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

There is no specific treatment for an overdose with AZD2816 or AZD1222. If overdose occurs, the participant should be treated supportively with appropriate monitoring as necessary.

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

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

The designated Sponsor representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.11) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

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

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

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

8.5.1 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5.2 Immunogenicity Assessments

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

8.5.2.1 SARS-CoV-2 Serology Assessments

Serum samples will be collected to assess SARS-CoV-2 antigen-specific antibody levels from all participants according to the Schedule of Activities (Section 1.3). Authorized laboratories will assess serologic responses to AZD1222 and AZD2816 using validated (or qualified, where appropriate) assays. Serologic assessment to the S protein from different SARS-CoV-2 variants (which include Wuhan-Hu-1, B.1.351, B.1.1.7, and P.1) will be assessed quantitatively using a validated multiplexed ECL based immunoassay. Additionally, seroresponse will be assessed for each antigen over time. The rate of SARS-CoV-2 infection in participants receiving AZD2816 versus AZD1222 will be determined by seroconversion in a SARS-CoV-2 nucleocapsid antigen in a multiplexed electrochemiluminescence-based assay performed at an authorized laboratory. Additional exploratory assessments may be performed to measure binding antibodies to SARS-CoV-2 variants of interest (which may include B.1.429, B.1.525, B.1.526, P.2, P.3, B.1.617, and the Q677H mutation observed in multiple variants).

8.5.2.2 CCI

8.5.2.3 CCI

8.5.2.4 CCI

CCI

8.5.3 Pharmacodynamics

Pharmacodynamics are not evaluated in this study.

8.6 Human Biological Sample Biomarkers

Already collected samples may be analysed for biomarkers thought to play a role in COVID-19 severity or outcomes based upon emerging immunogenicity and pharmacodynamic analysis from this or other studies involving the study interventions. These analyses include but are not limited to serum or plasma cytokines, quantification of RNA, micro-RNA, and/or non-coding RNA using quantitative reverse transcriptase polymerase chain reaction (RT-PCR), microarray, sequencing, or other technologies in blood, or peripheral blood mononuclear cells to evaluate their association with AZD1222/2816 and observed clinical responses to these study interventions.

8.7 Optional Genomics Initiative Sample

Not applicable.

8.8 Medical Resource Utilization and Health Economics

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

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

There is no statistical hypothesis testing planned for this study. Descriptive analyses will support evaluation of safety, reactogenicity and immunogenicity.

9.2 Sample Size Determination

Primary Objective: Characterise Immunogenicity (Precision)

Historical data were available for the immunogenicity responses to AZD1222 from the pooled COV001/002/003/005 studies. Table 10 presents the log transformed immunogenicity responses (ie, geometric mean titres) by assay for participants that received 2 standard doses

of AZD1222. These results indicate that the pseudo-neutralising antibodies exhibited the largest variation (standard deviation of 1.20 and 1.10 for the 4-week and 12-week dosing intervals respectively), while live-neutralising antibodies had the lowest (standard deviation of 0.72 for the 4-week dosing interval).

Table 10 Historic Immunogenicity Responses by Dosing Interval (Geometric Mean Antibody Titres, Standard Dose Immunogenicity Analysis Set)

	Post-1st Dose			Post-2nd dose with a 4-week dosing interval[a]			Post-2nd dose with a 12-week dosing interval[b]		
Assay	**N**	**Mean**	**Std Dev**	**N**	**Mean**	**Std Dev**	**N**	**Mean**	**Std Dev**
Pseudo	476	4.3	1.34	166	5.3	1.20	113	5.4	1.10
Live	51	4.9	1.15	42	6.2	0.72	0	-	-
Spike protein	1139	9.1	1.14	293	10.1	0.96	302	10.7	0.83

[a] Estimates from pooled COV001/002/003/005 study data from participants with 2- to 6-week dosing interval
[b] Estimates from pooled COV001/002/003/005 study data from participants with 10- to 14-week dosing interval

Table 11 presents the seroresponse (ie, > 4 fold increase from baseline) by assay. These results indicate that the pseudo-neutralising antibodies exhibited the lowest proportion of seroresponse (59.7% and 85.5% for the 4-week and 12-week dosing intervals respectively), while both live-neutralising and spike-binding seroresponse rates exceeded 95%.

Table 11 Historic Seroresponse Rates by Dosing Interval (>4-fold Increase from Baseline, Standard Dose Immunogenicity Analysis Set)

	Post-1st Dose		Post-2nd dose with a 4-week dosing interval[a]		Post-2nd dose with a 12-dose week interval[b]	
Assay	**N**	**Proportion**	**N**	**Proportion**	**N**	**Proportion**
Pseudo	499	32%	382	59.7%	117	85.5%
Live	96	75%	95	96.8%	-	-
Spike protein	940	96.6%	636	95.9%	304	99.3%

[a] Estimates from pooled COV001/002/003/005 study data from participants with 2- to 6-week dosing interval
[b] Estimates from pooled COV001/002/003/005 study data from participants with 10- to 14-week dosing interval

Under the assumption that the immunogenicity responses (ie, geometric mean antibody titres) associated with AZD2816 will be similar to the responses associated with AZD1222 in participants that received 2 standard doses in the pooled COV001/002/003/005 studies, in which standard deviations ranged from 0.72 to 1.2 (Table 10), 150 participants will provide a 95% confidence interval half-width between 0.115 and 0.192 (see Table 12). Similarly, 300 participants will provide a 95% confidence interval half-width between 0.081 and 0.136.

Table 12 Estimated Half-width of the 95% Confidence Intervals for Immunogenicity Responses (Geometric Mean Titres) Based on Historic Immunogenicity Assay Variances and the Proposed Sample Sizes

Standard Deviation	Number of participants	Estimated half-width of the 95% confidence interval (natural log scale)
0.72	150	0.115
	300	0.081
0.83	150	0.133
	300	0.094
0.96	150	0.154
	300	0.109
1.1	150	0.176
	300	0.124
1.2	150	0.192
	300	0.136

Under the assumption that the seroresponse rates associated with AZD2816 will be similar to the response rates in adults that received 2 standard doses of AZD1222 in the pooled COV001/002/003/005 studies (Table 11), 150 participants will provide a 95% confidence interval half-width between 1.33% and 7.85%, and 300 participants will provide a 95% confidence interval half-width between 0.94% and 5.55% (Table 13).

Table 13 Estimated Half-Width of the 95% Confidence Interval for the Seroresponse Rates based on Historic Seroconversion Rates and Proposed Sample Sizes

Observed seroconversion rate	Number of participants	Estimated half-width of the 95% confidence interval
59.7%	150	7.85%
	300	5.55%
85.5%	150	5.63%
	300	3.98%
95.9%	150	3.17%
	300	2.24%
96.8%	150	2.82%
	300	1.99%
99.3%	150	1.33%
	300	0.94%

For a fixed sample size, the precision with which the 95% confidence interval of the binary seroresponse rate can be estimated is a function of the response rate. Table 13 provides the lower bounds of the 95% confidence interval for selected response proportions for alternate sample sizes. For a given response rate, we can be 95% confident that the true seroresponse rate is at least as large as the lower bound of the confidence interval.

Primary Objective: Safety

Table 14 indicates the probability of observing 1 or more safety events, such as solicited injection site or systemic reactogenicity events or an unsolicited non-serious AE of a particular type for participants in each treatment arm. With the sample size of 300 participants, at least 1 participant with an AE of incidence rate of 1% can be detected with probability of about 95%.

Table 14 Probability of detecting 1 or more safety events (N = 300)

Event Frequency	Probability (> 1 event)
≥ 10% (Very Common)	> 99%
≥ 1% (Common)	95%
≥ 0.1% (Uncommon)	26%
≥ 0.01% (Rare)	3%

Secondary Objective: Compare Immunogenicity

Although this study will describe and compare the immune responses between AZD2816 and AZD1222 for selected group pairs, no-formal non-inferiority margin for either the geometric mean titre ratio or the difference in seroresponse is prospectively defined.

Under the assumption that there is no difference between treatment arms of interest (ie, a ratio of 1, difference on the log scale of 0), the power conferred by 150 and 300 participants respectively for the comparison of geometric mean titre ratio using a noninferiority margin of 1.5 (equivalent to a difference on the log scale of 0.405) is presented in Table 15.

Table 15 Power for Non-inferiority Using 1.5 as the Upper Bound of the Geometric Mean Titre Ratio

Sides	Null difference	Assumed mean treatment difference	Assumed standard deviation	N of participants in comparator group	N of participants in reference group	Alpha	Power
Upper	ln1.5 = 0.405	0	0.72	150	300	0.025	> 0.999
				300	300		> 0.999
			0.83	150	300		0.998
				300	300		> 0.999
			0.96	150	300		0.988
				300	300		> 0.999
			1.10	150	300		0.957
				300	300		0.994
			1.20	150	300		0.920
				300	300		0.985

Similarly, if there is no difference between treatment arms of interest (ie, a ratio of 1) in the proportion of seroresponders, 300 participants provides 80% power for to establish non-inferiority to within margin of -10% if the seroresponse rate is > 75%. The observed pseudo-neutralising response rates (> 4 fold increase from baseline) from the COV001/002/003/005 studies for AZD1222 were 59.7% and 85.5% for the 4-week and 12-week dosing interval respectively (Table 11). A population of 300 participants provides 70% power to detect non-inferiority (using a non-inferiority margin of -10%) if the observed response rate is 59.7% (Table 16).

Table 16 Power for Non-inferiority Using -10% as the Upper Bound of the Difference in Seroresponse Rate

Sides	Null proportion difference	Assumed proportion of seroresponders in both groups	Assumed difference in proportion of seroresponders	N in comparator group	N in reference group	Alpha	Power
Lower	-0.1	0.597	0	150	300	0.025	0.546
				300	300		0.707
		0.855		150	300		0.844
				300	300		0.929
		0.959		150	300		0.998
				300	300		> 0.999
		0.968		150	300		> 0.999
				300	300		> 0.999
		0.993		150	300		> 0.999
				300	300		> 0.999

9.3 Populations for Analyses

The following populations are defined:

Table 17 Populations for Analysis

Population	Description
All participants analysis set	All participants screened for the study, to be used for reporting disposition and screening failures.
Full analysis set	All randomised participants who received study treatment, irrespective of their protocol adherence and continued participation in the study. Participants will be analysed according to their randomised treatment, irrespective of whether or not they have prematurely discontinued, according to the intent-to-treat principle. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination.
Safety analysis set	The safety analysis set consists of all participants who have received study treatment. Erroneously-treated participants (eg, those randomised to AZD2816, but were actually given treatment AZD12222) are accounted for in this analysis set by assigning them to the treatment they actually received.

Table 17 Populations for Analysis

Population	Description
Immunogenicity analysis set	The vaccine immunogenicity analysis set will include all randomised participants, received at least 1 dose of planned study treatment (ie, 1 dose of either AZD2816 or 1 dose of AZD1222), had baseline and post-dose antibody measurements, have at least 1 post-dose quantifiable serum titre, and had no protocol deviations judged to have the potential to interfere with the generation or interpretation of an antibody response. The analyses conducted using this analysis set will be based on the actual treatment received.
Seronegative immunogenicity analysis set	The subset of the immunogenicity analysis set who were seronegative at baseline.
Seropositive immunogenicity analysis set	The subset of the immunogenicity analysis set who were seropositive at baseline.

Participants that are SARS-CoV-2 seropositive at screening will be included in seropositive analysis sets analogous to the above seronegative analysis sets. Further definition is provided in the Statistical Analysis Plan.

9.4 Statistical Analyses

This section provides a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints. A more technical and detailed description of the statistical analyses will be described in the Statistical Analysis Plan, and an approved version will be finalized prior to the interim analyses.

9.4.1 General Considerations

An interim analysis will occur when all previously vaccinated participants have completed their Day 29 visit (ie, 28 days after booster dose). It is estimated that this early analysis has the potential to provide clear signals about whether AZD2816 provides a strong neutralizing response against the B.1.351 strain while retaining immunogenicity against the Wuhan strain, and thereby influence programmatic decisions early.

A second interim analysis may be performed when previously unvaccinated participants have completed their Day 29 visit (ie, 28 days after fist dose). This analysis is intended to assess immunogenicity variability. The number of previously unvaccinated participants per treatment arm may be increased based upon the results of this analysis. The details of this interim analysis, including the trigger and methods, will be specified in the Statistical Analysis Plan to be finalized prior to any interim analysis.

The primary analysis will occur when all participants have completed their Day 29 visit and safety and immunogenicity data from all unvaccinated participants randomised to a 4-week

dosing interval are available through completion of their visit 28 days after the second priming dose.

A secondary analysis will occur when all participants have completed their Day 29 visit and safety and immunogenicity data from all unvaccinated participants (including those randomised to a 12-week dosing interval) are available through completion of the visit 28 days after the second dose.

The final analysis will occur when data from all vaccinated participants is available through completion of the last study visit (180 days after the single dose for previously vaccinated participants / 180 days after the second dose for unvaccinated participants).

To maintain trial integrity sponsor roles with direct input into participant management and safety monitoring will not have access to unblinded participant level data or associated outputs from the interim analyses until end of study.

Further details on the tools and processes to maintain the blind will be presented in the Study Integrity Plan.

9.4.2 Safety

9.4.2.1 Primary Endpoints

Overview

Descriptive analyses will support evaluation of safety, reactogenicity and immunogenicity. The primary safety analysis includes:

- Incidence of local and systemic solicited AEs for 7 days following each vaccination will be summarised by day and overall.
- Incidence of unsolicited AEs for 28 days following each vaccination will be summarised by system organ class and preferred term, and by relationship to vaccination as assessed by the investigator.
- MAAEs, SAEs, and AESIs following the first vaccination and throughout the study duration will be summarised by system organ class and preferred term and by relationship to vaccination as assessed by the investigator.
- The change from baseline for safety laboratory measures at 7 and 28 days after vaccination.

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

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

A listing will cover details for each individual AE. Full details of all AE analyses will be provided in the Statistical Analysis Plan, including intercurrent events for safety due to potential unblinding of participants for administration of licensed and/or approved SARS-CoV-2 or COVID-19 vaccine.

At the time of the interim analyses, group assignment will not be presented when safety event data has the potential to unblind participant's study group attribution.

9.4.2.2 Other Safety Endpoints

Vital Signs

Vital sign measurements will be performed as specified in the Schedule of Activities (Section 1.3). The set of assessments will include pulse oximetry, blood pressure, and body temperature.

Details of all vital sign analyses will be provided in the Statistical Analysis Plan, which will include descriptive statistics presented for observed values for all vital sign parameters.

COVID-19

This study will describe the incidence of COVID-19 adverse events from the first dose of the vaccine to study end (180 days post-vaccination). Descriptive statistics will be produced based on the safety analysis set. Full details will be documented in the statistical analysis plan.

9.4.3 Immunogenicity

9.4.3.1 Immunogenicity Endpoints

The immunogenicity endpoints of interest in this study are:

- Geometric mean antibody titre.
- Seroresponse, defined as ≥ 4-fold increase in the geometric mean antibody titre from baseline

Both the geometric mean antibody titre and seroresponse of participants will be summarized descriptively by strain, treatment arm, and timepoint for the immunogenicity population.

9.4.3.1.1 Estimand framework for immunogenicity descriptions and comparisons

Target populations:

1) Previously unvaccinated participants

a. Seronegative Analysis Set: and with no evidence of prior or current infection

2) Participants who previously received SARS-CoV-2 vaccination with either AZD1222 or a licensed mRNA vaccine according to the authorized dose and dosing regimen at least 3 months prior to first study intervention (see Section 5.1.2).

Outcome variable: neutralizing antibody and binding titres to SARS-CoV-2 at 28 days after each treatment administration (1 treatment administration for the previously vaccinated population and 2 planned treatment administrations for the unvaccinated population).

Treatment conditions:

Previously unvaccinated population

- 2 doses of AZD1222 given on Day 1 and on Day 29 (4-week interval)
- 2 doses of AZD2816 given on Day 1 and on Day 29 (4-week dosing interval)
- 1 dose of AZD1222 given on Day 1 and 1 dose of AZD2816 on Day 29 (4-week dosing interval)
- 2 doses of AZD2816 given on Day 1 and on Day 85 (12-week dosing interval)

Previously vaccinated population

- 1 dose of AZD1222 given on Day 1.
- 1 dose of AZD2816 given on Day 1.

Intercurrent events: the following intercurrent events could impact the antibody levels achieved:

- missing the second vaccination (for the unvaccinated population)
- receiving of immune-modifying drugs or vaccines
- subsequent infection with SARS-CoV-2.

All immunogenicity descriptions and comparisons will use the principal stratum strategy, ie, all analyses will exclude participants who experience any of the intercurrent events above

Population-level summary:

Descriptive Analyses (see Table 19 and Table 20)

- geometric means of the antibody titres

- seroresponse proportions

Comparative Analyses (see Table 21 and Table 22)

- ratio of geometric means of the antibody titres.
- difference in seroresponse proportion

Planned Descriptive Analyses:

Table 19 and Table 20 present planned descriptive immunogenicity analyses for the unvaccinated and previously vaccinated populations respectively (each one exploring an individual treatment arm at a specific timepoint against a particular strain).

The tables show that without introduction of further variants, there are 24 planned descriptive analyses for the unvaccinated population and 16 planned descriptive analyses for the previously immunised population (index). Within each table there is an analysis key which describes the population (see Table 18). The descriptive analyses presented in Tables 19 and 20 will be repeated for the subset of participants who are seropositive at screening.

Table 18 Description of the Analysis Keys for Tables 19 and 20

Population	Analysis Key	Example
Previously unvaccinated	Primary series dosing interval: P4 (4-week dosing interval) or P12 (12-week dosing interval) Treatment received: 1222 (2 doses of AZD1222) or 2816 (2 doses of AZD2816) or 1222/2816 (1 dose of AZD1222 followed by 1 dose of AZD2816) Strain: W (Wuhan-Hu-1) or V (Variant B.1.351) Analysis Timepoint: 1 (28 days post-dose 1) 2 (28 days post-dose 2)	[P4:1222:W:1] = Immunogenicity following primary vaccination with a 4-week dosing interval of 2 doses of AZD1222 against Wuhan-Hu-1 28 days post-dose 1
Previously vaccinated	Pre-study primary vaccination: P1222 (2 doses of AZD1222) or PmRNA (2 doses of an mRNA vaccine) Treatment received: B1222 (1 booster dose of AZD1222) or B2816 (1 booster dose of AZD2816) Strain: W (Wuhan-Hu-1) or V (Variant B.1.351)	[P1222:B1222:V] = Immunogenicity in participants who were previously vaccinated with 2 doses of AZD1222 as primary vaccination series and received a single boost dose of AZD1222 against the B.1.351 variant

Table 19 Immunogenicity Descriptive Analysis for Previously Unvaccinated Treatment Groups (with Separate Seronegative and Seropositive Analyses)

Objective	Treatment	Dosing interval	Strain	Timepoint	Endpoint	Index	Analysis Key
To describe the humoral immune responses induced by a 2-dose primary vaccination with AZD1222 with a 4-week interval in unvaccinated participants	AZD1222	4 weeks	Wuhan-Hu-1	28 days after 1st dose	GMT	1	[P4:1222:W:1]†
					Seroresponse	2	
				28 days after 2nd dose	GMT	3	[P4:1222:W:2]
					Seroresponse	4	
			B.1.351	28 days after 1st dose	GMT	5	[P4:1222:V:1]†
					Seroresponse	6	
				28 days after 2nd dose	GMT	7	[P4:1222:V:2]
					Seroresponse	8	
To describe the humoral immune responses induced by a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in unvaccinated participants	AZD2816	4 weeks	Wuhan-Hu-1	28 days after 1st dose	GMT	9	[P4:2816:W:1]‡
					Seroresponse	10	
				28 days after 2nd dose	GMT	11	[P4:2816:W:2]
					Seroresponse	12	
			B.1.351	28 days after 1st dose	GMT	13	[P4:2816:V:1]‡
					Seroresponse	14	
				28 days after 2nd dose	GMT	15	[P4:2816:V:2]
					Seroresponse	16	
To describe the humoral immune responses against induced by a 2-dose primary heterologous vaccination with AZD1222/AZD2816 with a 4-week dosing interval in unvaccinated participants	AZD1222/2816	4 weeks	Wuhan-Hu-1	28 days after 2nd dose	GMT	17	[P4:1222/2816:W:2]
					Seroresponse	18	
			B.1.351	28 days after 2nd dose	GMT	19	[P4:1222/2816:V:2]
					Seroresponse	20	
To describe the humoral immune responses induced by a 2-dose primary vaccination with AZD2816 with a 12-week interval in unvaccinated participants	AZD2816	12 weeks	Wuhan-Hu-1	28 days after 1st dose	GMT	21	[P12:2816:W:2]
					Seroresponse	22	
			B.1.351	28 days after 2nd dose	GMT	23	[P12:2816:V:2]
					Seroresponse	24	

† descriptive summaries for 28 days after 1st dose will pool all treatment groups who received AZD1222 as their first dose (ie, homologous and heterologous series).
‡ descriptive summaries for 28 days after 1st dose will pool all treatment groups who received AZD2816 as their first dose (4-week interval and 12-week interval treatment arms).

GMT: Geometric mean titre

Table 20 Immunogenicity Descriptive Analysis for Previously Vaccinated Treatment Groups (with Separate Seronegative and Seropositive Analyses)

Objective	Primary vaccination	Booster Treatment	Strain	Timepoint	Endpoint	Index	Analysis Key
To assess the humoral immune response induced by 1 dose of AZD1222 in participants previously vaccinated with AZD1222	AZD1222	AZD1222	Wuhan-Hu-1	28 days after booster dose	GMT	1	[P1222:B1222:W]
					Seroresponse	2	
			B.1.351	28 days after booster dose	GMT	3	[P1222:B1222:V]
					Seroresponse	4	
To assess the humoral immune response induced by 1 dose of AZD2816 in participants previously vaccinated with AZD1222		AZD2816	Wuhan-Hu-1	28 days after booster dose	GMT	5	[P1222:B2816:W]
					Seroresponse	6	
			B.1.351	28 days after booster dose	GMT	7	[P1222:B2816:V]
					Seroresponse	8	
To assess the humoral immune response induced by 1 dose of AZD2816 in participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	mRNA	AZD2816	Wuhan-Hu-1	28 days after booster dose	GMT	9	[PmRNA:B2816:W]
					Seroresponse	10	
			B.1.351	28 days after booster dose	GMT	11	[PmRNA:B2816:V]
					Seroresponse	12	
To assess the humoral immune response induced by 1 dose of AZD1222 in participants previously vaccinated with a SARS-CoV-2 mRNA vaccine		AZD1222	Wuhan-Hu-1	28 days after booster dose	GMT	13	[PmRNA:B1222:W]
					Seroresponse	14	
			B.1.351	28 days after booster dose	GMT	15	[PmRNA:B1222:V]
					Seroresponse	16	

GMT: Geometric mean titre

In addition to descriptive immunogenicity assessments for all treatment arms, geometric mean titre ratios and differences in seroresponse will be evaluated for the pairs of groups as detailed in Table 21 and Table 22. For each pair, the two-sided 95% confidence intervals for the ratio of the geometric mean titre and difference in seroresponse will be calculated. The geometric mean titre ratio assume a normal distribution for the natural log of the concentration. All confidence intervals will be unadjusted for multiple analyses and are provided solely as a guide to clinical and scientific judgment. It is acknowledged that the chance of falsely concluding that one or more differences in immunogenicity outcomes exist will be greater than the nominal two-sided 0.05 level used for each individual comparison.

Table 21 Immunogenicity Comparisons for Previously Unvaccinated Groups

Objective	$\frac{[\mathbf{GMT}_{\mathbf{comparator}}]}{[\mathbf{GMT}_{\mathbf{reference}}]}$	$\Delta = [\mathbf{Seroresponse}_{\mathbf{comparator}}] - [\mathbf{Seroresponse}_{\mathbf{reference}}]$
To evaluate the immune responses elicited by a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week interval in previously unvaccinated participants	$\frac{[\mathrm{P4:2816:V:2}]}{[\mathrm{P4:1222:W:2}]}$	$[\mathrm{P4:2816:V:2}] - [\mathrm{P4:1222:W:2}]$
	$\frac{[\mathrm{P4:2816:V:1}]}{[\mathrm{P4:1222:W:1}]}$	$[\mathrm{P4:2816:V:1}] - [\mathrm{P4:1222:W:1}]$
	$\frac{[\mathrm{P4:2816:W:2}]}{[\mathrm{P4:1222:W:2}]}$	$[\mathrm{P4:2816:W:2}] - [\mathrm{P4:1222:W:2}]$
	$\frac{[\mathrm{P4:2816:W:1}]}{[P4:1222:W:1]}$	$[\mathrm{P4:2816:W:1}] - [\mathrm{P4:1222:W:1}]$
	$\frac{[\mathrm{P4:2816:V:2}]}{[\mathrm{P4:1222:V:2}]}$	$[\mathrm{P4:2816:V:2}] - [\mathrm{P4:1222:V:2}]$
	$\frac{[P4:2816:V:1]}{[P4:1222:V:1]}$	$[\mathrm{P4:2816:V:1}] - [\mathrm{P4:1222:V:1}]$
To evaluate the immune responses elicited by a 2-dose primary heterologous vaccination with AZD1222/AZD2816 with a 4-week dosing interval relative to the response elicited by a 2-dose primary homologous vaccination with AZD1222 with a 4-week interval in previously unvaccinated participants	$\frac{[\mathrm{P4:1222/2816:V:2}]}{[\mathrm{P4:1222:W:2}]}$	$[\mathrm{P4:1222/2816:V:2}] - [\mathrm{P4:1222:W:2}]$
	$\frac{[\mathrm{P4:1222/2816:W:2}]}{[\mathrm{P4:1222:W:2}]}$	$[\mathrm{P4:1222/2816:W:2}] - [\mathrm{P4:1222:W:2}]$
	$\frac{[\mathrm{P4:1222/2816:V:2}]}{[\mathrm{P4:1222:V:2}]}$	$[\mathrm{P4:1222/2816:V:2}] - [\mathrm{P4:1222:V:2}]$
To evaluate the immune responses elicited by a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval relative to the response elicited by a 2-dose primary vaccination with AZD2816 with a 4-week interval in previously unvaccinated participants	$\frac{[\mathrm{P12:2816:W:2}]}{[\mathrm{P4:2816:W:2}]}$	$[\mathrm{P12:2816:W:2}] - [\mathrm{P4:2816:W:2}]$
	$\frac{[\mathrm{P12:2816:V:2}]}{[\mathrm{P4:2816:V:2}]}$	$[\mathrm{P12:2816:V:2}] - [\mathrm{P4:2816:V:2}]$

Table 22 Immunogenicity Comparisons for Previously Vaccinated Groups

Objective	$\frac{[\mathbf{GMT_{comparator}}]}{[\mathbf{GMT_{reference}}]}$	$\Delta = [\mathbf{Seroresponse_{comparator}}] - [\mathbf{Seroresponse_{reference}}]$
To evaluate the immune responses elicited by 1 dose of AZD2816 in participants previously vaccinated with AZD1222 relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated participants	$\frac{[\text{P1222: B2816: V}]}{[\text{P4: 1222: W: 2}]}$	$[\text{P1222: B2816: V}] - [\text{P4: 1222: W: 2}]$
	$\frac{[\text{P1222: B2816: W}]}{[\text{P4: 1222: W: 2}]}$	$[\text{P1222: B2816: W}] - [\text{P4: 1222: W: 2}]$
To evaluate the immune responses elicited by 1 dose of AZD2816 in participants previously vaccinated with a mRNA vaccine relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated participants	$\frac{[\text{PmRNA: B2816: V}]}{[\text{P4: 1222: W: 2}]}$	$[\text{PmRNA: B2816: V}] - [\text{P4: 1222: W: 2}]$
	$\frac{[\text{PmRNA: B2816: W}]}{[\text{P4: 1222: W: 2}]}$	$[\text{PmRNA: B2816: W}] - [\text{P4: 1222: W: 2}]$
To evaluate the immune responses elicited by 1 dose of AZD2816 in participants previously vaccinated with an mRNA vaccine relative to the response with 1 dose of AZD1222 in participants previously vaccinated with AZD1222	$\frac{[\text{PmRNA: B2816: V}]}{[\text{P1222: B1222: W}]}$	$[\text{PmRNA: B2816: V}] - [\text{P1222: B1222: W}]$
	$\frac{[\text{PmRNA: B2816: W}]}{[\text{P1222: B1222: W}]}$	$[\text{PmRNA: B2816: W}] - [\text{P1222: B1222: W}]$
	$\frac{[\text{PmRNA: B2816: V}]}{[\text{P1222: B1222: V}]}$	$[\text{PmRNA: B2816: V}] - [\text{P1222: B1222: V}]$
To evaluate the immune responses elicited by 1 dose of AZD2816 relative to the response with 1 dose of AZD1222 in participants previously vaccinated with AZD1222	$\frac{[\text{P1222: B2816: V}]}{[\text{P1222: B1222: W}]}$	$[\text{P1222: B2816: V}] - [\text{P1222: B1222: W}]$
	$\frac{[\text{P1222: B2816: W}]}{[\text{P1222: B1222: W}]}$	$[\text{P1222: B2816: W}] - [\text{P1222: B1222: W}]$
	$\frac{[\text{P1222: B2816: V}]}{[\text{P1222: B1222: V}]}$	$[\text{P1222: B2816: V}] - [\text{P1222: B1222: V}]$
To evaluate the immune responses elicited by 1 dose of AZD1222 in participants previously vaccinated with AZD1222 relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated participants	$\frac{[\text{P1222: B1222: V}]}{[\text{P4: 1222: W: 2}]}$	$[\text{P1222: B1222: V}] - [\text{P4: 1222: W: 2}]$
	$\frac{[\text{P1222: B1222: W}]}{[\text{P4: 1222: W: 2}]}$	$[\text{P1222: B1222: W}] - [\text{P4: 1222: W: 2}]$
To evaluate the immune responses elicited by 1 dose of AZD1222 in	$\frac{[\text{PmRNA: B1222: V}]}{[\text{P4: 1222: W: 2}]}$	$[\text{PmRNA: B1222: V}] - [\text{P4: 1222: W: 2}]$

Table 22 Immunogenicity Comparisons for Previously Vaccinated Groups

Objective	$\frac{[\mathbf{GMT}_{\mathbf{comparator}}]}{[\mathbf{GMT}_{\mathbf{reference}}]}$	$\Delta = [\mathbf{Seroresponse}_{\mathbf{comparator}}] - [\mathbf{Seroresponse}_{\mathbf{reference}}]$
participants previously vaccinated with an mRNA vaccine relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated participants	$\frac{[\mathrm{PmRNA:B1222:W}]}{[\mathrm{P4:1222:W:2}]}$	$[\mathrm{PmRNA:B1222:W}] - [\mathrm{P4:1222:W:2}]$
To evaluate the immune responses elicited by 1 dose of AZD2816 versus 1 dose of AZD1222 in participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	$\frac{[\mathrm{PmRNA:B2816:V}]}{[\mathrm{PmRNA:B1222:W}]}$	$[\mathrm{PmRNA:B2816:V}] - [\mathrm{PmRNA:B1222:W}]$
	$\frac{[\mathrm{PmRNA:B2816:W}]}{[\mathrm{PmRNA:B1222:W}]}$	$[\mathrm{PmRNA:B2816:W}] - [\mathrm{PmRNA:B1222:W}]$
	$\frac{[\mathrm{PmRNA:B2816:V}]}{[\mathrm{PmRNA:B1222:V}]}$	$[\mathrm{PmRNA:B2816:V}] - [\mathrm{PmRNA:B1222:V}]$

9.4.4 Data Safety Monitoring Board

An independent COVID-19 Vaccine Data Safety Monitoring Board will provide oversight, to ensure safe and ethical conduct of the study. During the study, the benefit/risk assessment will be continuously monitored by the Board to ensure that the balance remains favourable. Further details, composition, and operation of the COVID-19 Vaccine Data Safety Monitoring Board will be described in a separate charter. For further details, see Appendix A 5.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Not applicable.

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

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

Regulatory Reporting Requirements for SAEs

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

A 2 Financial Disclosure

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

A 3 Informed Consent Process

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

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

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

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

A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

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

A 5 Committee Structure

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

A COVID-19 Vaccine Data Safety Monitoring Board comprised of independent experts will be convened to provide oversight and to ensure safe and ethical conduct of the study. The COVID 19 Vaccine Data Safety Monitoring Board will have the responsibility of evaluating cumulative safety and other clinical study data at regular intervals and making appropriate recommendations based on the available data. During the study, the benefit/risk assessment will be continuously monitored by the COVID-19 Vaccine Data Safety Monitoring Board to ensure that the balance remains favourable. Full details of the COVID-19 Vaccine Data Safety Monitoring Board composition and operations can be found in the COVID-19 Vaccine Data Safety Monitoring Board Charter.

An independent Neurological AESI Expert Committee will be available to review and provide on request about the diagnosis and causality assessment of selected neurological AEs of special interest occurring in the study. Details on the composition and operation of this committee are described in the Neurological AESI Expert Committee Charter.

A 6 Dissemination of Clinical Study Data

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

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

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

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A 9 Study and Site Start and Closure

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

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or ICH/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 IRB/IECs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of 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 SAEs and non-SAEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

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

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

AEs for **malignant tumours** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-SAE**. 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 hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life Threatening

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

Hospitalization

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

Important Medical Event or Medical Treatment

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

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used. Examples of important medical events include such events as listed below:

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

Intensity Rating Scale

A revised toxicity grading scale found in the US FDA guidance for healthy volunteers enrolled in a preventive vaccine clinical study (FDA 2007) will be utilized for all events with an assigned severity grading including Grade 5.

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

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

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 investigational product.

- 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 investigational product?
- Consistency with known investigational product profile. Was the AE consistent with the previous knowledge of the suspect investigational product (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 investigational product?
- 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 investigational product was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

- Is this a recognized feature of overdose of the investigational medicinal product?
- 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 3 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 investigational product, but rather a human or process related failure while the investigational product 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 investigational product
- 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:

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

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

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

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

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

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

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

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

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

C 2 Withdrawal of Informed Consent for Donated Biological Samples

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

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

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

The investigator:

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

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

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

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

Appendix D 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 23: Clinical Abnormalities, Local Reactions to Injectable Product
- Table 24: Clinical Abnormalities, Vital Signs
- Table 25: Clinical Abnormalities, Systemic (General or Illness)

Table 23 Tables for Clinical Abnormalities: Local Reactions to Injectable Product

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

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

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

ER: emergency room.

Table 24 Tables for Clinical Abnormalities: Vital Signs

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

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

Table 25 Tables for Clinical Abnormalities: Systemic (General or Illness)

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

Appendix E Adverse Events of Special Interest

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

Table 26 Adverse Events of Special Interest

Category	Medical Concept
Neurologic	Generalized convulsion: episodes of neuronal hyperactivity most commonly resulting in sudden, involuntary muscular contractions. They may also manifest as sensory disturbances, autonomic dysfunction and behavioural abnormalities, and impairment or loss of consciousness.
	Guillain-Barré syndrome: a peripheral nerve demyelinating disease, which can present as temporary ascending paralysis.
	Acute disseminated encephalomyelitis: defined as a uniphasic syndrome of brain inflammation and demyelination occurring in temporal association with an antecedent immunologic challenge, such as infection or an immunization. ADEM most commonly occurs in the paediatric population.
	Other neurologic events: include new onset event (acute or subacute) motor and sensory disturbances (eg, weakness, numbness, paraesthesia, hypoesthesia, hyperesthesia, dysesthesias), bowel/bladder dysfunction, gait impairment, or visual disturbance, or any event of myelitis, encephalomyelitis, myelitis transverse, or other sudden neurological deficit.
Vascular	Thrombotic, thromboembolic, and neurovascular events: events that can manifest as transient or permanent vision problems, dizziness, trouble understanding, facial droop, slurred speech, unilateral weakness, deep vein thrombosis with swollen, warm or painful leg, pulmonary embolism with shortness of breath, chest pain or irregular heart rate.
Hematologic	Thrombocytopenia: a disorder in which there is an abnormally low platelet count; a normal platelet count ranges from 150 000 to 450 000 platelets per µL.
Immunologic	Vasculitides: a group of related disorders characterized by inflammation of blood vessels (vasculitis) leading to tissue or end-organ injury.
	Anaphylaxis: an acute hypersensitivity reaction with multi-organ-system involvement that can present as, or rapidly progress to, a severe life-threatening reaction requiring immediate medical attention.
	Vaccine-associated enhanced respiratory disease: pathogenicity has been linked to a vaccine immune response characterized by induction of non-neutralizing antibodies, and a T-cell response of the Th2 type with hypereosinophilia (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: 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 27.

Table 27 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

Table 27 List of Potential Immune-mediated Medical Conditions

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, Bechet's syndrome, leukocytoclastic vasculitis

Table 27 List of Potential Immune-mediated Medical Conditions

Category	Condition
Other	Antiphospholipid syndrome
	Autoimmune haemolytic anaemia
	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 anaemia
	Raynaud's phenomenon
	Sarcoidosis
	Sjögren's syndrome
	Stevens-Johnson syndrome
	Uveitis

Appendix F Actions Required in Cases of Thrombotic Events With Thrombocytopenia and/or Bleeding

F 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of thrombotic events with thrombocytopenia and/or bleeding. It is not intended to be a comprehensive guide to the management of all venous thromboembolic events.

During the course of the study, the investigator will remain vigilant for occurrence of thrombotic events with thrombocytopenia and/or bleeding. Appropriate investigations (eg, imaging) to diagnose these events should be made on a case-by-case basis. The investigator is responsible for determining whether a participant meets criteria for thrombotic events with thrombocytopenia and/or bleeding at any point during the study.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting criteria for thrombotic events with thrombocytopenia and/or bleeding. The Study Physician contacts the investigator to provide guidance, discuss, and agree an approach for the participant's follow-up and the continuous review of data. Guidance from the International Society of Thrombosis and Haemostasis for management of thrombocytopenic thromboembolism occurring after vaccination can be found at www.isth.org. Notably, participants should only be treated with heparin if a test for heparin-induced thrombocytopenia antibodies is negative. An alternative explanation for thrombocytopenia should be considered (eg, alcohol use, liver cirrhosis, concomitant medications, exposure to toxic chemicals, viral infections).

The investigator is responsible for recording data pertaining to thrombotic events with thrombocytopenia and/or bleeding and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

F 2 Tests that Should Be Considered if Thrombotic Events With Thrombocytopenia and/or Bleeding Are Suspected

The following tests should be considered, but not limited to:

1. Measurement of platelet levels, prothrombin time, activated partial thromboplastin time, D-dimer levels, and fibrinogen levels

2. Complete blood count, reticulocyte count, blood film, haptoglobins

3. Anti-platelet factor 4 antibodies

4. Anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies, rheumatoid factor, human leucocyte antigen B27, ADAMTS13 activity, anti-cardiolipin antibodies IgG + IgM, and anti-B2GPI antibodies IgG + IgM

5. Complement (eg, C3, C4, complement complex C5b-9, C5a), autoantibodies (eg, antinuclear IgG, anti-double stranded DNA IgG, anti-Smith IgG, anti-SSA IgG, anti-SSB IgG, anti-Jo1 IgG, anti-MPO IgG, anti-PR3 IgG, anti-glomerular basement membrane IgG)

6. Factor V Leiden, Factor II (prothrombin) variant

7. Platelet activation markers and functional assays (eg: sCD40L, soluble glycoproteins, degranulation markers [PF4, vWF, P-selectin, annexin V]), anti-PF4-plasma-serotonin release assay (if anti-PF4 ELISA positive)

8. Inflammatory markers: TNFa, IL-1, IL-4, IL-6, IL-10, IL-13

9. Cell adhesion molecules: VCAM, ICAM, E-selectin

10. Adenovirus serology

11. Additional viral serology: Cytomegalovirus (IgG and IgM), Ebstein-Barr virus (IgG and IgM), HIV, Parvo virus B19

12. COVID-19 testing, including PCR and serology

13. Calculation of an International Society of Thrombosis and Haemostatis score for Disseminated Intravascular Coagulation (derived from platelet levels, fibrinogen, and D-Dimer)

Appendix G Abbreviations

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ChAdOx1 MERS	Chimpanzee adenovirus Ox1 with MERS Spike antigen
ChAdOx1 nCoV-19	AZD1222 when initially developed by the University of Oxford
COVID-19	Coronavirus disease 2019
eCRF	Electronic case report form
e-Diary	Electronic diary
GMT	Geometric mean titre
ICF	Informed consent form
ICH/GCP	International Council for Harmonisation/Good Clinical Practice
IRB/IEC	Institutional Review Board/ Independent Ethics Committee
IRT	Interactive Response Technology
MAAEs	Medically attended adverse events
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
S	Spike
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome-coronavirus-2

Appendix H Protocol Amendment History

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	2 June 2021
Version 1	14 May 2021

Amendment 1: 2 June 2021

Version 1 of the protocol was amended prior to the commencement of the study (ie, prior to approval of the protocol by an ethics committee) based on feedback from internal and regulatory authority reviews. The most substantial changes were as follows:

- addition of 2 treatment arms: 1) AZD1222 as a single booster vaccination in participants previously vaccinated with an mRNA COVID-19 vaccine and 2) heterologous vaccination with AZD1222 plus AZD2816 in previously unvaccinated participants
- further definition of analysis sets
- addition of thrombotic events with thrombocytopenia as a discontinuation criteria

In addition, corrections and revisions to text to improve readability were made.

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SIGNATURE PAGE

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Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.

Clinical Study Protocol	
Study Intervention	AZD2816
Study Code	D7220C00001
Version	Amendment 2
Date	29 July 2021

TITLE PAGE

A Phase II/III Partially Double-Blinded, Randomised, Multinational, Active-Controlled Study in Both Previously Vaccinated and Unvaccinated Adults to Determine the Safety and Immunogenicity of AZD2816, a Vaccine for the Prevention of COVID-19 Caused by Variant Strains of SARS-CoV-2

Sponsor Name:	**AstraZeneca AB**
Legal Registered Address:	151 85 Södertälje, Sweden
Regulatory Agency Identifier Numbers:	EudraCT: 2021-002530-17

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: D7220C00001

Amendment Number: 2

Study Intervention: AZD2816

Study Phase: II/III

Short Title: Phase II/III Study of AZD2816, a Vaccine for the Prevention of COVID-19 in Adults

Study Physician Name and Contact Information will be provided separately.

International Coordinating Investigator: Andrew J Pollard, FRCPCH PhD FMedSci
University of Oxford
Oxford, United Kingdom

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	29 July 2021
Amendment 1	2 June 2021
Version 1	14 May 2021

Amendment 2: 29 July 2021

The principal reason for this amendment was to

1) add an additional interim analysis to evaluate immunogenicity in a subset of AZD1222 previously vaccinated subjects boosted with AZD1222 or AZD2816

2) revise Objectives/Endpoints from descriptive to comparative, with ranking of primary, key secondary, other secondary, and exploratory objectives

3) add non-inferiority margins to primary analysis and add additional participants to maintain power

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.1 Synopsis (Objectives and Endpoints)	Revised this section from primarily descriptive to primarily comparative. Comparative immunogenicity objectives created and ranked as primary, key secondary, other secondary.	Objectives of study changed from descriptive to comparative, testing for non-inferiority across treatment comparisons	Substantial
1.1 Synopsis (Number of Participants; Statistical Methods)	Overall size increased to 2590 participants	Adjustments made to maintain power with the added non-inferiority margins	Substantial
1.1 Synopsis (Statistical Methods)	An additional interim analysis added. Second interim analysis changed to include only the previously vaccinated with AZD1222 cohort.	Interim analysis plan was reviewed and revised.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.2 Schema	Figures updated with increased participant numbers	Adjustments made to maintain power with the added non-inferiority margins	Substantial
1.3 Schedule of Activities	Table 2: footnote clarification added Table 3: minor corrections	Clarification/Correction	Non-substantial
2.1 Study Rationale (and elsewhere in protocol)	Clarification on previous vaccination criteria	Clarification	Non-substantial
3 Objectives	Section completely rewritten. Divided into 2 sections: Previously unvaccinated and previously vaccinated. Immunogenicity objectives created for comparisons. Objectives ranked as primary, key secondary, other secondary, or exploratory.	Objectives of study changed to show non-inferiority across treatments.	Substantial
4.1 Overall design	Participant numbers increased	Adjustments made to maintain power with the added non-inferiority margins	Substantial
4.1 Overall design	Cap on age added	To ensure good representation across age groups	Substantial
8.3.2	Removal of severity grade 5	Correction	Non-substantial
8.5.2.3 CCI [redacted]	Addition of information on number of patients sampled for CCI [redacted]	Clarification	Non-substantial
9.1 Statistical Hypotheses	Addition of statistical hypotheses	Include hypothesis being tested.	Substantial
9.2 Sample size determination	Confidence intervals for populations of 350 and 380 added to Table 14 and Table 15	Updated to include current populations of 350 and 380 participants	Non-substantial
9.2 Sample size determination	Power estimates for populations of 350 and 380 added to Table 17 and Table 18	Updated to include current populations of 350 and 380 participants	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
9.4.1 General considerations	Details on the initial interim, second interim, and third interim analysis added	Include revised information on the analysis plan, including interim analyses	Substantial
9.4.3.1.1 Estimand framework for immunogenicity descriptions and comparisons	Objectives removed from descriptive analysis Table 23 and Table 24	Objectives of study changed from descriptive to comparative, showing non-inferiority across treatments	Substantial
9.4.3.1.1 Estimand framework for immunogenicity descriptions and comparisons	Section of Immunogenicity Comparisons added.	Objectives of study changed from descriptive to comparative, showing non-inferiority across treatments	Substantial
9.4.3.1.1 Estimand framework for immunogenicity descriptions and comparisons	Table 25 and Table 26 on immunogenicity comparisons revised, aligned with the revised objectives/endpoints.	Objectives of study changed from descriptive to comparative, showing non-inferiority across treatments	Substantial
9.4.4 Multiple Comparisons	Section added.	Objectives of study changed from descriptive to comparative, showing non-inferiority across treatments	Substantial

In addition, the protocol has been revised with minor corrections and clarifications.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A phase II/III partially double-blinded, randomised, multinational, active-controlled study in both previously vaccinated and unvaccinated adults to determine the safety and immunogenicity of AZD2816, a vaccine for the prevention of COVID-19 caused by variant strains of SARS-CoV-2.

Short Title: Phase II/III study of AZD2816, a vaccine for the prevention of COVID-19 in adults.

Rationale: Recently, several variants of the SARS-CoV-2 virus with increased transmissibility have emerged, including B.1.1.7, first identified in the UK, P.1, first identified in Brazil, and B.1.351, first identified in South Africa. In an ongoing clinical trial of AZD1222 in South Africa, interim results failed to show protection against mild to moderate disease caused by the B.1.351 variant; protection against severe disease could not be determined as no severe cases were identified (Madhi et al 2021).

Based on available evidence about vaccine effectiveness and molecular epidemiology of emerging variants, B.1.351 is estimated to have a potential to escape vaccine-elicited immunity. B.1.351 carries sequence mutations in common with other variants of concerns; immunity to B.1.351 therefore has the potential to provide some cross-immunity against other emerging strains. Development of candidate vaccines that include the B.1.351 S-protein variant is underway. AstraZeneca is developing AZD2816, a vaccine against the B.1.351 SARS-CoV-2 variant using the same ChAdOx1 platform and manufacturing processes used for AstraZeneca's currently available COVD-19 vaccine, AZD1222.

Objectives and Endpoints:

The purpose of this study is to characterize the safety and immunogenicity of AZD2816, AstraZeneca's candidate ChAdOx1 vector vaccine against SARS-CoV-2 variant strain B.1.351, when administered:

- As a single dose to SARS-CoV-2 seronegative participants who previously received a 2-dose primary vaccination against SARS-CoV-2 with AZD1222 or an mRNA COVID-19 vaccine
- As a 2-dose primary homologous vaccination to SARS-CoV-2 seronegative participants who are unvaccinated
- As the second dose of 2-dose primary heterologous vaccination (with AZD1222 as first dose) to SARS-CoV-2 seronegative participants who are unvaccinated.

The following table lists the primary and secondary endpoints:

Objectives	Endpoints
Safety Objectives: Previously unvaccinated participants	
- Primary	
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose
- Secondary	
To characterize the safety and tolerability of a 2-dose primary heterologous vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in previously unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety and tolerability of a heterologous primary vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
Immunogenicity objectives: Previously unvaccinated participants	
To determine if the pseudoneutralizing antibody GMT response elicited by a 2-dose AZD2816 primary vaccination is non-inferior to the response elicited by a 2-dose AZD1222 primary vaccination Estimand:	

Treatment	AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Primary	B.1.351	Wuhan-hu-1
Key Secondary 2.2	B.1.351	B.1.351
Key Secondary 2.4	Wuhan-hu-1	Wuhan-hu-1

Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD2816 vaccination/AZD1222 vaccination	
To determine if the seroresponse rate elicited by a 2-dose AZD2816 primary vaccination is non-inferior to the seroresponse rate elicited by a 2-dose AZD1222 primary vaccination Estimand:		
Treatment	AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Key Secondary 2.1	B.1.351	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 vaccination - AZD1222 vaccination	
To determine if the neutralizing antibody GMT response elicited by a 2-dose AZD1222+AZD2816 heterologous primary vaccination is non-inferior to the response elicited by a 2-dose AZD1222 primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Key Secondary 2.3	B.1.351	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD1222+AZD2816 vaccination/AZD1222 vaccination	
To determine if the seroresponse rate elicited by a 2-dose AZD1222+AZD2816 heterologous primary vaccination is non-inferior to the seroresponse rate elicited by a 2-dose AZD1222 primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD1222+AZD2816 vaccination - AZD1222 vaccination	
To determine if the neutralizing antibody GMT response against the B.1.351 variant is non-inferior to the response against the original Wuhan-hu-1 strain following a 2-dose AZD2816 primary vaccination Estimand:		
Treatment	AZD2816 vaccination	AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	

Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 2-dose AZD2816 primary vaccination Estimand:		
Treatment	AZD2816 vaccination	AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) against B.1.351 versusWuhan-hu-1	
To determine if the neutralizing antibody GMT response against the B.1.351 variant is non-inferior to the response against the original Wuhan-hu-1 strain following a 2-dose AZD1222+AZD2816 heterologous primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222+AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 2-dose AZD1222+AZD2816 heterologous primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222+AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) against B.1.351 versusWuhan-hu-1	
To also determine non-inferiority of the s-protein binding antibody response for the above comparisons as other secondary objectives		
To also determine the neutralizing antibody GMT responses 28 days after first vaccination dose in the above primary and key secondary objectives		
Safety Objectives: Previously vaccinated participants		
- Primary		
To characterize the safety and tolerability of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Incidence of local and systemic solicited AEs for 7 days post dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose	

- Secondary	•
To characterize the safety and tolerability of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination

Immunogenicity objectives: previously vaccinated participants

To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination
Estimand:

Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Primary	B.1.351	Wuhan-hu-1
Key Secondary 2.1	B.1.351	B.1.351
Key Secondary 2.3	Wuhan-hu-1	Wuhan-hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 vaccination	

To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose is non-inferior to response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222
Estimand:

Treatment	AZD2816 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Key Secondary 2.2	B.1.351	B.1.351
Key Secondary 2.5	Wuhan-hu-1	Wuhan-hu-1

Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 booster	
To determine if the neutralizing antibody GMT response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 is non-inferior to the response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD1222 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective Level:	Serotype comparison:	
Key Secondary 2.4	Wuhan-hu-1	Wuhan-hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD1222 booster/AZD1222 vaccination	
To determine if the seroresponse elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other secondary	B.1.351	Wuhan-hu-1
Other secondary	B.1.351	B.1.351
Other secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 primary vaccination	
To determine if the seroresponse elicited by an AZD2816 booster dose is non-inferior to response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 booster	
To determine if the seroresponse elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD1222 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 primary vaccination	
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose in participants previously vaccinated with an mRNA-based vaccine is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD2816 booster	AZD1222 primary vaccination

Population	mRNA vaccine vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 vaccination	
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with an mRNA-based vaccine Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	mRNA vaccine vaccinated seronegative participants	mRNA vaccine vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 booster	
To determine if the seroresponse elicited by an AZD2816 booster dose in participants previously vaccinated with an mRNA-based vaccine is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	mRNA vaccine vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 primary vaccination	
To determine if the seroresponse elicited by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with an mRNA-based vaccine Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	mRNA vaccine vaccinated seronegative participants	mRNA vaccine vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 booster	
To determine if the neutralizing antibody GMT response rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 2816 booster dose. Estimand:		
Treatment	AZD2816 booster	AZD2816 booster

Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster version
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-hu-1	
To determine if the neutralizing antibody GMT response against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 1222 booster dose. Estimand:		
Treatment	AZD1222 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 2816 booster dose. Estimand:		
Treatment	AZD2816 booster	AZD2816 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for B.1.351/Wuhan-hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 1222 booster dose. Estimand:		
Treatment	AZD1222 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for B.1.351/Wuhan-hu-1	
To also determine non-inferiority of the s-protein binding antibody response for the above comparisons as other secondary objectives.		

SAEs: serious adverse events; MAAEs: medically attended adverse events; AESIs: adverse events of special interest.

[a] At least a 4-fold increase in geometric mean titre from baseline

Overall Design: This is a phase II/III, multinational, randomised, partially double-blind, controlled study in two distinct cohorts: previously vaccinated and previously unvaccinated participants.

Disclosure Statement: This is a parallel-group preventive study with 8 treatment arms.

Number of Participants: Approximately 2590 SARS-CoV-2 nucleocapsid seronegative participants will be assigned to study intervention to support the primary and secondary objectives of this study. In addition, participants that are SARS-Cov-2 nucleocapsid seropositive at screening will be enrolled and assigned to study intervention for an exploratory analysis, with a cap of 10% of the seronegative population (ie, approximately 259 total participants).

Intervention Groups and Duration: Previously vaccinated participants will receive 1 dose of AZD1222 or AZD2816 on Day 1. Previously unvaccinated participants will receive one of the following 2-dose vaccinations:

- 1 dose of AZD2816 on Day 1 and on Day 29
- 1 dose of AZD1222 on Day1 and on Day 29
- 1 dose of AZD1222 on Day 1 and 1 dose of AZD2816 on Day 29
- 1 dose of AZD2816 on Day 1 and on Day 85.

Participants will be followed up for safety for 180 days after last study vaccine administration.

Data Monitoring Committee: A Data Safety Monitoring Board will provide oversight to ensure safe and ethical conduct of the study.

Statistical Methods:

Sample sizes of 300-380 seronegative participants per group are deemed appropriate based upon available immunogenicity data from previous clinical studies with AZD1222 for the primary and secondary objectives of this study.

The safety analysis set for adverse events consists of all participants who have received at least one dose of study intervention. The immunogenicity analysis set includes all participants in the safety analysis set who have no protocol deviations or intercurrent events judged to have the potential to interfere with the generation or interpretation of an immune response.

An initial interim analysis will be performed on a subset of previously AZD1222 vaccinated participants that have received a booster dose to consider unblinded sample size adjustment. A second interim analysis will be performed when all previously AZD1222 vaccinated participants have completed their Day 29 visit to support registration of a booster dose. A third interim analysis will be performed on a subset of naïve previously unvaccinated participants that have received their second dose to consider blinded sample size adjustment in this population. The primary analysis will be performed when there are data from all naïve participants, 28 days after the second dose of the 4-week dosing intervals to support assessment of these 2-dose primary vaccinations to support registration of the booster dose and a 2-dose primary vaccination. A secondary analysis will be performed on data from 28 days after the second dose of the 12-week dosing interval to support assessment of this 2-dose

primary vaccination. The final analysis will be performed on data from 6 months follow-up after participant's vaccination.

1.2 Schema

Figure 1 Study Design for Unvaccinated Seronegative/Seropositive Participants Receiving a 2-Dose Primary Vaccination

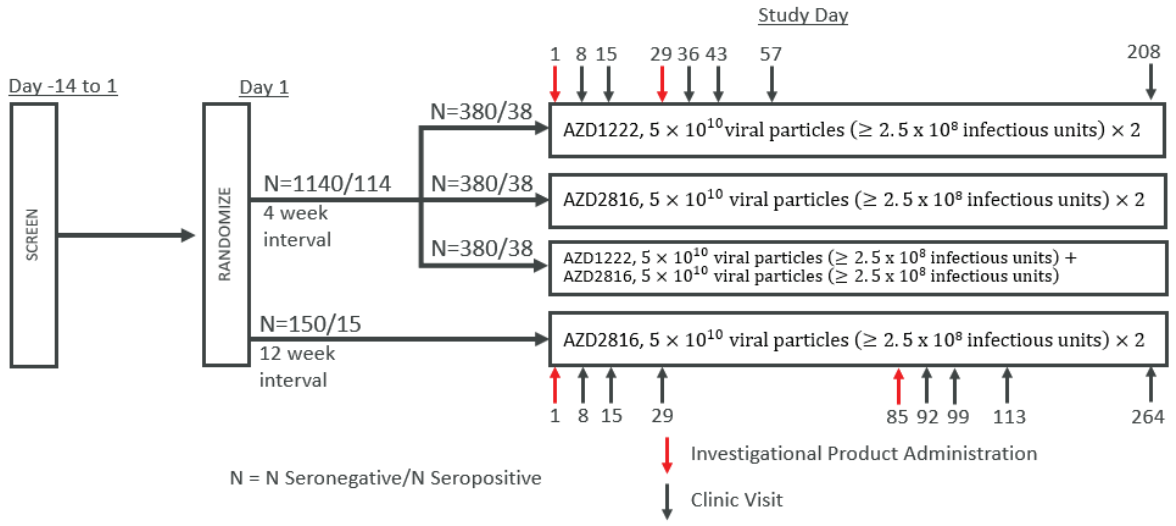
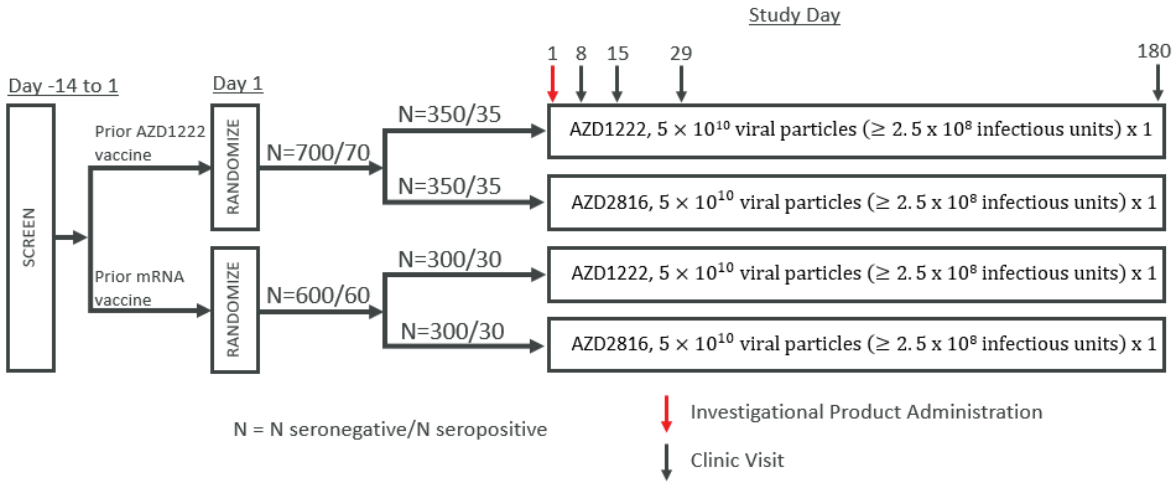


Figure 2 Study Design for Previously Vaccinated Seronegative/Seropositive Participants Receiving a 1-Dose Booster



Note: In addition to the planned 2590 seronegative participants enrolled to support the primary/secondary objectives, seropositive participants will also be enrolled in the study to support exploratory objectives in this population, with a cap of

10% of the planned seronegative participants (ie, a maximum of 259 seropositive participants, bringing total planned enrollment to 2849).

1.3 Schedule of Activities

Table 1 Schedule of Activities: Screening

Procedure	Day -14 to Day 1	See Section
Informed consent	X	5.1, Appendix A 3
Demography	X	-
Medical and surgical history	X	-
Prior and concomitant medications	X	6.5
Complete physical examination, including height and weight	X	8.2.1
Vital signs	X	8.2.2
Urine pregnancy test (for women of childbearing potential only)	X	8.2.3
Clinical safety laboratory assessments	X	8.2.3
Assessment of serious adverse events	X	8.3, Appendix B
Blood sample for SARS-CoV-2 antibody testing (lateral flow test)	X	8.5.2
Verify eligibility criteria	X	5.1, 5.2

Note: Screening activities can occur at same visit as initial vaccination with investigational product (ie, Visit 1 in Table 2, Table 3, and Table 4).

Table 2 Schedule of Activities: Treatment/Follow-up Period for Participants Previously Vaccinated with 2 Doses of AZD1222 or an mRNA Vaccine

Procedure	Treatment and Follow-up Period					Section
Day	**1**	**8**	**15**	**29**	**180**	
Window (days)	**-**	**±2**	**±2**	**±3**	**±14**	
Medical and surgical history	X	-	-	-	-	-
Urine pregnancy test (women of childbearing potential)	X	-	-	-	-	8.2.3
Concomitant medications/vaccinations	X	X	X	X	X	6.5
Verify eligibility criteria	X	-	-	-	-	5.1, 5.2
Monitoring of COVID-19	X	X	X	X	X	8.3.8
Vaccine administration (after screening activities, the activities listed above, and the pre-dose sampling activities listed below)	X	-	-	-	-	6.1.1
Immunological assessments						
Serum sample to assess SARS-CoV-2 serology/neutralising antibodies	X (pre-dose)	-	X	X	X	8.5.2
Serum sample to assess additional immunogenicity	X (pre-dose)	-	X	X	X	8.5.2
Blood sample to assess B-cell and T-cell responses in a sub-group of participants	X (pre-dose)	-	X	X	X	8.5.2.3
Blood sample for B-cell and T-cell response sequencing in a sub-group of participants	X (pre-dose)	-	X	X	X	8.5.2.3
Safety assessments						
Targeted physical examination	X	-	-	-	-	8.2.1
Vital signs	X	X	X	X	X	8.2.2
e-Diary provided with training	X	-	-	-	-	8.3.7
e-Diary collected	-	X	-	-	-	8.3.7
Unsolicited AEs	X (post-dose)	X	X	X	-	8.3
MAAEs, SAEs, and AESIs	X[a]	X	X	X	X	8.3.8, 8.3.8
Clinical safety laboratory assessments	X (pre-dose)[b]	X	-	X	X	8.2.3

[a] Only SAEs pre-dose
[a] Not required to be repeated if performed on screening day prior to Day 1.
AE: adverse event; AESI: adverse event of special interest; MAAE: medically-attended adverse event; SAE: serious adverse event

Table 3 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 4-Week Dosing Interval

Procedure	Treatment and Follow-up Period								Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	
Day	**1**	**8**	**15**	**29**	**V4+7**	**V4+14**	**V4+28**	**V4+180**	
Window (days)	**-**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
Medical and surgical history	X	-	-	-	-	-	-	-	-
Urine pregnancy test (women of childbearing potential)	X	-	-	X	-	-	-	-	8.2.3
Concomitant medications/vaccinations	X	X	X	X	X	X	X	X	6.5
Verify eligibility criteria	X	-	-	-	-	-	-	-	5.1, 5.2
Monitoring of COVID-19	X	X	X	X	X	X	X	X	8.3.8
Vaccine administration (after screening activities, the activities listed above, and the pre-dose sampling activities listed below)	X	-	-	X	-	-	-	-	6.1.1
Immunogenicity assessments									
Serum sample for SARS-CoV-2 serology/neutralising antibodies	X (pre-dose)	-	X	X (pre-dose)	-	X	X	X	8.5.2
Serum sample for additional immunogenicity	X (pre-dose)	-	X	X (pre-dose)	-	X	X	X	8.5.2
Blood sample to assess B-cell and T-cell responses in a sub-group of participants	X (pre-dose)	-	X	X (pre-dose)	-	-	X	X	8.5.2.3
Blood sample for B-cell and T-cell response sequencing in a sub-group of participants	X (pre-dose)	-	X	X (pre-dose)	-	-	X	X	8.5.2.3
Safety assessments									
Targeted physical examination	X	-	-	X	-	-	-	-	8.2.1
Vital signs	X	X	X	X	X	X	X	X	8.2.2
e-Diary provided with training	X	-	-	X	-	-	-		8.3.7

Table 3 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 4-Week Dosing Interval

Procedure	**Treatment and Follow-up Period**								**Section**
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	
Day	**1**	**8**	**15**	**29**	**V4+7**	**V4+14**	**V4+28**	**V4+180**	
Window (days)	**-**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
e-Diary collected	-	X	-	-	X	-	-		8.3.7
Unsolicited AEs	X (post-dose)	X	X	X	X	X	X		8.3
MAAEs, SAEs, and AESIs	X[a]	X	X	X	X	X	X	X	8.3.8
Clinical safety laboratory assessments	X (pre-dose)	X	-	X (pre-dose)	X	-	X	X	8.2.3

[b] Only SAEs pre-dose

AE: adverse event; AESI: adverse event of special interest; MAAE: medically-attended adverse event; SAE: serious adverse event

Table 4 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 12-Week Dosing Interval

Procedure	Treatment and Follow-up Period									Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	
Day	**1**	**8**	**15**	**29**	**85**	**V5+7**	**V5+14**	**V5+28**	**V5+180**	
Window (days)	**-**	**±2**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
Medical and surgical history	X	-	-	-	-	-	-	-	-	-
Urine pregnancy test (women of childbearing potential)	X	-	-	-	X	-	-	-	-	8.2.3
Concomitant medications/vaccinations	X	X	X	X	X	X	X	X	X	6.5
Verify eligibility criteria	X	-	-	-	-	-	-	-	-	5.1, 5.2
Monitoring of COVID-19	X	X	X	X	X	X	X	X	X	8.3.8
Vaccine administration (after screening activities, the activities listed above, and the pre-dose sampling activities listed below)	X	-	-	-	X	-	-	-	-	6.1.1
Immunogenicity assessments										
Serum sample to assess SARS-CoV-2 serology/neutralising antibodies	X (pre-dose)	-	X	X	X (pre-dose)	-	X	X	X	8.5.2
Serum sample to assess additional immunogenicity	X (pre-dose)	-	X	X	X (pre-dose)	-	X	X	X	8.5.2
Blood sample to assess B-cell and T-cell responses in a sub-group of participants	X (pre-dose)	-	X	X	X (pre-dose)	-	-	X	X	8.5.2.3
Blood sample for B-cell and T-cell response sequencing in a sub-group of participants	X (pre-dose)	-	X	X	X (pre-dose)	-	-	X	X	8.5.2.3
Safety assessments										
Targeted physical examination	X	-	-	-	X	-	-	-	-	8.2.1
Vital signs	X	X	X	X	X	X	X	X	X	8.2.2
e-Diary provided with training	X	-	-	-	X	-	-	-		8.3.7

Table 4 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 12-Week Dosing Interval

Procedure	Treatment and Follow-up Period									Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	
Day	**1**	**8**	**15**	**29**	**85**	**V5+7**	**V5+14**	**V5+28**	**V5+180**	
Window (days)	**-**	**±2**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
e-Diary collected	-	X	-	-	-	X	-	-	-	8.3.7
Unsolicited AEs	X (post-dose)	X	X	X	X	X	X	X	-	8.3
MAAEs, SAEs, and AESIs	X[a]	X	X	X	X	X	X	X	X	8.3.8, 8.3.8
Clinical safety laboratory assessments	X (pre-dose)	X	-	X	X (pre-dose)	X	-	X	X	8.2.3

[a] Only SAEs pre-dose

AE: adverse event; AESI: adverse event of special interest; MAAE: medically-attended adverse event; SAE: serious adverse event

2 INTRODUCTION

AZD2816 is being developed for the prevention of COVID-19. It is a modified version of the current AstraZeneca SARS-CoV-2 vaccine (referred to as AZD1222 in clinical documentation) that has been modified to also provide immunity against the newly emerging SARS-CoV-2 variant strain B.1.351. Like AZD1222, AZD2816 is a recombinant replication-defective chimpanzee adenovirus vector (ChAdOx1) expressing the SARS-CoV-2 S surface glycoprotein driven by the human cytomegalovirus major immediate early promoter that includes intron A with a human tissue plasminogen activator leader sequence at the N terminus. AZD2816 differs from AZD1222 in that the S glycoprotein gene sequence used is from the B.1.351 variant strain instead of the original Wuhan-Hu-1 variant.

2.1 Study Rationale

The aim of the study is to assess the safety and immunogenicity of AZD2816 for prevention of COVID-19 as both a 2-dose primary vaccination in previously unvaccinated participants and a 1-dose booster vaccination in participants previously vaccinated against the original Wuhan-Hu-1 strain of SARS-CoV-2 by either AZD1222 or an mRNA-based vaccine. A safe and effective vaccine for COVID-19 prevention, including against the B.1.351 variant, would have significant global public health impact.

The study will also investigate the safety and immunogenicity of 1) a heterologous 2-dose vaccination with AZD1222 as first dose and AZD2816 as the second dose and 2) a single dose of AZD1222 as a booster vaccination in participants that have been previously vaccinated with an mRNA COVID-19 vaccine targeting the original Wuhan-Hu-1 strain.

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, which was named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (Zhou et al 2020). The disease these patients contracted was subsequently named Coronavirus Disease 2019 (COVID-19). The World Health Organization declared the novel coronavirus a pandemic on 11 March 2020. The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has resulted in significant global morbidity and mortality as well as major disruption to healthcare systems. Measures to change the course of the pandemic have included the accelerated development vaccines against the original Wuhan-Hu-1 strain.

Coronaviruses are spherical, enveloped viruses with positive-sense single-stranded RNA genomes. SARS-CoV-2 belongs to the phylogenetic lineage B of the genus *Betacoronavirus*, and it is the seventh corona virus known to cause human infections and the third known to cause severe disease after SARS-CoV and MERS-CoV. One fourth of the viral genome is

responsible for coding structural proteins, such as the S glycoprotein, envelope, membrane, and nucleocapsid proteins. Envelope, membrane, and nucleocapsid proteins are mainly responsible for virion assembly while the S protein is involved in cellular receptor binding, mediating fusion of virus and cell membranes and virus entry into host cells during infection. The SARS-CoV-2 spike (S) glycoprotein is a type I trimeric, transmembrane protein that is located at the surface of the viral envelope forming spike-shaped protrusions. The S protein's subunits are responsible for cellular receptor angiotensin-converting enzyme 2 binding via the receptor binding domain and subsequent fusion of virus and cell membranes, thereby mediating the entry of SARS-CoV-2 into the target cells. The S protein has an essential role in virus entry and determines tissue and cell tropism, as well as host range. The roles of the S-protein in receptor binding and membrane fusion have made it a desirable target for vaccine and antiviral development. The AstraZeneca vaccine AZD1222 expresses a codon-optimized coding sequence for S protein from the SARS-CoV-2 genome sequence accession MN908947 (ie, the Wuhan-Hu-1 isolate).

To date, 5 vaccines that rely upon the expression of the SARS CoV-2 S glycoprotein to stimulate/prime a protective immune response against the virus have demonstrated safety and efficacy in phase III clinical trials. Four of these, AZD1222 (also referred to as ChAdOx1 nCoV-19, a recombinant replication-defective chimpanzee adenoviral vectored), BNT162b2 (Pfizer-BioNTech, mRNA), mRNA-1273 (Moderna, mRNA), and Ad26.COV2-S (Janssen, adenovirus serotype 26 vectored) have received Emergency Use Authorization or Conditional Marketing Approval in the United States and/or the European Union, and elsewhere, and NVX-CoV2373 (Novavax; recombinant 86 protein) has also shown efficacy and is likely to be in use in the near future. These vaccines have been designed based upon the initial reported genetic sequence of the S protein from Wuhan in January 2020 (Lu et al 2020).

The immunogenicity and efficacy of AZD1222 has been shown in clinical trials (Ramasamy et al 2020, Voysey et al 2021a, Voysey et al 2021b). Immunogenicity data indicate that a single dose of AZD1222 elicits both humoral and cellular immunogenicity responses and that antibody responses are boosted after a second dose. In a pooled analysis of the 4 studies conducted in the United Kingdom, Brazil, and South Africa (database lock 7 December 2020), the vaccine was highly immunogenic; seroresponse of S binding antibody was > 98% after a single dose of AZD1222. Seroresponse of live neutralising antibody was 82.4% after 1 dose, which rose to 99.4% after a second dose. Efficacy analyses of the pooled DCO2 data demonstrated effective protection of AZD1222 against COVID-19 with a vaccine efficacy of 66.73% (95.84% CI: 57.41%, 74.01%) ($p < 0.001$) from 15 days after the second dose in seronegative participants receiving 2 doses. The DCO2 data also demonstrated that the standard dose of AZD1222 (5×10^{10} viral particles) provides complete protection against COVID-19 hospital admission ≥ 22 days after the first dose in the seronegative analysis set (0 versus 14 cases in the control group, 2 of which were severe, including one with a fatal outcome). Vaccine efficacy was similar in participants with pre-existing comorbidities, being

those at greatest risk of severe outcomes of COVID-19, compared to that in the general population. Recently available primary analysis data from a Phase III study performed in the United States and Latin America showed primary endpoint vaccine efficacy of 76% (95% CI: 67.60%, 82.22%; p-value < 0.001).

A sharp rise in COVID-19 cases was reported in late 2020, which was attributed to the emergence of new SARS-CoV-2 variant strains: B.1.1.7 in the United Kingdom, B.1.351 in South Africa, and P.1 in Brazil. These variant strains carry a number mutations in the S protein sequence: 9 amino acids in B.1.1.7, 10 amino acids in B.1.351, and 12 amino acids in P.1 compared with the Wuhan-Hu-1 sequence. These mutations may result in an increase of transmissibility and/or reduced vaccine effectiveness. Variant B.1.351 was first identified in South Africa in October 2020. Its attributes include approximately 50% increased transmission and moderate impact of neutralization by monoclonal antibody therapeutics, convalescent plasma and vaccine sera. In vitro neutralization assays suggest that the B.1.351 lineage viruses may be the most antigenically distinct from the original Wuhan-like strains (Zhou et al 2021). In addition, evidence suggests that AZD1222 may afford diminished protection against mild-moderate COVID-19 disease arising from the B.1.351 variant (Madhi et al 2021).

The development of candidate vaccines that would be effective against the B.1.351 variant strain is underway. AZD2816 is being developed as an updated ChAdOx-nCov19 (AZD1222) vaccine designed to provide protective immunity against the newly arising B.1.351 variant strain, using the same ChAdOx1 platform and manufacturing processes used for AstraZeneca's currently approved COVID-19 vaccine, AZD1222. The purpose of this Phase II/III, multinational, randomised, partially double-blind, active-controlled study is to demonstrate the safety and characterize the immunogenicity of AZD2816, AstraZeneca's candidate ChAdOx1 vector vaccine against B.1.351, when administered:

- As a single booster dose to SARS-CoV-2 seronegative participants who have previously received a 2-dose primary vaccination series against the original SARS-CoV-2 Wuhan-hu-1 strain (AZD1222 or an mRNA vaccine).
- As a 2-dose homologous primary vaccination to SARS-CoV-2 seronegative participants who have not been vaccinated previously.

The immunogenicity of a 2-dose primary heterologous vaccination (with AZD1222 as first dose and AZD2816 as second dose) to SARS-CoV-2 seronegative participants who are unvaccinated and a single booster dose of AZD1222 to SARS-CoV-2 seronegative participants who have previously received a 2-dose primary mRNA vaccination series against the original Wuhan-hu-1 strain will also be investigated.

SARS-CoV-2 seropositive participants will also be enrolled to support a parallel exploratory analysis in these participants.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD1222 and AZD2816 is provided in the respective Investigator's Brochures.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of AZD2816 and AZD1222 can be found in the respective Investigator's Brochures.

2.3.1 Risk Assessment

AZD2816 has been developed using the same vaccine vector, ChAdOx1, as AZD1222 and only differs in the sequence for SARS-CoV-2 S glycoprotein that is inserted in the vector. The anticipated safety profile of AZD2816 is the same as the observed safety profile of AZD1222. Risks associated with AZD2816 are thus the same as the risks associated with AZD1222, and no additional risks are anticipated due to the change in the targeted sequence.

A number of essentially mild and moderate adverse reactions to AZD1222 have been identified and resemble reactions frequently observed after many vaccines. Based on pooled clinical data from studies with AZD1222, the most commonly expected local solicited AEs for participants in this study are vaccination site pain and tenderness. The most commonly expected systemic solicited AEs are fatigue, headache, and malaise. The majority of reported events have been 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.

Post-authorisation hypersensitivity reactions, including anaphylaxis and angioedema, have occurred following administration of AZD1222 and are considered an identified risk.

A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with COVID-19 Vaccine (ie, AZD1222) during post-authorisation use. No events have been observed in the AZD1222 clinical development programme. Thrombosis in combination with thrombocytopenia is thus considered to be an important identified risk. This includes cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. Considering the frequency of this rare event and the size of this study, the risk for participants in this trial is considered to be low. The protocol includes exclusion criteria and instructions for heightened vigilance and thorough investigations for suspected cases to mitigate against further the risk for these rare event.

Important potential risks are 1) neurologic events and potential immune-mediated neurologic conditions and 2) vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease.

2.3.2 Benefit Assessment

All participants will receive active treatment: either AZD1222, which has been shown to be effective in providing protection against SARS-CoV-2, or AZD2816, which as a modified form of AZD1222 designed to be effective against the emergent B.1.351 variant strain and may also provide participants with protection. The information gained from this study will inform development decisions with regard to the efficacy of AZD2816 as both a primary 2-dose vaccination in participants that have not been previously vaccinated and a 1-dose booster vaccination in participants previously vaccinated against SARS-CoV-2.

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 and close monitoring of participants to minimize known and potential risks.

An independent Data Safety Monitoring Board will provide study oversight, evaluating cumulative safety and other clinical data at regular intervals.

Taking these measures into account, the potential risks identified in association with the administration of AZD2816 and AZD1222 are justified by the anticipated benefit that may be afforded to participants for the prevention of COVID-19.

3 OBJECTIVES AND ENDPOINTS

3.1 Naïve unvaccinated cohort receiving a 2-dose primary vaccination

The primary safety objective for the cohort of previously unvaccinated participants receiving a 2-dose dose primary vaccination is to characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in previously unvaccinated seronegative participants.

The primary and key secondary immunogenicity objectives for this cohort are as follows:

Primary:

1: To determine if the neutralizing antibody GMT response against the B.1.351 variant elicited by a 2-dose AZD2816 vaccination is non-inferior to the response against the original Wuhan-hu-1 strain elicited by a 2-dose AZD1222 vaccination.

Key secondary:

2.1: To determine if seroresponse against the B.1.351 variant elicited by a 2-dose AZD2816 vaccination is non-inferior to seroresponse against the original Wuhan-hu-1 strain elicited by a 2-dose AZD1222 vaccination**.**

2.2: To determine if the neutralizing antibody GMT response against the B.1.351 variant elicited by a 2-dose AZD2816 vaccination is non-inferior to the response elicited by a 2-dose AZD1222 vaccination.

2.3: To determine if the neutralizing antibody GMT response against the B.1.351 variant elicited by a 2-dose heterologous AZD1222 + AZD2816 vaccination is non-inferior to the response against the original Wuhan-hu-1 strain elicited by a 2-dose AZD1222 vaccination

2.4: To determine if the neutralizing antibody GMT response against the original Wuhan-hu-1 elicited by a 2-dose AZD2816 vaccination is non-inferior to the response elicited by a 2-dose AZD1222 vaccination

The above primary and the key secondary immunogenicity objectives will be supported by other secondary immunogenicity objectives (see below) for which there will be no formal hypothesis testing.

Table 5 further describes the objectives and endpoints for this cohort of participants, including estimands for the immunogenicity objectives.

Table 5 Study Objectives and Endpoints for Previously Unvaccinated Participants Receiving a 2-Dose Primary Vaccination

Safety Objectives	**Endpoints**
- Primary	
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose
- Secondary	
To characterize the safety and tolerability of a heterologous primary vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in previously unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety and tolerability of a heterologous primary vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in previously unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
Immunogenicity Objectives	
To determine if the pseudoneutralizing antibody GMT response elicited by a 2-dose AZD2816 primary vaccination is non-inferior to the response elicited by a 2-dose AZD1222 primary vaccination Estimand:	

Treatment	AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Primary	B.1.351	Wuhan-hu-1
Key Secondary 2.2	B.1.351	B.1.351
Key Secondary 2.4	Wuhan-hu-1	Wuhan-hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD2816 vaccination/AZD1222 vaccination	

To determine if the seroresponse rate elicited by a 2-dose AZD2816 primary vaccination is non-inferior to the seroresponse rate elicited by a 2-dose AZD1222 primary vaccination Estimand:

Treatment	AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Key Secondary 2.1	B.1.351	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 vaccination - AZD1222 vaccination	
To determine if the neutralizing antibody GMT response elicited by a 2-dose AZD1222+AZD2816 heterologous primary vaccination is non-inferior to the response elicited by a 2-dose AZD1222 primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Key Secondary 2.3	B.1.351	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD1222+AZD2816 vaccination/AZD1222 vaccination	
To determine if the seroresponse rate elicited by a 2-dose AZD1222+AZD2816 heterologous primary vaccination is non-inferior to the seroresponse rate elicited by a 2-dose AZD1222 primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD1222+AZD2816 vaccination - AZD1222 vaccination	
To determine if the neutralizing antibody GMT response against the B.1.351 variant is non-inferior to the response against the original Wuhan-hu-1 strain following a 2-dose AZD2816 primary vaccination Estimand:		
Treatment	AZD2816 vaccination	AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 2-dose AZD2816 primary vaccination Estimand:		

Treatment	AZD2816 vaccination	AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) against B.1.351 versusWuhan-hu-1	
To determine if the neutralizing antibody GMT response against the B.1.351 variant is non-inferior to the response against the original Wuhan-hu-1 strain following a 2-dose AZD1222+AZD2816 heterologous primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222+AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 2-dose AZD1222+AZD2816 heterologous primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222+AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) against B.1.351 versusWuhan-hu-1	
To also determine non-inferiority of the s-protein binding antibody response for the above comparisons as other secondary objectives		
To also determine the neutralizing antibody GMT responses 28 days after first vaccination dose in the above primary and key secondary objectives		
To explore anti-vector responses to the ChAdOx-1 adenovirus vector following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in sub-groups of seronegative and seropositive participants	• GMT of ChAdOx1 neutralizing antibody titres • Seroresponse rate of ChAdOx1 neutralizing antibody titres Pairwise correlations between anti-S, pseudo-neutralization, and ChAdOx1 neutralizing antibody titres, 1 month after both Dose 1 and Dose 2	
Exploratory Objectives		
Objective	Endpoints	
To explore the immune response elicited by a 2-dose AZD2816 primary vaccination with a 12-week dosing interval compared to the response elicited by a 2-dose AZD2814 primary vaccination with a 4-week dosing interval	• GMT ratio of pseudoneutralizing antibodies • Seroresponse	

To explore antibody response to selected SARS-CoV-2 variants of interest/variants of concern following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in a sub-group of seronegative participants	• GMT of SARS-CoV-2 anti-S binding antibodies for selected variants of concern/variants of interest • Seroresponse rate of SARS-CoV-2 specific binding antibody titres for selected variants of concern/variants of interest • GMT of SARS-CoV-2 pseudoneutralizing antibody responses against the B.1.617.2 (delta) variant • Seroresponse rate of SARS-CoV-2 pseudoneutralizing antibody responses against the B.1.617.2 (delta) variant
To explore B-cell and T-cell responses following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in a sub-group of seronegative participants	• Intracellular cytokine staining and flow cytometry for T-cell responses over time • Quantification of (IFN-γ) ELISpot responses to SARS-CoV-2 B.1.351 or Wuhan-Hu-1 S protein from day of dosing baseline over time • Breadth and depth of peripheral blood B-cell and T-cell repertoire over time through immunosequencing
To monitor the incidence of SARS-CoV-2 infection following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in previously unvaccinated seronegative participants	• The incidence of SARS-CoV-2 infection defined by the seroresponse to nucleocapsid antibodies occurring post-second dose of study intervention
To monitor the incidence of COVID-19 following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in previously unvaccinated seronegative participants	• Incidence of COVID-19, defined as SARS-CoV-2 RT-PCR-positive symptomatic illness.
To explore the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in sub-groups of seronegative and seropositive participants	• Magnitude of SARS-CoV-2 neutralization titres (geometric mean titre) as determined by a live virus neutralization assay • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres as determined by a live virus neutralization assay
To explore additional immune responses following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in sub-groups of seronegative and seropositive participants	• Other exploratory assays for humoral and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data
• To explore the immunogenicity objectives in seropositive participants	• GMT of pseudoneutralizing antibodies • Seroresponse rates

MAAEs: medically attended adverse events; SAEs: serious adverse events; AESIs: adverse events of special interest

[a] Seroresponse: An at least 4-fold increase in geometric mean titre from baseline.

3.2 Previously vaccinated cohort receiving a 1-dose booster vaccination

The primary safety objective for the cohort of seronegative previously vaccinated participants receiving a booster dose is to characterize the safety and tolerability of 1 booster dose of AZD2816 in participants previously vaccinated with AZD1222.

The primary and key secondary immunogenicity objectives for this cohort are as follows:

Primary:

1: To determine if the humoral immune response against the B.1.351 variant elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to the response against the original Wuhan-hu-1 strain elicited by 2-dose AZD1222 vaccination administered to vaccination naïve participants.

Key secondary:

2.1: To determine if the humoral immune response against the B.1.351 variant elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to the response elicited by 2-dose AZD1222 vaccination administered to vaccination naïve participants.

2.2: To determine if the humoral immune response elicited against the B.1.351 variant by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222.

2.3: To determine if the humoral immune response against the original Wuhan-hu-1 strain elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to the response elicited by 2-dose AZD1222 vaccination administered to vaccination naïve participants.

2.4: To determine if the humoral immune response against the original Wuhan-hu-1 strain elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 is non-inferior to the response elicited by a 2-dose AZD1222 vaccination

2.5: To determine if the humoral immune response against the original Wuhan-hu-1 strain elicited by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222.

The primary and key secondary immunogenicity objectives will be supported by other secondary objectives for which there will be no formal hypothesis testing. Table 6 further describes the objectives and endpoints for this cohort of participants, including estimands for the primary and secondary immunogenicity objectives.

Table 6 Study Objectives and Endpoints for Previously Vaccinated Participants Receiving a 1-Dose Booster Vaccination

Safety Objectives	Endpoints
- Primary	
To characterize the safety and tolerability of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Incidence of local and systemic solicited AEs for 7 days post dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose
- Secondary	
To characterize the safety and tolerability of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
Immunogenicity objectives	
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:	

Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Primary	B.1.351	Wuhan-hu-1
Key Secondary 2.1	B.1.351	B.1.351
Key Secondary 2.3	Wuhan-hu-1	Wuhan-hu-1

Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 vaccination	
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose is non-inferior to response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Key Secondary 2.2	B.1.351	B.1.351
Key Secondary 2.5	Wuhan-hu-1	Wuhan-hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 booster	
To determine if the neutralizing antibody GMT response elicited by an AZD1222 booster dose in patients previously vaccinated with AZD1222 is non-inferior to the response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD1222 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective Level:	Serotype comparison:	
Key Secondary (2.4)	Wuhan-hu-1	Wuhan-hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD1222 booster/AZD1222 vaccination	
To determine if the seroresponse elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other secondary	B.1.351	Wuhan-hu-1
Other secondary	B.1.351	B.1.351
Other secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 primary vaccination	
To determine if the seroresponse elicited by an AZD2816 booster dose is non-inferior to response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 booster	

To determine if the seroresponse elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD1222 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 primary vaccination	
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose in participants previously vaccinated with an mRNA-based vaccine is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	mRNA vaccine vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 vaccination	
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with an mRNA-based vaccine Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	mRNA vaccine vaccinated seronegative participants	mRNA vaccine vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 booster	
To determine if the seroresponse elicited by an AZD2816 booster dose in participants previously vaccinated with an mRNA-based vaccine is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	mRNA vaccine vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-hu-1	Wuhan-hu-1

Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 primary vaccination	
To determine if the seroresponse elicited by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with an mRNA-based vaccine Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	mRNA vaccine vaccinated seronegative participants	mRNA vaccine vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 booster	
To determine if the neutralizing antibody GMT response rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 2816 booster dose. Estimand:		
Treatment	AZD2816 booster	AZD2816 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster vaccination
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-hu-1	
To determine if the neutralizing antibody GMT response against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 1222 booster dose. Estimand:		
Treatment	AZD1222 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 2816 booster dose. Estimand:		
Treatment	AZD2816 booster	AZD2816 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for B.1.351/Wuhan-hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 1222 booster dose. Estimand:		

Treatment	AZD1222 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for B.1.351/Wuhan-hu-1	
To also determine non-inferiority of the s-protein binding antibody response for the above comparisons as other secondary objectives.		
To explore anti-vector responses to the ChAdOx-1 adenovirus vector following a booster dose of AZD2816 in sub-groups of seronegative and seropositive participants	• Magnitude of ChAdOx1 nAb titres (geometric mean titre) • Seroresponse rate of ChAdOx1 neutralizing antibody titres Pairwise correlations between anti-S, pseudo-neutralization, and ChAdOx1 neutralizing antibody titres, 1 month after both Dose 1 and Dose 2	
Exploratory objectives		
Objective	Endpoints	
To explore antibody response to selected SARS-CoV-2 variants of interest/variants of concern following a booster dose of AZD2816 and in a sub-group of seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding titres (geometric mean titre) for selected variants of concern/variants of interest • Seroresponse rate of SARS-CoV-2 specific antibody binding titres for selected variants of concern/variants of interest • GMT of SARS-CoV-2 pseudoneutralizing antibody responses against the B.1.617.2 (delta) variant • Seroresponse rate of SARS-CoV-2 pseudoneutralizing antibody responses against the B.1.617.2 (delta) variant	
To explore B-cell and T-cell responses following a booster dose of AZD2816 in a sub-group of seronegative participants	• Intracellular cytokine staining and flow cytometry for T-cell responses over time • Quantification of (IFN-γ) ELISpot responses to SARS-CoV-2 B.1.351 or Wuhan-Hu-1 S protein from day of dosing baseline over time • Breadth and depth of peripheral blood B-cell and T-cell repertoire over time through immunosequencing	
To monitor the incidence of SARS-CoV-2 infection following a booster dose of AZD2816 in previously vaccinated seronegative participants	• The incidence of SARS-CoV-2 infection defined by the presence of nucleocapsid antibodies occurring post-dose of study intervention	
To monitor the incidence of COVID-19 following a booster dose of AZD2816 in previously vaccinated seronegative participants	• Incidence of COVID-19, defined as SARS-CoV-2 RT-PCR-positive symptomatic illness.	
To explore the immunogenicity objectives in seropositive participants	• GMT of pseudoneutralizing antibodies • Seroresponse rates	

MAAEs: medically attended adverse events; SAEs: serious adverse events; AESIs: adverse events of special interest.

[a] Seroresponse: An at least 4-fold increase in geometric mean titre from baseline.

4 DESIGN

4.1 Overall Design

This is a multi-country Phase II/III study to evaluate the safety and immunogenicity of AZD2816 as single-dose vaccination in previously vaccinated adult participants and as a 2-dose primary vaccination in previously unvaccinated adult participants.

A total of approximately 2590 SARS-CoV-2 nucleocapsid seronegative participants that have been screened and judged to be eligible for the study will be enrolled across these 2 populations with the goal of 1300 previously vaccinated participants receiving single-dose vaccination and 1290 unvaccinated participants receiving 2-dose primary vaccination. In addition, seropositive participants will be enrolled (with a cap of 10% of the seronegative population or 259 participants) to support exploratory analysis is these participants.

The enrollment and randomization strategy is intended to minimize group differences in terms of age, gender and the presence of comorbidities, to support this strategy the study randomisation will include caps to ensure that at least 25% of enrolled participants within each treatment arm will be ≥ 65 years of age.

In both the single-dose booster treatment regimen and the 2-dose primary vaccination treatment regimen, participants will receive study intervention consisting of intramuscular administration of either AZD1222 (5×10^{10} viral particles) or AZD2816 (5×10^{10} viral particles).

Approximately 700 seronegative participants previously vaccinated with AZD1222 will be randomised 1:1 to receive a single intramuscular dose of either AZD1222 or AZD2816 in a double-blinded fashion.

Approximately 600 seronegative participants previously vaccinated with an approved mRNA based vaccination against the original Wuhan-hu-1 strain will be randomised 1:1 to receive a single intramuscular dose of AZD2816 or AZD1222 in a double-blinded fashion.

Approximately 1290 seronegative, previously unvaccinated participants will be randomised approximately 5:5:5:2 to receive a 2-dose primary vaccination of the following:

- 2 doses of AZD1222 with a 4-week dosing interval
- 2 doses of AZD2816 with a 4-week dosing interval
- 1 dose of AZD1222 followed by 1 dose of AZD2816 with a 4-week dosing interval
- 2 doses of AZD2816 with a 12-week dosing interval.

The 3 treatments with a 4-week dosing interval will be double-blinded while the treatment with the 12-week interval will be open-label due to the difference in dosing interval.

In addition, a smaller population seropositive participants (approximately 10% of the seronegative population), will be randomised to treatment in a similar manner as above.

Immunogenicity (ie, anti-Wuhan-Hu-1 and anti-B.1.351 immune responses including S-binding antibody titres and neutralizing antibody levels [pseudo-neutralization]) will be assessed in serum samples collected pre-dose on the day of each vaccination (baseline levels before vaccination), 14 and 28 days after each vaccination, and 180 days after the last vaccination.

All participants will be given a thermometer, tape measure or ruler, and a proprietary e-diary application designed for use with a smart device with instructions for use. All participants will be asked to report on solicited signs and symptoms for 7 days following vaccination (Days 1-8 for all participants and Days 29-36 for the 4-week dosing interval and Days 85-92 for the 12-week dosing interval). An e-diary will be used to collect information on the timing and severity of the solicited signs and symptoms.

Follow-up visits will take place as per the schedule of assessment within respective windows. All participants will be assessed for local and systemic AE, physical examination, review of e-diaries at these time points as detailed in the schedule of assessment. Blood will also be taken for safety assessments and immunology purposes.

All study participants will be followed for safety for 180 days after administration of their last vaccination dose. In every participant, solicited local and systemic events will be reported for up to 7 days after each dose, all unsolicited AEs will be reported for up to 28 days after each dose, and SAEs and AEs of special interest will be evaluated through study completion (up to 180 days after the last study vaccination).

An independent COVID-19 Vaccine Data Safety Monitoring Board will provide oversight, to ensure safe and ethical conduct of the study.

4.1.1 COVID-19 Assessments

Occurrence of COVID-19 in the trial will be reported as safety events, including monitoring of the potential risk of vaccine-elicited enhanced disease as an AE of special interest (see Appendix E). COVID-19 will be diagnosed and treated as per standard medical practice. In addition, experimental treatments are permitted. Detailed information will be collected in a standard way and reported on a specific case report form.

4.1.2 Screening

All potential participants will be screened, which may take place at a visit up to 14 days prior to Day 1 or on Day 1 itself.

Informed consent will be obtained before screening/enrollment. If written consent is obtained, the screening procedures specified in the Schedule of Activities (Section 1.3) will be undertaken including a medical history, physical examination, height and weight, a SARS-CoV-2 screening test and clinical safety laboratory assessments. Baseline information collected in the previously vaccinated participants will include which vaccine was received, immunization dose interval, and time since last vaccination.

For women of childbearing potential, it will be recorded that they verbally confirmed use of one highly effective form of birth control for at least 28 days prior to the planned vaccination and a urine pregnancy test will be performed that must be negative for the participant to be enrolled. (Note: Women with urine test results that are positive or undetermined will not be enrolled and should be advised to seek medical attendance outside the context of the trial if pregnancy is suspected.)

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 enrollment or to withdraw a participant from the study will be at the discretion of the Investigator.

4.1.3 Vaccination Visit

Participants will be considered enrolled at the point of vaccination. Before vaccination, the eligibility of the participant will be reviewed. Body temperature will be observed and a medical history and physical examination will be undertaken before the first vaccination to determine need to postpone vaccination or screen fail the participant. A negative pregnancy test (urine test) will need to be obtained from women of childbearing potential before vaccination. Baseline blood samples will be obtained before the first vaccination.

Participants will receive 1 dose of AZD2816 or AZD1222 at vaccination visits, administered by intramuscular injection. Previously immunized participants will have a single vaccination visit, Day 1. Participants that have not been previously vaccinated at baseline will have a second vaccination visit on Day 29 (4-week interval) or Day 85 (12-week interval).

All participants will be given a thermometer, tape measure or ruler, and a proprietary e-diary application designed for use with a smart device with instructions for use. All participants will be asked to report on solicited signs and symptoms for 7 days following vaccination (Days 1 to 8 and Days 29 to 36 or Days 85 to 92 when applicable).

4.1.4 Follow-up visits

Follow-up visits will take place as specified in the Schedule of Activities (Section 1.3). All participants will be assessed for local and systemic AE, physical examination, review of the e-diary and blood tests at these time points as detailed in the Schedule of Activities. Blood will also be taken for safety and immunogenicity assessments.

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 the last study visit in order to collect information on any SAEs/AE of special interest.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Study Design and Participant Population

The participant population includes adults ≥ 18 years of age. Persons who are healthy or have medically stable underlying conditions will be eligible. Adults with medically-stable chronic diseases may participate if, according to the judgement of the investigator, hospitalization within the study period is not anticipated and the participant appears likely to be able to remain on study through the end of protocol-specified follow-up.

For the primary and secondary objectives, those enrolled in the study must test negative for SARS-CoV-2 nucleocapsid protein antibody during screening. Some seropositive participants (capped at 10% of the seronegative participant population) will be enrolled to support an exploratory analysis.

Those enrolled in the single-dose vaccination part of the study must have received 2 doses of AZD1222 (with a dosing interval of 4-12 weeks) or 2 doses of an approved mRNA-based COVID-19 vaccine (with a dosing interval of 3-12 weeks for the BNT162b2 mRNA vaccine [Pfizer-BioNTech] and 4-12 weeks for the mRNA-1273 vaccine [Moderna]) with the second doses administered at least 3 months prior to first study intervention administration.

Pregnant/breastfeeding women, persons with severe immunodeficiency or severe underlying disease will be excluded from participation in the study. Persons previously vaccinated with AZD1222 in the context of an AZD1222 vaccine trial are eligible for enrollment as previously vaccinated participants in the trial. Persons who have previously received any other investigational product for the prevention of COVID-19 will be excluded from participation in this study.

Participants with known risk factors for thrombosis and thrombocytopenia (excluding contraceptive hormonal therapy or replacement hormonal therapy) are excluded.

4.2.2 Rationale for Study Endpoints

The primary safety analysis includes:

- Incidence of local and systemic solicited AEs for 7 days following each vaccination will be summarized by day and overall.
- Incidence of unsolicited AEs for 28 days following each vaccination will be summarized by system organ class and preferred term, and by relationship to vaccination as assessed by the investigator.
- SAEs and AEs of special interest following the first vaccination and throughout the study duration will be summarized by system organ class and preferred term and by relationship to vaccination as assessed by the investigator.

Solicited AEs will be collected for 7 days after each dose of study intervention, a period that has proven adequate to describe reactogenicity events in previous vaccine studies. For all participants, AEs will be collected through 28 days after each dose of study intervention. SAEs, medically-attended AEs, and AEs of special interest and will be collected from Day 1 through end of the study. AEs of special interest include terms identified by the Brighton Collaboration involving events associated with vaccination in general .

The immunogenicity endpoints of interest in this study are:

- Geometric mean titre
- Seroresponse, defined as ≥ 4-fold increase in the geometric mean titre from baseline

Geometric mean titre ratios and differences in seroresponses with 95% confidence intervals will be presented to support selected comparisons of immunogenicity across groups of interest.

Immunogenicity against SARS-CoV-2 Wuhan-Hu-1 and B.1.351 strains will be characterized through the quantification of Spike-binding antibodies, pseudo-neutralization and, in a subset of participants, live neutralization. Exploratory analysis of immunogenicity against other strains and induction of other immune effectors including cell-mediated immunity will be conducted.

4.3 Justification for Dose

The AZD2816 nominal dose of 5×10^{10} viral particles is the same dose as the approved dose for AZD1222, which was based on the accumulated non-clinical data and clinical data from the AZD1222 clinical studies, as well as from other SARS-CoV-2 vaccines in development. Safety and immunogenicity data from an additional clinical study, MERS001(NCT03399578), using the same ChAdOx1 vector, also helped inform dose selection. MERS001 was the first clinical study of a ChAdOx1-vectored vaccine expressing the full-length S protein from a

separate, but related, beta-coronavirus. ChAdOx1 MERS has been given to 31 participants to date at doses ranging from 5×10^9 viral particles to 5×10^{10} viral particles. Despite higher reactogenicity observed at the 5×10^{10} viral particles, this dose was safe, with self-limiting AEs and no serious adverse reactions recorded. The 5×10^{10} viral particles was the most immunogenic, in terms of inducing neutralizing antibodies 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} viral particles dose was chosen for AZD1222.

Based on accumulating nonclinical and clinical data gathered for AZD1222, a 2-dose regimen was selected for vaccination of unvaccinated participants with AZD2816 (AZD1222 Investigators Brochure). A single dose vaccination has been selected for participants previously vaccinated in line with both FDA and EMA guidance (FDA 2021, EMA 2021).

4.4 End of Study Definition

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

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

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as a protocol waiver or exemption, is not permitted.

5.1 Inclusion Criteria

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

5.1.1 All Participants:

Age

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

COVID-19

For inclusion in the SARS-CoV-2 seronegative population supporting the primary and secondary objectives:

2 No history of laboratory-confirmed SARS-CoV-2 infection (ie, no positive nucleic acid amplification test and no positive antibody test).

3 Seronegative for SARS-CoV-2 at screening (lateral flow test to detect reactivity to the nucleoprotein).

Note, patients failing to meet criteria 2 and/or 3 may be included in the separate seropositive population supporting the seropositive exploratory objectives.

Type of Participant

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

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

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

6 Signed informed consent obtained before conducting any study-related procedures

Reproduction

7 Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
Female participants:

(a) Women of childbearing potential must:

- Have a negative pregnancy test on the day of screening and on days of vaccination
- 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 30 days following administration of the 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 7). Periodic abstinence, the rhythm method, and withdrawal are NOT acceptable methods of contraception.

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

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

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

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

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

Table 7 Highly Effective Methods of Contraception

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

[a] This is also considered a hormonal method
[b] Provided that partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success
[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse from 28 days prior to Day 1 through 30 days following administration of the second dose of study intervention, and if it is the preferred and usual lifestyle of the participant

5.1.2 Previously COVID-19 Vaccinated Participants

8 Prior completion of a 2-dose primary homologous vaccination regimen against the original SARS-CoV-2 Wuhan-hu-1 strain with either AZD1222 (2 standard doses as authorized vaccine or as investigational product in a clinical trial with a 4- to 12-week dosing interval) or with an mRNA vaccine approved for emergency or conditional use (eg, BNT162b2 vaccine [Pfizer-BioNTech] with a 3- to 12-week dosing interval or mRNA-1273 vaccine [Moderna] with a 4- to 12-week dosing interval). The second dose in all cases should have been administered at least 3 months prior to first administration of study intervention.

5.2 Exclusion Criteria

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

Medical Conditions

1 History of allergy to any component of AZD1222/AZD2816.

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

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

4 Any confirmed or suspected immunosuppressive or immunodeficient state, including asplenia or HIV/AIDS.

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

- Topical/inhaled steroids or short-term oral steroids (course lasting ≤ 14 days)

6 History of primary malignancy except for:

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

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

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

(d) Localized prostate cancer

7 History of thrombocytopenia and/or thrombosis, including participants who have experienced major venous and/or arterial thrombosis in combination with thrombocytopenia following vaccination with any COVID-19 vaccine

8 History of heparin-elicited thrombocytopenia, congenital thrombophilia (ie, factor V Leiden, prothrombin G20210A, antithrombin III deficiency, protein C deficiency and protein S deficiency, factor XIII mutation, familial dysfibrinogenemia), auto-immune thrombophilia (antiphospholipid syndrome, anti-cardiolipin antibodies, anti-β_2-glycoprotein 1 antibodies), or paroxysmal nocturnal haemoglobinuria.

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

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

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

12 Any autoimmune conditions, except mild psoriasis and vitiligo

Note: The AEs of special interest as outlined in Appendix E (including Table 28) should be considered when evaluating a participant for exclusion criteria as the presence of these AEs of special interest, especially if untreated or uncontrolled, may be a safety risk to the participant,

affect the ability of the participant to participate in the study, and/or impair interpretation of the study data. Investigators should review and consider the list of conditions in Appendix E. If any of these conditions are present in a participant, the Investigator is asked to utilize his/her clinical judgment in determining the participant's eligibility for the study. Should the participant have conditions as outlined in Appendix E and the participant is enrolled, the Investigator is asked to document notes on site regarding the final rationale for enrollment.

Prior/Concomitant Therapy

13 Receipt of or planned receipt of investigational products indicated for the treatment or prevention of SARS-CoV-2 or COVID-19 with the exception of prior vaccination with AZD1222 or an mRNA COVID-10 vaccine (2 doses of the same vaccine within an approved dosing interval, see Section 5.1.2), which is allowed for participants in the previously vaccinated cohort
Note: For participants who develop COVID-19, receipt of licensed treatment options and/or participation in investigational treatment studies is permitted

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

15 Receipt of any influenza vaccine (licensed or investigational) within 7 days prior to and after administration of AZD1222/AZD2816.

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

Other Exclusions

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

18 Women who are currently pregnant (confirmed with positive pregnancy test), breastfeeding, having given birth less than 3 months before or planning pregnancy during the study.

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

20 Participants with a history of chronic alcohol or drug abuse or any condition associated with poor compliance.

21 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements or if vaccination would interfere with the participant's ongoing treatment.

22 Previous enrollment in the present study.

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 assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

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

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention, marketed product, or placebo intended to be administered to or medical device utilized by a study participant according to the study protocol. Study intervention is defined as AZD2816 or AZD1222 (Table 8).

6.1 Study Interventions Administered

6.1.1 Investigational Products

Table 8 Investigational Products

Intervention Name	AZD2816	AZD1222
Type	Vaccine	Vaccine
Dose Formulation	CCI [redacted]	CCI [redacted]
Unit Dose Strength	1×10^{11} viral particles/mL	1×10^{11} viral particles/mL
	$\geq 5 \times 10^{8}$ infectious units/mL	$\geq 5 \times 10^{8}$ infectious units/mL
Dosage Level	5×10^{10} viral particles (nominal, $\pm 1.5 \times 10^{10}$ viral particles)	5×10^{10} viral particles (nominal, $\pm 1.5 \times 10^{10}$ viral particles)
	$\geq 2.5 \times 10^{8}$ infectious units	$\geq 2.5 \times 10^{8}$ infectious units
Route	Intramuscular	Intramuscular

Use	Experimental	Experimental
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labelling	Will be provided in vials within a carton. Each carton and vial will be labelled as required per country requirement	Will be provided in vials within a carton. Each carton and vial will be labelled as required per country requirement
Current/Former Name	-	Previous clinical documentation: ChAdOx1 nCoV-19 Current tradename: Vaxzevria

IMP: investigational medicinal product; NIMP: non-investigational medical product; w/v: weight/volume.

AZD2816 will be supplied by the Sponsor as a vial solution for injection. It is a sterile, clear to slightly opaque solution, practically free from visible particles. Each vial of AZD2816 has a label-claim volume of 5 mL and can provide up to ten 0.5 mL doses.

AZD1222 will be supplied by the Sponsor as a vial solution for injection. It is a sterile, clear to slightly opaque solution, practically free from visible particles. Each vial of AZD1222 has a label-claim volume of 4 mL and can provide up to eight 0.5 mL doses.

Unopened vials of AZD2816 and AZD1222 must be stored at 2-8 ºC (36-46 ºF) for the duration of the assigned shelf-life and must not be frozen. Both investigational products must be kept in original packaging until use to prevent prolonged light exposure.

6.1.2 Dosing Instructions

Previously unvaccinated participants will receive 2 doses of either AZD1222, AZD2816, or AZD1222 plus AZD2816, with the first dose administered on Day 1 and the second dose on Day 29 (for a 4-week dosing interval) (Table 3) or Day 85 (for a 12-week dosing interval) (Table 4).

Previously vaccinated participants will receive 1 dose of either AZD1222 or AZD2816 (Table 2).

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

All study participants will be observed in the clinic for at least 15 minutes after vaccination. Allergic reactions to vaccines are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

6.2 Preparation/Handling/Storage/Accountability

The procedures for preparation, handling, storage, and accountability are identical for AZD2816 and AZD1222.

1 The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2 Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
3 The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4 Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual or specified handling instructions.

6.2.1 Dose Preparation and Administration

Doses of AZD2816 and 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 AZD2816 or AZD1222 in a sterile syringe.

AZD2816 and AZD1222 do not contain preservatives. Each vial must be assigned a beyond-use-date of 6 hours at 2-30 °C (36-86 °F) from first needle puncture of the vial, after which any unused portion must be discarded.

Once an AZD2816 or AZD1222 dose is drawn into a syringe for administration, the dose must be administered within the beyond-use-date of the vial. If dose administration is not completed within the 6-hour vial beyond-use-date, a new dose must be prepared from a new vial.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization

The study contains 3 cohorts that are randomised to a total of 8 treatments:

- Participants that have previously been vaccinated with 2 doses of AZD1222 will be randomised 1:1 to 1 dose of AZD2816 or 1 dose of AZD1222.

- Participants that have been previously vaccinated with an mRNA COVID-19 vaccine will be randomised 1:1 to 1 dose of AZD2816 or AZD1222.
- Vaccination naïve participants that will be randomised 5:5:5:2 to 2 doses of AZD2816 with a 4-week dosing interval, 2 doses of AZD1222 with a 4-week dosing interval, 1 dose of AZD1222 followed by 1 dose of AZD216 with a 4-week dosing interval, or 2 doses of AZD2816 with a 12-week dosing interval.

Separate populations of SARS-CoV-2 seronegative participants (supporting the primary and secondary objectives) and SARS-CoV-2 seropositive participants (supporting exploratory objectives) will be randomised/included in the above cohorts.

Randomization will be stratified based on age (less than 65, 65 and above), gender, and presence of at least one of the following comorbidities that are known risk factors for severe illness from COVID-19 (based on the participant's past and current medical history):

- Obesity (BMI $\geq$ 30 kg/m^2 at baseline)
- Significant cardiovascular disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, or pulmonary hypertension)
- Chronic lung disease (eg, chronic obstructive pulmonary disease, idiopathic pulmonary disease, cystic fibrosis, or moderate to severe asthma)
- Diabetes.

The randomised participants will be centrally assigned to randomised study intervention using an Interactive Response Technology (IRT)/Randomisation and Trial Supply Management. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information & directions for the Randomisation and Trial Supply Management will be provided to each site.

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

6.3.2 Blinding

Treatment will be double-blinded for previously vaccinated participants randomised to a single dose of either AZD2816 or AZD1222. Treatment will also be double-blind for previously unvaccinated participants randomised to 2 dose vaccinations with a 4-week dosing interval (ie, homologous AZD2816 or AZD1222 vaccination or heterologous AZD1222/AZD2816 vaccination). Previously unvaccinated participants randomised to a homologous AZD2816 vaccination with a 12-week dosing interval will receive treatment in an open-label fashion due to the different dosing interval.

For the double-blinded treatments, neither the participant nor any of the investigators or Sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the study intervention received. Since AZD2816 and AZD1222 are visually distinct prior to dose preparation (due to differences in container closure), all investigational 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, AZD2816 and AZD1222 are not visually distinct from each other.

The IRT will provide the investigators with a dose tracking number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IRT user manual that will be provided to each study site.

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

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

6.3.3 Procedures for Unblinding

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

In the event that a study participant is contacted about receiving a licensed and/or authorized COVID-19 vaccine outside of this clinical study, unblinding instructions are being provided to the sites. If the participant is unblinded, the Sponsor needs to be notified within 24 hours, and this should be documented in the site source documents.

6.4 Study Intervention Compliance

Participants are dosed at the study site, receiving study intervention directly from the investigator or designee, under medical supervision. The date, and time if applicable, of dose

administered will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5 Concomitant Therapy

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

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

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

6.5.1 Permitted Concomitant Medications

- Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance.
- Primary care providers, or where appropriate investigators, should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study.
- Participants who develop COVID-19 after receiving study intervention should be treated with licensed medications and interventions according to standard of care. All routine vaccinations other than influenza are permitted beginning > 30 days after last dose of study intervention. Licensed influenza vaccines are permitted 7 days before and 7 days after administration of study intervention.
- Topical/inhaled steroids or short-term oral steroids (course lasting ≤ 14 days) are permitted

6.5.2 Prohibited Concomitant Medications

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

- Primary or booster vaccinations, other than AZD2816 or AZD1222, for prevention of SARS-CoV-2 or COVID-19.

Note: Participants choosing to receive a licenced and/or authorized COVID-19 vaccine should inform the Investigator so it can be properly documented. Participants, who receive a licenced and/or authorized COVID-19 vaccine outside the study, should be encouraged to continue study conduct to be followed for safety reporting and all assessments.

- Receipt of any vaccine (licensed or investigational) other than licensed influenza vaccines within 30 days prior to and after administration of study intervention. Thirty days after the second vaccination, other routine vaccinations are permitted as clinically indicated.
- Glucocorticoids at a dose ≥ 20 mg/day of prednisone or equivalent given daily or on alternate days for ≥ 14 consecutive days between randomization and the participant's scheduled final visit
- Other systemically administered drugs with significant immunosuppressive activity, such as azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy between randomization and the participant's scheduled final visit
- Immunoglobulins and/or any blood product.

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

6.6 Dose Modification

Study intervention will be administered as described in Section 6.1. Dose modification is not permitted.

6.7 Intervention After the End of the Study

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

An individual participant will not receive the first or second dose (if applicable) of study intervention if any of the following occur in the participant in question:

1 Withdrawal of consent after signing informed consent

2 Participant meets one or more of the exclusion criteria or fails to meet all inclusion criteria for study participation

3 Participant is pregnant or nursing

4 Any grade 3 or greater allergic reaction including anaphylaxis that is assessed as related to study intervention

5 Occurrence of any thrombosis with concurrent thrombocytopenia

6 Any SAE assessed as related to study intervention

7 Any AE that, in the judgment of the site investigator, is related to study intervention and may jeopardize the safety of the study participant

8 Receipt of a prohibited concomitant medication that may jeopardize the safety of the study participant or interpretation of the data

Each participant who has received at least 1 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.

In the event that a study participant receives a licensed and/or authorized COVID-19 vaccine during the study, AstraZeneca needs to be notified within 24 hours and this should be documented in the site source documents. Participants who have received study intervention, regardless of reason, will be followed for the full study period.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Sponsor Study Team. If the participant does not specifically request withdrawal of consent for use of samples, then the samples collected prior to the consent withdrawal will be destroyed once per protocol analysis is complete.

7.3 Lost to Follow-up

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

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

- The study site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Schedule of Activities (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 Schedule of Activities (Section 1.3) is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities.

8.1 Efficacy Assessments

Not applicable.

8.2 Safety Assessments

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

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

8.2.2 Vital Signs

Vital signs, including heart rate, pulse oximetry, blood pressure, and body temperature, will be performed as specified in the Schedule of Activities (Section 1.3). The participant should be resting prior to the collection of vital signs. On vaccination days, vital signs should be assessed prior to vaccine administration.

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

8.2.3 Clinical Laboratory Assessments

Blood samples for determination of clinical chemistry and haematology will be taken at the visits indicated in the Schedule of Activities (Section 1.3). Additional unscheduled safety samples may be collected if clinically indicated at the discretion of the investigator, with the date and time of collection recorded in the appropriate eCRF.

The standard clinical chemistry and haematology analysis will be performed at a local laboratory at or near to the investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The following laboratory variables will be measured:

Table 9 Laboratory Safety Variables	
Blood	**Serum/Plasma**
Haemoglobin	Activated partial thromboplastin time
Leukocyte count	Prothrombin time
Leukocyte differential count (absolute count)	Fibrinogen
Platelet count	D-dimer
-	Creatinine
-	Bilirubin, total
-	Alkaline phosphatase
-	Aspartate aminotransferase
-	Alanine aminotransferase

In case a participant shows an aspartate aminotransferase **or** alanine aminotransferase ≥ 3 × upper limit of normal together with total bilirubin ≥ 2 × the upper limit of normal, please refer to Section 8.3.6

For women participants of childbearing potential, a urine sample for pregnancy testing will be collected according to the Schedule of Activities (Section 1.3). Urine pregnancy tests for β-human chorionic gonadotropin may be performed at the site using a licensed dipstick test.

8.3 Adverse Events and Serious Adverse Events

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

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

Solicited AEs are local or systemic predefined events for assessment of reactogenicity. Solicited AEs will be collected in a e-diary (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 the reporting of solicited AEs via e-diary unless otherwise noted..

All other AEs are considered to be unsolicited AEs (collected by ‘open question’ at study visits).

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

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

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

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

Solicited AEs will be recorded for 7 days after each dose of study intervention (ie, Day 1 through Day 8). If a solicited AE is not resolved within the e-diary reporting period, the event will be reported as a non-solicited adverse event in the eCRF, with a start date of when started and the actual stop date.

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

Medically-attended AEs and AEs of special interest will be recorded from Day 1 through the last participant contact.

See the Schedule of Activities for the scheduled timepoints (Section 1.3).

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 Adverse Events and Serious Adverse Events

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. The Sponsor retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

AE variables

The following variables will be collected for each AE:

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

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

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

A revised toxicity grading scale from US FDA guidance for healthy volunteers enrolled in a preventive vaccine clinical study (FDA 2007) will be utilized for all unsolicited events.

8.3.3 Causality Collection

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

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

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

8.3.4 Adverse Events Based on Signs and Symptoms

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

8.3.5 Adverse Events Based on Examinations and Tests

The results from the Clinical Study Protocol-mandated vital signs and laboratory safety assessments will be summarized in the Clinical Study Report.

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

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

8.3.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation. Any occurrences of aspartate aminotransferase or alanine aminotransferase ≥ 3 × the upper limit of normal together with total bilirubin ≥ 2 × upper limit of normal at any point during the study following the administration of study medication should be reported to the Sponsor as a potential Hy's Law SAE within 1 day with a serious criteria of 'Important medical event' and causality assessment 'yes/related'.

The study physician will contact the investigator to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.

8.3.7 Solicited Adverse Events

Local and systemic predefined solicited AEs for reactogenicity assessment (Table 10) will be collected in a Solicited AE e-Diary for 7 days following administration of each dose of study intervention via e-diary collection. If a solicited AE is not resolved within the e-diary reporting period, the event will be also reported as a non-solicited adverse event in the eCRF, with a start date of when started and the actual stop date.

Solicited AEs should not be reported as unsolicited AEs unless they fulfil the criteria for SAEs or medically-attended AEs(see Sections 8.3 and 8.3.8, respectively).

Table 10 Predefined Solicited Adverse Events for Reactogenicity Assessment

Local	Systemic
Pain at the site of the injection	Fever (> 100 °F/37.8 °C)
Redness/erythema at the site of the injection	Chills
Tenderness at the site of the injection	Muscle pains
Induration/swelling at the site of the injection	Fatigue (physical or mental tiredness/exhaustion)
-	Headache
-	Malaise (general feeling of discomfort or uneasiness)
-	Nausea
-	Vomiting

Solicited AE e-Diary

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

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

Severity Assessment of Solicited AEs

Severity will be assessed for solicited AEs by the participant (or, if applicable, their caregiver, surrogate, or legally authorized representative) according to toxicity grading scales modified and abridged from the US FDA guidance (FDA 2007) as defined in Appendix D. Because solicited AEs are expected to occur after vaccination, they will not be assessed for relationship to study intervention.

8.3.8 COVID-19 Assessment

This study will describe the incidence of COVID-19 adverse events reported from Day 1 to 180 days after the participant's last/only dose of vaccine.

COVID-19 is defined as SARS-CoV 2-RT-PCR positive symptomatic illness. At all clinic visits following the initial vaccination, participants will be asked if they have had a diagnosis of COVID-19 since their last clinic visit (see Schedule of Activities in Section 1.3). Medical records will be obtained for confirmation of a participant-reported diagnoses of COVID-19. Qualifying symptoms are fever, shortness of breath, difficulty breathing, chills, cough, fatigue, muscle/body aches, headache, new loss of taste or smell, sore throat, congestion, runny nose, nausea, vomiting, or diarrhoea. Events will be reported as AEs/SAEs.

If a participant presents at clinic visit with COVID symptoms, diagnosis will be confirmed using RT-PCR.

8.3.9 Medically-Attended Adverse Events

Medically-attended AEs will be collected according to the timepoints specified in the Schedule of Activities (Section 1.3).

Medically-attended AEs are defined as AEs leading to medically-attended visits that were not routine visits for physical examination or vaccination, such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. AEs, including abnormal vital signs, identified on a routine study visit or during the scheduled illness visits will not be considered medically-attended AEs.

8.3.10 Adverse Events of Special Interest

AEs of special interest will be collected according to the timepoints specified in the Schedule of Activities (Section 1.3).

AEs of special interest 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. AEs of special interest are based on Brighton Collaboration case definitions (SPEAC 2020), clinical experience, and scientific interest. A list of events is provided in Appendix E.

An AE of special interest can be serious or non-serious. All AEs of special interest will be recorded in the eCRF. If any AE of special interest occurs in the course of the study, investigators or other site personnel will inform the appropriate Sponsor representatives within 1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it. Serious AEs of special interest will be recorded and reported as per Section 8.3.11.

8.3.10.1 Vascular/Hematologic Adverse Events of Special Interest

Both thrombotic, thromboembolic, and neurovascular events and thrombocytopenia events are considered to be adverse events of special interest. The investigator should remain vigilant for the occurrence of thrombotic events with thrombocytopenia and/or bleeding. If a participant experiences new onset thromboembolic events with thrombocytopenia, there should be prompt evaluation with a thorough haematological investigation. COVID-19 testing, including PCR and serology (nucleoprotein antibodies), should also be performed. See Appendix F for further guidance on investigation and management of suspected events.

In the event of such a case of thrombosis and in accordance with local laws and ethical procedures, one blood sample may be taken from the participant and whole genome

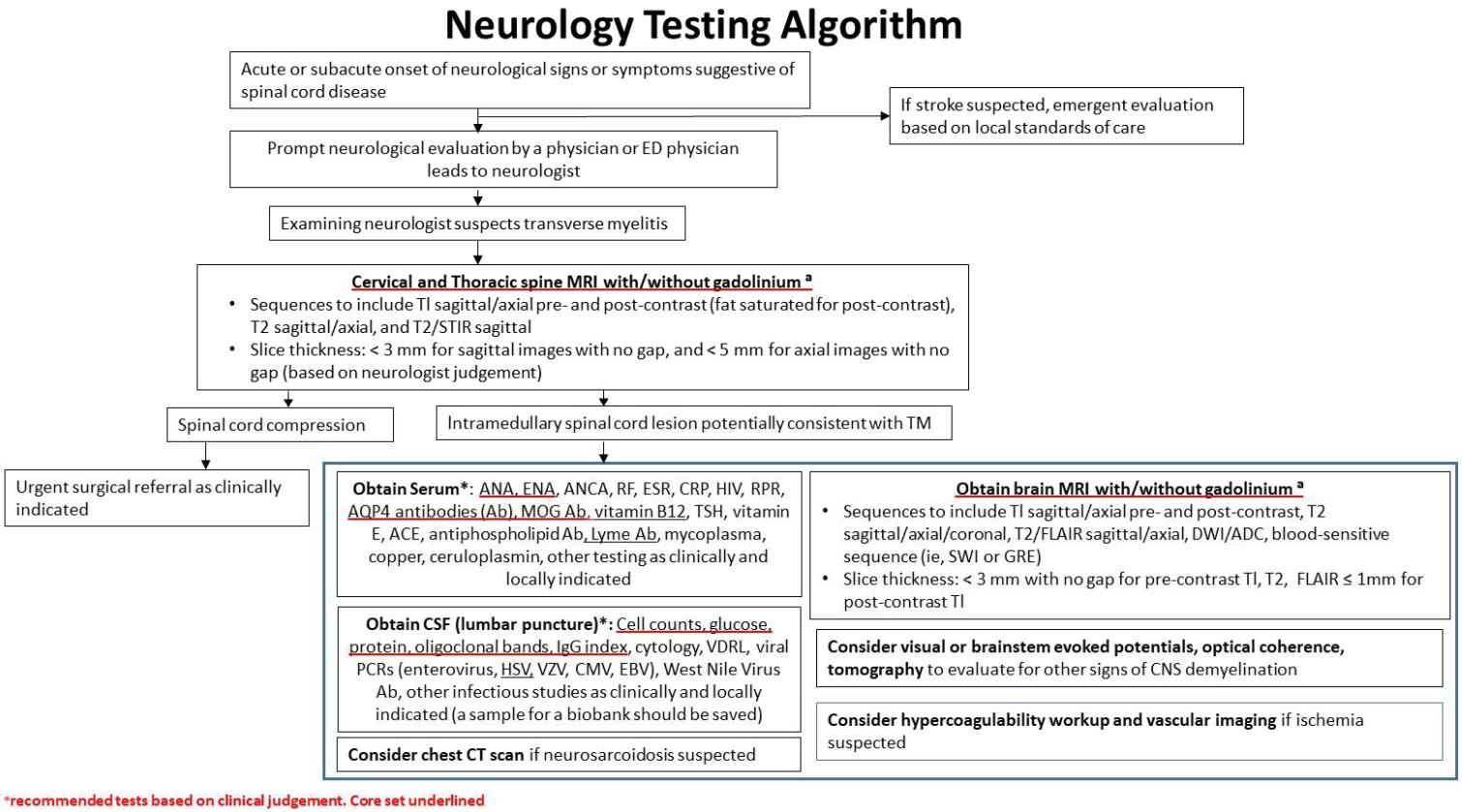
sequencing performed in order to enable investigations into the possible role of genetic polymorphisms as risk factors for these events.

8.3.10.2 Potential Neurological Adverse Events of Special Interest

If a participant experiences new onset (acute or subacute) motor and sensory disturbances (eg, weakness, numbness, paraesthesia, 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, including referral to a neurology specialist for further evaluation and testing, as clinically indicated. Testing can include evaluation for peripheral demyelinating conditions (eg, electromyography). In cases of concern for spinal cord disease, see Figure 3 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 AEs of special interest occurring in the AZD1222 clinical development program (see Appendix A 5).

Figure 3 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.

8.3.11 Reporting of Serious Adverse Events

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

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

The designated Sponsor representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform Sponsor representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but no later than 24 hours of when he or she becomes aware.

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 Sponsor representative.

If the Electronic Data Capture system is not available, then the investigator or other study site staff reports an SAE to the appropriate Sponsor representative by telephone or other method and the event is entered into the Electronic Data Capture system when available.

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

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

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

8.3.12 Pregnancy

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

8.3.12.1 Maternal Exposure

Female participants who are pregnant or have a confirmed positive pregnancy test at screening or Day 1 will be excluded from the study (see Section 5.2). Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and

spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the participant was discontinued from the study.

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

The designated Sponsor representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.11) and **within 30 days** for all other pregnancies that are not associated with an SAEs.

The same timelines apply when outcome information is available.

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

8.3.13 Medication Error

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

The designated Sponsor representative works with the investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) **or 5** (other serious initial and follow up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.11) and **within 30 days** for all other medication errors.

The definition of a Medication Error can be found in Appendix B 3.

8.4 Overdose

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

There is no specific treatment for an overdose with AZD2816 or AZD1222. If overdose occurs, the participant should be treated supportively with appropriate monitoring as necessary.

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

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

The designated Sponsor representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.11) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

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

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

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

8.5.1 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5.2 Immunogenicity Assessments

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

8.5.2.1 SARS-CoV-2 Serology Assessments

Serum samples will be collected to assess SARS-CoV-2 antigen-specific antibody levels from all participants according to the Schedule of Activities (Section 1.3). Authorized laboratories will assess serologic responses to AZD1222 and AZD2816 using validated (or qualified, where appropriate) assays. Serologic assessment to the S protein from different SARS-CoV-2 variants (which include Wuhan-Hu-1, B.1.351, B.1.1.7, and P.1) will be assessed quantitatively using a validated multiplexed ECL based immunoassay. Additionally, seroresponse will be assessed for each antigen over time. The rate of SARS-CoV-2 infection in participants receiving AZD2816 versus AZD1222 will be determined by seroresponse in a SARS-CoV-2 nucleocapsid antigen in a multiplexed electrochemiluminescence-based assay performed at an authorized laboratory. Additional exploratory assessments may be performed to measure binding antibodies to SARS-CoV-2 variants of interest (which may include B.1.429, B.1.525, B.1.526, P.2, P.3, B.1.617, and the Q677H mutation observed in multiple variants).

8.5.2.2 CCI

8.5.2.3 CCI

CCI

8.5.2.4 CCI

CCI

8.5.3 Pharmacodynamics

Pharmacodynamics are not evaluated in this study.

8.6 Human Biological Sample Biomarkers

Already collected samples may be analysed for biomarkers thought to play a role in COVID-19 severity or outcomes based upon emerging immunogenicity and pharmacodynamic analysis from this or other studies involving the study interventions. These analyses include but are not limited to serum or plasma cytokines, quantification of RNA, micro-RNA, and/or non-coding RNA using quantitative reverse transcriptase polymerase chain reaction (RT-PCR), microarray, sequencing, or other technologies in blood, or peripheral blood mononuclear cells to evaluate their association with AZD1222/2816 and observed clinical responses to these study interventions.

8.7 Optional Genomics Initiative Sample

Not applicable.

8.8 Medical Resource Utilization and Health Economics

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

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The overall hypothesis for this 8-armed study is that 28 days after vaccination (ie, following a single booster dose for the previously vaccinated participants or a second vaccination dose for previously unvaccinated participants), AZD2816 will be non-inferior to AZD1222 in terms of immunogenicity (ie, neutralising antibodies GMT ratio and difference in seroresponse rates). The specific null and alternative hypotheses for each objective are presented in Section 9.4.3.

9.2 Sample Size Determination

Primary Objective: Characterise Immunogenicity (Precision)

Historical data were available for the immunogenicity responses (ie, pseudovirus neutralising antibodies, live virus neutralising antibodies, and spike protein binding antibodies) to AZD1222 from the pooled COV001/002/003/005 studies. Table 11 presents the log transformed immunogenicity responses (ie, geometric mean titres) by assay for participants that received 2 standard doses of AZD1222. These results indicate that the pseudo-neutralising antibodies exhibited the largest variation (standard deviation of 1.20 and 1.10 for the 4-week and 12-week dosing intervals respectively), while live-neutralising antibodies had the lowest (standard deviation of 0.72 for the 4-week dosing interval).

Table 11 Historic Immunogenicity Responses by Dosing Interval (Geometric Mean Antibody Titres, Standard Dose Immunogenicity Analysis Set)

	Post-1st Dose			Post-2nd dose with a 4-week dosing interval[a]			Post-2nd dose with a 12-week dosing interval[b]		
Assay	**N**	**Mean**	**Std Dev**	**N**	**Mean**	**Std Dev**	**N**	**Mean**	**Std Dev**
Pseudo	476	4.3	1.34	166	5.3	1.20	113	5.4	1.10
Live	51	4.9	1.15	42	6.2	0.72	0	-	-
Spike protein	1139	9.1	1.14	293	10.1	0.96	302	10.7	0.83

[a] Estimates from pooled COV001/002/003/005 study data from participants with 2- to 6-week dosing interval
[b] Estimates from pooled COV001/002/003/005 study data from participants with 10- to 14-week dosing interval

Table 12 presents the seroresponse (ie, ≥ 4 fold increase from baseline) by assay. These results indicate that the pseudo-neutralising antibodies exhibited the lowest proportion of seroresponse (59.7% and 85.5% for the 4-week and 12-week dosing intervals respectively), while both live-neutralising and spike-binding seroresponse rates exceeded 95%.

Table 12 Historic Seroresponse Rates by Dosing Interval (>4-fold Increase from Baseline, Standard Dose Immunogenicity Analysis Set)

	Post-1st Dose		Post-2nd dose with a 4-week dosing interval[a]		Post-2nd dose with a 12-dose week interval[b]	
Assay	**N**	**Proportion**	**N**	**Proportion**	**N**	**Proportion**
Pseudo	499	32%	382	59.7%	117	85.5%
Live	96	75%	95	96.8%	-	-
Spike protein	940	96.6%	636	95.9%	304	99.3%

[a] Estimates from pooled COV001/002/003/005 study data from participants with 2- to 6-week dosing interval
[b] Estimates from pooled COV001/002/003/005 study data from participants with 10- to 14-week dosing interval

Under the assumption that the immunogenicity responses (ie, geometric mean antibody titres) associated with AZD2816 will be similar to the responses associated with AZD1222 in participants that received 2 standard doses in the pooled COV001/002/003/005 studies, in which standard deviations ranged from 0.72 to 1.2 (Table 11), 150 participants will provide a 95% confidence interval half-width between 0.115 and 0.192 (see Table 13). Similarly, 380 participants will provide a 95% confidence interval half-width between 0.072 and 0.120.

Under the assumption that the seroresponse rates associated with AZD2816 will be similar to the response rates in adults that received 2 standard doses of AZD1222 in the pooled COV001/002/003/005 studies (Table 12), 150 participants will provide a 95% confidence interval half-width between 1.33% and 7.85%, and 380 participants will provide a 95% confidence interval half-width between 0.84% and 4.93% (Table 14).

Table 13 Estimated Half-width of the 95% Confidence Intervals for Immunogenicity Responses (Geometric Mean Titres) Based on Historic Immunogenicity Assay Variances and the Proposed Sample Sizes

Standard Deviation	Number of participants	Estimated half-width of the 95% confidence interval (natural log scale)
0.72	150	0.115
	300	0.081
	350	0.075
	380	0.072
0.83	150	0.133
	300	0.094
	350	0.087
	380	0.084
0.96	150	0.154
	300	0.109
	350	0.101
	380	0.097
1.1	150	0.176
	300	0.124
	350	0.115
	380	0.111
1.2	150	0.192
	300	0.136
	350	0.126
	380	0.120

Table 14 Estimated Half-Width of the 95% Confidence Interval for the Seroresponse Rates based on Historic Seroresponse Rates and Proposed Sample Sizes

Observed seroresponse rate	Participants (N)	Estimated half-width of the 95% confidence interval
59.7%	150	7.85%
	300	5.55%
	350	5.14%
	380	4.93%
85.5%	150	5.63%
	300	3.98%
	350	3.69%
	380	3.54%
95.9%	150	3.17%
	300	2.24%
	350	2.08%
	380	1.99%
96.8%	150	2.82%
	300	1.99%
	350	1.84%
	380	1.77%
99.3%	150	1.33%
	300	0.94%
	350	0.87%
	380	0.84%

For a fixed sample size, the precision with which the 95% confidence interval of the binary seroresponse rate can be estimated is a function of the response rate. Table 14 provides the lower bounds of the 95% confidence interval for selected response proportions for alternate sample sizes. For a given response rate, we can be 95% confident that the true seroresponse rate is at least as large as the lower bound of the confidence interval.

Primary Objective: Safety

Table 15 indicates the probability of observing 1 or more safety events, such as solicited injection site or systemic reactogenicity events or an unsolicited non-serious AE of a

particular type for participants in each treatment arm. With the sample size of 300 participants, at least 1 participant with an AE of incidence rate of 1% can be detected with probability of about 95%.

Table 15 Probability of detecting 1 or more safety events (N = 300)

Event Frequency	Probability (> 1 event)
≥ 10% (Very Common)	> 99%
≥ 1% (Common)	95%
≥ 0.1% (Uncommon)	26%
≥ 0.01% (Rare)	3%

Secondary Objective: Compare Immunogenicity

Under the assumption that there is no difference between treatment arms of interest (ie, a ratio of 1, difference on the log scale of 0), the power conferred by 150 to 380 participants for the comparison of geometric mean titre ratio using a noninferiority margin of 1.5 (equivalent to a difference on the log scale of 0.405) is presented in .

Table 16 Power for Non-inferiority Using 1.5 as the Upper Bound of the Geometric Mean Titre Ratio

and for the comparison of seroresponse rate using the non-inferiority margin of -15% as the upper bound of the difference is presented in Table 17.

If there is no difference between treatment arms of interest (ie, a ratio of 1) in the proportion of seroresponders, 380 participants provides 98% power to establish non-inferiority to within margin of -15% if the seroresponse rate is >50%. The observed pseudo-neutralising response rates (> 4 fold increase from baseline) from the COV001/002/003/005 studies for AZD1222 were 59.7% and 85.5% for the 4-week and 12-week dosing interval respectively (Table 12). A population of 380 participants provides 99% power to detect non-inferiority (using a non-inferiority margin of -15%) if the observed response rate is 59.7%.

Table 16 Power for Non-inferiority Using 1.5 as the Upper Bound of the Geometric Mean Titre Ratio

Sides	Null difference	Assumed mean treatment difference	Assumed standard deviation	Number in comparator group	Number in reference group	Alpha	Power
Upper	ln1.5 = 0.405	0	0.72	150	300	0.025	>.999
				150	350		>.999
				150	380		>.999
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999
			0.83	150	300		0.998
				150	350		0.999
				150	380		>.999
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999
			0.96	150	300		0.988
				150	350		0.991
				150	380		0.992
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999
			1.10	150	300		0.957
				150	350		0.965
				150	380		0.968
				300	300		0.994
				300	350		0.997
				300	380		0.997
				350	380		0.999
				350	350		0.998
				380	380		>.999
			1.20	150	300		0.920
				150	350		0.932
				150	380		0.937
				300	300		0.985
				300	350		0.990
				300	380		0.992
				350	380		0.995
				350	350		0.994
				380	380		0.996

Table 17 Power for Non-inferiority Using -15% as the Upper Bound of the Difference in Seroresponse Rate

Sides	Null proportion difference	Assumed difference in proportion of seroresponders	Assumed proportion of seroresponders in both groups	Number in comparator group	Number in reference group	Alpha	Power
Lower	-0.15	0	0.597	150	300	0.025	0.878
				150	350		0.894
				150	380		0.902
				300	300		0.964
				300	350		0.975
				300	380		0.979
				350	380		0.986
				350	350		0.982
				380	380		0.989
			0.855	150	300		0.993
				150	350		0.995
				150	380		0.996
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999
			0.959	150	300		>.999
				150	350		>.999
				150	380		>.999
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999
			0.968	150	300		>.999
				150	350		>.999
				150	380		>.999
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999
			0.993	150	300		>.999
				150	350		>.999
				150	380		>.999
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999

9.3 Populations for Analyses

The following populations are defined:

Table 18 Populations for Analysis

Population	Description
All participants analysis set	All participants screened for the study, to be used for reporting disposition and screening failures.
Full analysis set	All randomised participants who received study treatment, irrespective of their protocol adherence and continued participation in the study. Participants will be analysed according to their randomised treatment, irrespective of whether or not they have prematurely discontinued, according to the intent-to-treat principle. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination.
Safety analysis set	The safety analysis set consists of all participants who have received study treatment. Erroneously-treated participants (eg, those randomised to AZD2816, but were actually given treatment AZD12222) are accounted for in this analysis set by assigning them to the treatment they actually received.
Immunogenicity analysis set	The vaccine immunogenicity analysis set will include all randomised participants, received at least 1 dose of planned study treatment (ie, 1 dose of either AZD2816 or 1 dose of AZD1222), had baseline and post-dose antibody measurements, have at least 1 post-dose quantifiable serum titre, and had no protocol deviations judged to have the potential to interfere with the generation or interpretation of an antibody response. The analyses conducted using this analysis set will be based on the actual treatment received.
Seronegative immunogenicity analysis set	The subset of the immunogenicity analysis set who were seronegative at baseline.
Seropositive immunogenicity analysis set	The subset of the immunogenicity analysis set who were seropositive at baseline.

Participants that are SARS-CoV-2 seropositive at screening will be included in seropositive analysis sets analogous to the above seronegative analysis sets. Further definition is provided in the Statistical Analysis Plan.

9.4 Statistical Analyses

This section provides a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints. A more technical and detailed description of the statistical analyses will be described in the Statistical Analysis Plan, and an approved version will be finalized prior to the interim analyses.

9.4.1 General Considerations

An initial interim analysis will occur when a subset of participants previously vaccinated with AZD1222 have completed their Day 29 visit (ie, 28 days after booster dose). This sample will include both participants randomised to receive a booster dose of AZD2816 as well as a those randomised to receive a booster dose of AZD1222. Analyses presenting treatment arm summaries of both the raw and model adjusted immunogenicity will be reviewed by an unblinded team within AstraZeneca to make a decision regarding the potential need for sample size re-estimation. Full details of this analyses are provided in the Interim Analysis Charter to be finalized prior to any interim analysis.

A second interim analysis will occur when all participants previously vaccinated with AZD1222 have completed their Day 29 visit (ie, 28 days after booster dose). It is estimated that this early analysis has the potential to provide clear signals about whether AZD2816 provides a strong neutralizing response against the B.1.351 strain while retaining immunogenicity against the Wuhan strain, and thereby influence programmatic decisions early. Analyses results will present treatment arm specific summaries of both the raw and model adjusted (baseline age and co-morbidities). The raw data outputs will be stratified by age group (<65, ≥ 65) while the model adjusted summaries will pool data across age groups. Full details of this analyses are provided in the Interim Analysis Statistical analysis Plan to be finalized prior to any interim analysis.

A third interim analysis may be performed when a subset of previously unvaccinated participants have completed their Day 57 visit (ie, 56 days after fist dose). The participant sample will include both participants randomised to AZD2816 as well as those randomised to AZD1222. This analysis is intended to assess immunogenicity variability. The number of previously unvaccinated participants per treatment arm may be increased based upon the results of this analysis. The details of this interim analysis, including the trigger and methods, will be specified in the Interim Analysis Charter.

The primary analysis will occur when all participants have completed their Day 29 visit and safety and immunogenicity data from all unvaccinated participants randomised to a 4-week dosing interval are available through completion of their visit 28 days after the second priming dose.

A secondary analysis will occur when all participants have completed their Day 29 visit and safety and immunogenicity data from all unvaccinated participants (including those randomised to a 12-week dosing interval) are available through completion of the visit 28 days after the second dose.

The final analysis will occur when data from all vaccinated participants is available through completion of the last study visit (180 days after the single dose for previously vaccinated participants / 180 days after the second dose for unvaccinated participants).

Further details of the primary analysis, secondary analysis and final analysis are contained within the Statistical Analysis Plan

To maintain trial integrity sponsor roles with direct input into participant management and safety monitoring will not have access to unblinded participant level data or associated outputs from the interim analyses until end of study.

Further details on the tools and processes to maintain the blind will be presented in the Study Integrity Plan.

9.4.2 Safety

9.4.2.1 Primary Endpoints

Overview

Descriptive analyses will support evaluation of safety, reactogenicity and immunogenicity. The primary safety analysis includes:

- Incidence of local and systemic solicited AEs for 7 days following each vaccination will be summarised by day and overall.
- Incidence of unsolicited AEs for 28 days following each vaccination will be summarised by system organ class and preferred term, and by relationship to vaccination as assessed by the investigator.
- MAAEs, SAEs, and AESIs following the first vaccination and throughout the study duration will be summarised by system organ class and preferred term and by relationship to vaccination as assessed by the investigator.
- The change from baseline for safety laboratory measures at 7 and 28 days after vaccination.

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

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

A listing will cover details for each individual AE. Full details of all AE analyses will be provided in the Statistical Analysis Plan, including intercurrent events for safety due to potential unblinding of participants for administration of licensed and/or approved SARS-CoV-2 or COVID-19 vaccine.

At the time of the interim analyses, group assignment will not be presented when safety event data has the potential to unblind participant's study group attribution.

9.4.2.2 Other Safety Endpoints

Vital Signs

Vital sign measurements will be performed as specified in the Schedule of Activities (Section 1.3). The set of assessments will include pulse oximetry, blood pressure, and body temperature.

Details of all vital sign analyses will be provided in the Statistical Analysis Plan, which will include descriptive statistics presented for observed values for all vital sign parameters.

COVID-19

This study will describe the incidence of COVID-19 adverse events from the first dose of the vaccine to study end (180 days post-vaccination). Descriptive statistics will be produced based on the safety analysis set. Full details will be documented in the statistical analysis plan.

9.4.3 Immunogenicity

9.4.3.1 Immunogenicity Endpoints

The immunogenicity endpoints of interest in this study are:

- Geometric mean antibody titre.
- Seroresponse, defined as ≥ 4-fold increase in the geometric mean antibody titre from baseline

Both the geometric mean antibody titre and seroresponse of participants will be summarized descriptively by strain, treatment arm, and timepoint for the immunogenicity population.

9.4.3.1.1 Estimand framework for immunogenicity descriptions and comparisons

Target populations:

1) Previously unvaccinated participants

    a. Seronegative Analysis Set: and with no evidence of prior or current infection

2) Participants who previously received SARS-CoV-2 vaccination with either AZD1222 or a licensed mRNA vaccine according to the authorized dose and dosing regimen at least 3 months prior to first study intervention (see Section 5.1.2).

Outcome variable: neutralizing antibody and binding titres to SARS-CoV-2 at 28 days after each treatment administration (1 treatment administration for the previously vaccinated population and 2 planned treatment administrations for the unvaccinated population).

Treatment conditions:

Previously unvaccinated population

- 2 doses of AZD1222 given on Day 1 and on Day 29 (4-week dosing interval)
- 2 doses of AZD2816 given on Day 1 and on Day 29 (4-week dosing interval)
- 1 dose of AZD1222 given on Day 1 and 1 dose of AZD2816 on Day 29 (4-week dosing interval)
- 2 doses of AZD2816 given on Day 1 and on Day 85 (12-week dosing interval)

Previously vaccinated population

- 1 dose of AZD1222 given on Day 1.
- 1 dose of AZD2816 given on Day 1.

Intercurrent events: the following intercurrent events could impact the antibody levels achieved:

- missing the second vaccination (for the unvaccinated population)
- receiving of immune-modifying drugs or vaccines
- subsequent infection with SARS-CoV-2.

All immunogenicity descriptions and comparisons will use the principal stratum strategy, ie, all analyses will exclude participants who experience any of the above intercurrent events.

Population-level summary:

Descriptive Analyses (see Table 20 and Table 21)

- geometric means of the antibody titres
- seroresponse proportions

Comparative Analyses (see Table 22 and Table 23**Error! Reference source not found.**)

- ratio of geometric means of the antibody titres.
- difference in seroresponse proportion

Planned Descriptive Analyses:

Table 20 and Table 21 present planned descriptive immunogenicity analyses for the unvaccinated and previously vaccinated populations respectively (each one exploring an individual treatment arm at a specific timepoint against a particular strain).

The tables show that without introduction of further variants, there are 24 planned descriptive analyses for the unvaccinated population and 16 planned descriptive analyses for the previously immunised population (index). Within each table there is an analysis key which describes the population (see Table 19). The descriptive analyses presented in Tables 19 and 20 will be repeated for the subset of participants who are seropositive at screening.

Table 19 Description of the Analysis Keys for Tables 19 and 20

Population	Analysis Key	Example
Previously unvaccinated	Primary series dosing interval: P4 (4-week dosing interval) or P12 (12-week dosing interval) Treatment received: 1222 (2 doses of AZD1222) or 2816 (2 doses of AZD2816) or 1222/2816 (1 dose of AZD1222 followed by 1 dose of AZD2816) Strain: W (Wuhan-Hu-1) or V (Variant B.1.351) Analysis Timepoint: 1 (28 days post-dose 1) 2 (28 days post-dose 2)	[P4:1222:W:1] = Immunogenicity following primary vaccination with a 4-week dosing interval of 2 doses of AZD1222 against Wuhan-Hu-1 28 days post-dose 1
Previously vaccinated	Pre-study primary vaccination: P1222 (2 doses of AZD1222) or PmRNA (2 doses of an mRNA vaccine) Treatment received: B1222 (1 booster dose of AZD1222) or B2816 (1 booster dose of AZD2816) Strain: W (Wuhan-Hu-1) or V (Variant B.1.351)	[P1222:B1222:V] = Immunogenicity in participants who were previously vaccinated with 2 doses of AZD1222 as primary vaccination series and received a single boost dose of AZD1222 against the B.1.351 variant

Table 20 Immunogenicity Descriptive Analysis for Previously Unvaccinated Treatment Groups (with Separate Seronegative and Seropositive Analyses)

Treatment	Interval	Strain	Timepoint	Endpoint	Index	Analysis Key
AZD1222	4 weeks	Wuhan-Hu-1	28 days after 1st dose	GMT	1	[P4:1222:W:1]†
				Seroresponse	2	
			28 days after 2nd dose	GMT	3	[P4:1222:W:2]
				Seroresponse	4	
		B.1.351	28 days after 1st dose	GMT	5	[P4:1222:V:1]†
				Seroresponse	6	
			28 days after 2nd dose	GMT	7	[P4:1222:V:2]
				Seroresponse	8	
AZD2816	4 weeks	Wuhan-Hu-1	28 days after 1st dose	GMT	9	[P4:2816:W:1]‡
				Seroresponse	10	
			28 days after 2nd dose	GMT	11	[P4:2816:W:2]
				Seroresponse	12	
		B.1.351	28 days after 1st dose	GMT	13	[P4:2816:V:1]‡
				Seroresponse	14	
			28 days after 2nd dose	GMT	15	[P4:2816:V:2]
				Seroresponse	16	
AZD1222/2816	4 weeks	Wuhan-Hu-1	28 days after 2nd dose	GMT	17	[P4:1222/2816:W:2]
				Seroresponse	18	
		B.1.351	28 days after 2nd dose	GMT	19	[P4:1222/2816:V:2]
				Seroresponse	20	
AZD2816	12 weeks	Wuhan-Hu-1	28 days after 2nd dose	GMT	21	[P12:2816:W:2]
				Seroresponse	22	
		B.1.351	28 days after 2nd dose	GMT	23	[P12:2816:V:2]
				Seroresponse	24	

† descriptive summaries for 28 days after 1st dose will pool all treatment groups who received AZD1222 as their first dose (ie, homologous and heterologous series).
‡ descriptive summaries for 28 days after 1st dose will pool all treatment groups who received AZD2816 as their first dose (4-week interval and 12-week interval treatment arms).

GMT: Geometric mean titre

Table 21 Immunogenicity Descriptive Analysis for Previously Vaccinated Treatment Groups (with Separate Seronegative and Seropositive Analyses)

Primary vaccination	Booster Treatment	Strain	Timepoint	Endpoint	Index	Analysis Key
AZD1222	AZD1222	Wuhan-Hu-1	28 days after booster	GMT	1	[P1222:B1222:W]
				Seroresponse	2	
		B.1.351	28 days after booster	GMT	3	[P1222:B1222:V]
				Seroresponse	4	
	AZD2816	Wuhan-Hu-1	28 days after booster	GMT	5	[P1222:B2816:W]
				Seroresponse	6	
		B.1.351	28 days after booster	GMT	7	[P1222:B2816:V]
				Seroresponse	8	
mRNA	AZD2816	Wuhan-Hu-1	28 days after booster	GMT	9	[PmRNA:B2816:W]
				Seroresponse	10	
		B.1.351	28 days after booster	GMT	11	[PmRNA:B2816:V]
				Seroresponse	12	
	AZD1222	Wuhan-Hu-1	28 days after booster	GMT	13	[PmRNA:B1222:W]
				Seroresponse	14	
		B.1.351	28 days after booster	GMT	15	[PmRNA:B1222:V]
				Seroresponse	16	

GMT: Geometric mean titre

Immunogenicity comparisons:

Immunogenicity analysis

A number of comparisons of geometric mean titres and seroresponse rates between vaccine regimens and vaccine types are intended to be made.

All non-inferiority comparisons of geometric mean titre ratios will be made utilizing the lower bound of two-sided score-based confidence intervals ($\alpha = 0.05$) with non-inferiority margin 0.67

All non-inferiority comparisons of seroresponse rates will be made utilizing the lower bound of two-sided score-based confidence intervals ($\alpha = 0.05$) with non-inferiority margin 15%, and superiority comparisons of seroresponse rates will be made using one-sided Fisher's exact test ($\alpha = 0.025$). Comparisons of Ab titres between treatment groups will be conducted using geometric mean titre (GMT) ratios and seroresponse rates, facilitated by an analysis of covariance (ANCOVA) model of the log2 titre, which adjusts for the baseline level, time since previous vaccination (for previously vaccinated individuals), baseline co-morbidities and gender as fixed effects. All analyses of antibody titres (GMT ratios and differences in seroresponse) will be repeated using the unadjusted (raw observed) concentration values.

Geometric Mean Titres

The statistical methodology will be based on a 2-sided 95% CI of the ratio of the GMTs. Non-inferiority will be demonstrated if the lower limit of the 2-sided 95% CI of the GMT ratio of the reference group and comparator group is >0.67 (see table xx). The 2-sided 95% CI for the ratio of GMTs will be calculated using normal approximation of log-transformed concentrations.

The 95% CI for the GMT ratio between 2 groups will be constructed as follows:

Logarithm transformation of the individual concentrations will be calculated.

The 95% CI for the difference in log(GMT) between 2 groups: $Group_C$ and $Group_R$ will be in the form:

$$\bar{X}_C - \bar{X}_R \pm t\left(1 - {}^{\alpha}/_{2}, n_C + n_R - 2\right) \times S\sqrt{{}^{1}/_{n_C} + {}^{1}/_{n_R}}$$

Where $\bar{X}_C$ and $\bar{X}_R = \log(GMT)$ are the means of the log-transformed concentration for $Group_C$ and $Group_R$, respectively,

$S^2 = {}^{[(n_C - 1)S_C^2 + (n_R - 1)S_R^2]}/_{(n_C + n_R - 2)}$ is the pooled sample variance,

n_C and n_R are the sample sizes for $Group_C$ and $Group_R$, respectively,

S_C and S_R are the sample variances for $Group_C$ and $Group_R$, respectively,

$t\left(1 - {}^{\alpha}/_{2}, n_C + n_R - 2\right)$ is the $100\left(1 - \frac{\alpha}{2}\right)$ percentile of the t-distribution with degrees of freedom $df = n_C + n_R - 2$

To test this hypothesis, a 2- sided 95% CI will be constructed around the ratio $\frac{GMT_C}{GMT_R}$, where GMT_C and GMT_R are the geometric mean of the antibody titres in the comparator and reference groups respectively, at the timepoints post vaccination for which the groups are being compared.

The hypothesis will be supported by the data, if the lower bound of the calculated of the calculated 95% CI is > 0.67. This is equivalent to testing the null hypothesis using a 1-sided type-I error rate of 0.025.

$$H_0: {}^{GMT_C}/_{GMT_R} \leq 0.67$$

$$H_A: {}^{GMT_C}/_{GMT_R} > 0.67$$

Or equivalently

$$H_0: \log(GMT_C) - \log(GMT_R) \leq \log(0.67)$$

$$H_A: \log(GMT_C) - \log(GMT_R) > \log(0.67)$$

For the separately considered GMT hypotheses, if the null hypothesis is rejected, then the alternative hypothesis of non-inferiority will be supported.

Seroresponse

The statistical methodology will be based on a 2-sided 95% CI of the difference in seroresponse rates. Non-inferiority will be demonstrated if the upper bound of the 2-sided 95% CI rate difference in seroresponse between the reference group and comparator group is <15%. The 95% CI of the difference in proportions $P_C - P_R$ will be computed using the Wilson score without continuity correction.

To test this hypothesis, a 2- sided 95% CI will be constructed around the difference $P_C - P_R$, whereP_C and P_R are the proportions of participants in the comparator and reference groups respectively who are classified as seroresponders (> 4 fold increase from baseline) at the timepoints post vaccination for which the groups are being compared.

The hypothesis will be supported by the data, if the lower bound of the calculated of the calculated 95% CI is ≥ 15%. This is equivalent to testing the null hypothesis using a 1-sided type-I error rate of 0.025.

$$H_0: P_C - P_R < -15\%$$

$$H_A: P_C - P_R \geq 15\%$$

If the null hypothesis is rejected, then the alternative hypothesis of non-inferiority will be supported.

Comparisons

The primary and secondary immunogenicity objectives and the GMT and seroresponse comparisons for the previously unvaccinated participants receiving a 2-dose primary vaccination are presented in Table 22

The immunogenicity objectives and the GMT and seroresponse comparisons for the previously vaccinated participants receiving a 1-dose booster vaccination are presented in Table 23.

Table 22 Immunogenicity Comparisons for Previously Unvaccinated Groups

Objective	$\frac{[\![\mathbf{[GMT]}]\!]_{\mathbf{comparator}}]}{[\![\mathbf{[GMT]}]\!]_{\mathbf{reference}}]}$	$[\![\mathbf{[Seroresponse]}]\!]_{\mathbf{comparator}}] - [\![\mathbf{[Seroresponse]}]\!]_{\mathbf{reference}}]$
To determine if the neutralizing antibody GMT response/seroresponse elicited by a 2-dose AZD2816 primary vaccination is non-inferior to the response elicited by a 2-dose AZD1222 primary vaccination	[P4: 2816: V: 2]/[P4: 1222: W: 2] (Primary)	[P4: 2816: V: 2] − [P4: 1222: W: 2] (Key Secondary 2.1)
	[P4: 2816: V: 1]/[P4: 1222: W: 1]	[P4: 2816: V: 1] − [P4: 1222: W: 1]
	[P4: 2816: V: 2]/[P4: 1222: V: 2] (Key Secondary 2.2)	[P4: 2816: V: 2] − [P4: 1222: V: 2] (Other Secondary)
	[*P*4: 2816: V: 1]/[*P*4: 1222: V: 1]	[P4: 2816: V: 1] − [P4: 1222: V: 1]
	[P4: 2816: W: 2]/[P4: 1222: W: 2] (Key Secondary 2.4)	[P4: 2816: W: 2] − [P4: 1222: W: 2] (Other Secondary)
	[P4: 2816: W: 1]/[*P*4: 1222: W: 1]	[P4: 2816: W: 1] − [P4: 1222: W: 1]
To determine if the neutralizing antibody GMT response/seroresponse elicited by a 2-dose AZD1222 + AZD2816 heterologous primary vaccination is non-inferior to the response elicited by a 2-dose AZD1222 primary vaccination	[P4: 1222/2816: V: 2]/[P4: 1222: W: 2] (Key Secondary 2.3)	[P4: 1222/2816: V: 2] − [P4: 1222: W: 2] (Other Secondary)
	[P4: 1222/2816: W: 2]/[P4: 1222: W: 2] (Other Secondary)	[P4: 1222/2816: W: 2] − [P4: 1222: W: 2] (Other Secondary)
	[P4: 1222/2816: V: 2])/([P4: 1222: V: 2] (Other Secondary)	[P4: 1222/2816: V: 2] − [P4: 1222: V: 2] (Other Secondary)

Table 22 Immunogenicity Comparisons for Previously Unvaccinated Groups

Objective	$\frac{[\![\mathbf{[GMT]}]\!]_{\mathbf{comparator}}]}{[\![\mathbf{[GMT]}]\!]_{\mathbf{reference}}]}$	$[\![\mathbf{[Seroresponse]}]\!]_{\mathbf{comparator}}] - [\![\mathbf{[Seroresponse]}]\!]_{\mathbf{reference}}]$
To determine if the neutralizing antibody GMT response/seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 2-dose AZD2816 primary vaccination	[P4: 2816: V: 2]/[P4: 2816: W: 2] (Other Secondary)	[P4: 2816: V: 2] − [P4: 2816: W: 2] (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 2-dose AZD1222/AZD2816 primary heterologous vaccination	[P4: 1222/2816: V: 2]/[P4: 1222/2816: W: 2] (Other Secondary)	[P4: 1222/2816: V: 2] − [P4: 1222/2816: W: 2] (Other Secondary)

Table 23 Immunogenicity Comparisons for Previously Vaccinated Group

Objective	$\frac{[\![\mathbf{[GMT]}]\!]_{\mathbf{comparator}}]}{[\![\mathbf{[GMT]}]\!]_{\mathbf{reference}}]}$	$[\![\mathbf{[Seroresponse]}]\!]_{\mathbf{comparator}}] - [\![\mathbf{[Seroresponse]}]\!]_{\mathbf{reference}}]$
To determine if the neutralizing antibody GMT response/seroresponse elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination	[P1222: B2816: V]/[P4: 1222: W: 2] (Primary)	[P1222: B2816: V] − [P4: 1222: W: 2] (Other Secondary)
	[P1222: B2816: V]/[P4: 1222: V: 2] (Key Secondary 2.1)	[P1222: B2816: V] − [P4: 1222: V: 2] (Other Secondary)
	[P1222: B2816: W]/[P4: 1222: W: 2] (Key Secondary 2.3)	[P1222: B2816: W] − [P4: 1222: W: 2] (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse elicited by an AZD2816 booster dose is non-inferior to response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222	[P1222: B2816: V]/[P1222: B1222: V] (Key Secondary 2.2)	[P1222: B2816: V] − [P1222: B1222: V] (Other Secondary)
	[P1222: B2816: W]/[P1222: B1222: W] (Key Secondary 2.5)	[P1222: B2816: W] − [P1222: B1222: W] (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse elicited by an AZD1222 booster dose in patients previously vaccinated with AZD1222 is non-inferior to the response elicited by a 2-dose AZD1222 vaccination	[P1222: B1222: W]/[P4: 1222: W: 2] (Key Secondary 2.4)	[P1222: B1222: W] − [P4: 1222: W: 2] (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse elicited by an AZD2816 booster dose in participants previously vaccinated with an mRNA-based vaccine is non-inferior to response elicited by a 2-dose AZD1222 vaccination	[PmRNA: B2816: V]/[P4: 1222: W: 2] (Other Secondary)	[PmRNA: B2816: V] − [P4: 1222: W: 2] (Other Secondary)
	[PmRNA: B2816: V]/[P4: 1222: V: 2] (Other Secondary)	[PmRNA: B2816: V] − [P4: 1222: V: 2] (Other Secondary)

Table 23 Immunogenicity Comparisons for Previously Vaccinated Group

Objective	$\frac{[\![\mathbf{GMT}]\!]_{\mathbf{comparator}}]}{[\![\mathbf{GMT}]\!]_{\mathbf{reference}}]}$	$[\![\mathbf{Seroresponse}]\!]_{\mathbf{comparator}}] - [\![\mathbf{Seroresponse}]\!]_{\mathbf{reference}}]$
	[PmRNA: B2816: W]/[P4: 1222: W: 2] (Other Secondary)	[PmRNA: B2816: W] − [P4: 1222: W: 2] (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse elicited by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with an mRNA-based vaccine	[PmRNA: B2816: W])/[PmRNA: B1222: W] (Other Secondary)	[PmRNA: B2816: W] − [PmRNA: B1222: W] (Other Secondary)
	[PmRNA: B2816: V])/[PmRNA: B1222: V] (Other Secondary)	[PmRNA: B2816: V] − [PmRNA: B1222: V] (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 2816 booster dose	[P1222: B2816: V]/[P1222: B2816: W] (Other Secondary)	[P1222: B2816: V] − [P1222: B2816: W] (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 1222 booster dose	[P1222: B1222: V]/[P1222: B1222: W] (Other Secondary)	[P1222: B1222: V] − [P1222: B1222: W] (Other Secondary)

9.4.4 Multiple Comparisons

A hierarchical approach will be used to control for multiplicity of the primary and key secondary efficacy endpoints. That is, the null hypotheses for the efficacy endpoints will be tested in a hierarchical order, and the subsequent null hypothesis will be tested only if the prior null hypothesis is rejected. Consequently, no adjustment to alpha for multiplicity will be made in the analysis of immune response. The primary statistical comparisons of safety data will not be adjusted for multiple comparisons. Further details are provided in the statistical analysis plan.

9.4.5 Data Safety Monitoring Board

An independent COVID-19 Vaccine Data Safety Monitoring Board will provide oversight, to ensure safe and ethical conduct of the study. During the study, the benefit/risk assessment will be continuously monitored by the Board to ensure that the balance remains favourable. Further details, composition, and operation of the COVID-19 Vaccine Data Safety Monitoring Board will be described in a separate charter. For further details, see Appendix A 5.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Not applicable.

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

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

Regulatory Reporting Requirements for SAEs

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

A 2 Financial Disclosure

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

A 3 Informed Consent Process

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

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

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

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

A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

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

A 5 Committee Structure

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

A COVID-19 Vaccine Data Safety Monitoring Board comprised of independent experts will be convened to provide oversight and to ensure safe and ethical conduct of the study. The COVID 19 Vaccine Data Safety Monitoring Board will have the responsibility of evaluating cumulative safety and other clinical study data at regular intervals and making appropriate recommendations based on the available data. During the study, the benefit/risk assessment will be continuously monitored by the COVID-19 Vaccine Data Safety Monitoring Board to ensure that the balance remains favourable. Full details of the COVID-19 Vaccine Data Safety Monitoring Board composition and operations can be found in the COVID-19 Vaccine Data Safety Monitoring Board Charter.

An independent Neurological AESI Expert Committee will be available to review and provide on request about the diagnosis and causality assessment of selected neurological AEs of special interest occurring in the study. Details on the composition and operation of this committee are described in the Neurological AESI Expert Committee Charter.

A 6 Dissemination of Clinical Study Data

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

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

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

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A 9 Study and Site Start and Closure

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

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or ICH/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 IRB/IECs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of 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 SAEs and non-SAEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

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

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

AEs for **malignant tumours** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-SAE**. 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 hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life Threatening

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

Hospitalization

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

Important Medical Event or Medical Treatment

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

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used. Examples of important medical events include such events as listed below:

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

Intensity Rating Scale

A revised toxicity grading scale found in the US FDA guidance for healthy volunteers enrolled in a preventive vaccine clinical study (FDA 2007) will be utilized for all events.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for

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

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 investigational product.

- 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 investigational product?
- Consistency with known investigational product profile. Was the AE consistent with the previous knowledge of the suspect investigational product (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 investigational product?
- 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 investigational product was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

- Is this a recognized feature of overdose of the investigational medicinal product?
- 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 3 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 investigational product, but rather a human or process related failure while the investigational product 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 investigational product
- 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:

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

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

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

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

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

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

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

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

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

C 2 Withdrawal of Informed Consent for Donated Biological Samples

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

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

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

The investigator:

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

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

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

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

Appendix D 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 24: Clinical Abnormalities, Local Reactions to Injectable Product
- Table 25: Clinical Abnormalities, Vital Signs
- Table 26: Clinical Abnormalities, Systemic (General or Illness)

Table 24 Tables for Clinical Abnormalities: Local Reactions to Injectable Product

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

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

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

ER: emergency room.

Table 25 Tables for Clinical Abnormalities: Vital Signs

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

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

Table 26 Tables for Clinical Abnormalities: Systemic (General or Illness)

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

Appendix E Adverse Events of Special Interest

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

Table 27 Adverse Events of Special Interest

Category	Medical Concept
Neurologic	Generalized convulsion: episodes of neuronal hyperactivity most commonly resulting in sudden, involuntary muscular contractions. They may also manifest as sensory disturbances, autonomic dysfunction and behavioural abnormalities, and impairment or loss of consciousness.
	Guillain-Barré syndrome: a peripheral nerve demyelinating disease, which can present as temporary ascending paralysis.
	Acute disseminated encephalomyelitis: defined as a uniphasic syndrome of brain inflammation and demyelination occurring in temporal association with an antecedent immunologic challenge, such as infection or an immunization. ADEM most commonly occurs in the paediatric population.
	Other neurologic events: include new onset event (acute or subacute) motor and sensory disturbances (eg, weakness, numbness, paraesthesia, hypoesthesia, hyperesthesia, dysesthesias), bowel/bladder dysfunction, gait impairment, or visual disturbance, or any event of myelitis, encephalomyelitis, myelitis transverse, or other sudden neurological deficit.
Vascular	Thrombotic, thromboembolic, and neurovascular events: events that can manifest as transient or permanent vision problems, dizziness, trouble understanding, facial droop, slurred speech, unilateral weakness, deep vein thrombosis with swollen, warm or painful leg, pulmonary embolism with shortness of breath, chest pain or irregular heart rate.
Hematologic	Thrombocytopenia: a disorder in which there is an abnormally low platelet count; a normal platelet count ranges from 150 000 to 450 000 platelets per µL.
Immunologic	Vasculitides: a group of related disorders characterized by inflammation of blood vessels (vasculitis) leading to tissue or end-organ injury.
	Anaphylaxis: an acute hypersensitivity reaction with multi-organ-system involvement that can present as, or rapidly progress to, a severe life-threatening reaction requiring immediate medical attention.
	Vaccine-associated enhanced respiratory disease: pathogenicity has been linked to a vaccine immune response characterized by induction of non-neutralizing antibodies, and a T-cell response of the Th2 type with hypereosinophilia (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: 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 28.

Table 28 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

Table 28 List of Potential Immune-mediated Medical Conditions

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, Bechet's syndrome, leukocytoclastic vasculitis

Table 28 List of Potential Immune-mediated Medical Conditions

Category	Condition
Other	Antiphospholipid syndrome
	Autoimmune haemolytic anaemia
	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 anaemia
	Raynaud's phenomenon
	Sarcoidosis
	Sjögren's syndrome
	Stevens-Johnson syndrome
	Uveitis

Appendix F Actions Required in Cases of Thrombotic Events With Thrombocytopenia and/or Bleeding

F 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of thrombotic events with thrombocytopenia and/or bleeding. It is not intended to be a comprehensive guide to the management of all venous thromboembolic events.

During the course of the study, the investigator will remain vigilant for occurrence of thrombotic events with thrombocytopenia and/or bleeding. Appropriate investigations (eg, imaging) to diagnose these events should be made on a case-by-case basis. The investigator is responsible for determining whether a participant meets criteria for thrombotic events with thrombocytopenia and/or bleeding at any point during the study.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting criteria for thrombotic events with thrombocytopenia and/or bleeding. The Study Physician contacts the investigator to provide guidance, discuss, and agree an approach for the participant's follow-up and the continuous review of data. Guidance from the International Society of Thrombosis and Haemostasis for management of thrombocytopenic thromboembolism occurring after vaccination can be found at www.isth.org. Notably, participants should only be treated with heparin if a test for heparin-elicited thrombocytopenia antibodies is negative. An alternative explanation for thrombocytopenia should be considered (eg, alcohol use, liver cirrhosis, concomitant medications, exposure to toxic chemicals, viral infections).

The investigator is responsible for recording data pertaining to thrombotic events with thrombocytopenia and/or bleeding and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

F 2 Tests that Should Be Considered if Thrombotic Events With Thrombocytopenia and/or Bleeding Are Suspected

The following tests should be considered, but not limited to:

1. Measurement of platelet levels, prothrombin time, activated partial thromboplastin time, D-dimer levels, and fibrinogen levels

2. Complete blood count, reticulocyte count, blood film, haptoglobins

3. Anti-platelet factor 4 antibodies

4. Anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies, rheumatoid factor, human leucocyte antigen B27, ADAMTS13 activity, anti-cardiolipin antibodies IgG + IgM, and anti-B2GPI antibodies IgG + IgM

5. Complement (eg, C3, C4, complement complex C5b-9, C5a), autoantibodies (eg, antinuclear IgG, anti-double stranded DNA IgG, anti-Smith IgG, anti-SSA IgG, anti-SSB IgG, anti-Jo1 IgG, anti-MPO IgG, anti-PR3 IgG, anti-glomerular basement membrane IgG)

6. Factor V Leiden, Factor II (prothrombin) variant

7. Platelet activation markers and functional assays (eg: sCD40L, soluble glycoproteins, degranulation markers [PF4, vWF, P-selectin, annexin V]), anti-PF4-plasma-serotonin release assay (if anti-PF4 ELISA positive)

8. Inflammatory markers: TNFa, IL-1, IL-4, IL-6, IL-10, IL-13

9. Cell adhesion molecules: VCAM, ICAM, E-selectin

10. Adenovirus serology

11. Additional viral serology: Cytomegalovirus (IgG and IgM), Ebstein-Barr virus (IgG and IgM), HIV, Parvo virus B19

12. COVID-19 testing, including PCR and serology

13. Calculation of an International Society of Thrombosis and Haemostatis score for Disseminated Intravascular Coagulation (derived from platelet levels, fibrinogen, and D-Dimer)

Appendix G Abbreviations

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ChAdOx1 MERS	Chimpanzee adenovirus Ox1 with MERS Spike antigen
ChAdOx1 nCoV-19	AZD1222 when initially developed by the University of Oxford
COVID-19	Coronavirus disease 2019
eCRF	Electronic case report form
e-Diary	Electronic diary
GMT	Geometric mean titre
ICF	Informed consent form
ICH/GCP	International Council for Harmonisation/Good Clinical Practice
IRB/IEC	Institutional Review Board/ Independent Ethics Committee
IRT	Interactive Response Technology
MAAEs	Medically attended adverse events
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
S	Spike
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome-coronavirus-2

Appendix H Protocol Amendment History

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	29 July 2021
Amendment 1	2 June 2021
Version 1	14 May 2021

Amendment 2: 15 July 2021

The principal reason for this amendment was to

1) add an additional interim analysis to evaluate immunogenicity in a subset of AZD1222 previously vaccinated subjects boosted with AZD1222 or AZD2816

2) revise Objectives/Endpoints from descriptive to comparative, with ranking of primary, key secondary, other secondary, and exploratory objectives

3) add non-inferiority margins to primary analysis and add additional participants to maintain power

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.1 Synopsis (Objectives and Endpoints)	Revised this section from primarily descriptive to primarily comparative. Comparative immunogenicity objectives created and ranked as primary, key secondary, other secondary.	Objectives of study changed from descriptive to comparative, testing for non-inferiority across treatment comparisons	Substantial
1.1 Synopsis (Number of Participants; Statistical Methods)	Overall size increased to 2590 participants	Adjustments made to maintain power with the added non-inferiority margins	Substantial
1.1 Synopsis (Statistical Methods)	An additional interim analysis added. Second interim analysis changed to include only the previously vaccinated with AZD1222 cohort.	Interim analysis plan was reviewed and revised.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.2 Schema	Figures updated with increased participant numbers	Adjustments made to maintain power with the added non-inferiority margins	Substantial
1.3 Schedule of Activities	Table 2: footnote clarification added Table 3: minor corrections	Clarification/Correction	Non-substantial
2.1 Study Rationale (and elsewhere in protocol)	Clarification on previous vaccination criteria	Clarification	Non-substantial
3 Objectives	Section completely rewritten. Divided into 2 sections: Previously unvaccinated and previously vaccinated. Immunogenicity objectives created for comparisons. Objectives ranked as primary, key secondary, other secondary, or exploratory.	Objectives of study changed to show non-inferiority across treatments.	Substantial
4.1 Overall design	Participant numbers increased	Adjustments made to maintain power with the added non-inferiority margins	Substantial
4.1 Overall design	Cap on age added	To ensure good representation across age groups	Substantial
8.3.2	Removal of severity grade 5	Correction	Non-substantial
8.5.2.3 CCI [redacted]	Addition of information on number of patients sampled for CCI [redacted]	Clarification	Non-substantial
9.1 Statistical Hypotheses	Addition of statistical hypotheses	Include hypothesis being tested.	Substantial
9.2 Sample size determination	Confidence intervals for populations of 350 and 380 added to Table 14 and Table 15	Updated to include current populations of 350 and 380 participants	Non-substantial
9.2 Sample size determination	Power estimates for populations of 350 and 380 added to Table 17 and Table 18	Updated to include current populations of 350 and 380 participants	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
9.4.1 General considerations	Details on the initial interim, second interim, and third interim analysis added	Include revised information on the analysis plan, including interim analyses	Substantial
9.4.3.1.1 Estimand framework for immunogenicity descriptions and comparisons	Objectives removed from descriptive analysis Table 23 and Table 24	Objectives of study changed from descriptive to comparative, showing non-inferiority across treatments	Substantial
9.4.3.1.1 Estimand framework for immunogenicity descriptions and comparisons	Section of Immunogenicity Comparisons added.	Objectives of study changed from descriptive to comparative, showing non-inferiority across treatments	Substantial
9.4.3.1.1 Estimand framework for immunogenicity descriptions and comparisons	Table 25 and Table 26 on immunogenicity comparisons revised, aligned with the revised objectives/endpoints.	Objectives of study changed from descriptive to comparative, showing non-inferiority across treatments	Substantial
9.4.4 Multiple Comparisons	Section added.	Objectives of study changed from descriptive to comparative, showing non-inferiority across treatments	Substantial

In addition, the protocol has been revised with minor corrections and clarifications.

Amendment 1: 2 June 2021

Version 1 of the protocol was amended prior to the commencement of the study (ie, prior to approval of the protocol by an ethics committee) based on feedback from internal and regulatory authority reviews. The most substantial changes were as follows:

- addition of 2 treatment arms: 1) AZD1222 as a single booster vaccination in participants previously vaccinated with an mRNA COVID-19 vaccine and 2) heterologous vaccination with AZD1222 plus AZD2816 in previously unvaccinated participants
- further definition of analysis sets
- addition of thrombotic events with thrombocytopenia as a discontinuation criteria

In addition, corrections and revisions to text to improve readability were made.

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SIGNATURE PAGE

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Clinical Study Protocol	
Study Intervention	AZD2816
Study Code	D7220C00001
Version	Amendment 3
Date	11 October 2021

TITLE PAGE

A Phase II/III Partially Double-Blinded, Randomised, Multinational, Active-Controlled Study in Both Previously Vaccinated and Unvaccinated Adults to Determine the Safety and Immunogenicity of AZD2816, a Vaccine for the Prevention of COVID-19 Caused by Variant Strains of SARS-CoV-2

Sponsor Name:	**AstraZeneca AB**
Legal Registered Address:	151 85 Södertälje, Sweden
Regulatory Agency Identifier Numbers:	EudraCT: 2021-002530-17

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: D7220C00001

Amendment Number: 3

Study Intervention: AZD2816

Study Phase: II/III

Short Title: Phase II/III Study of AZD2816, a Vaccine for the Prevention of COVID-19 in Adults

Study Physician Name and Contact Information will be provided separately.

International Coordinating Investigator: Andrew J Pollard, FRCPCH PhD FMedSci
University of Oxford
Oxford, United Kingdom

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	11 October 2021
Amendment 2	29 July 2021
Amendment 1	2 June 2021
Version 1	14 May 2021

Amendment 3: 11 October 2021

The principal reason for this amendment was to remove the age cap and revise the primary and key secondary non-inferiority analyses to included historical controls due to difficulties in recruiting the previously unvaccinated cohort

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Synopsis Section 4.1 Section 9.4..3.1.1	Inserted information on use of historical controls	Required based on anticipated confounding between previously vaccinated and previously unvaccinated cohorts.	Substantial
Section 3.2, Table 6	Inserted exploratory objectives on exploration of humoral immune response with live virus neutralization assay and exploration of additional immune response based on emerging data	Omitted in error	Non-substantial
Section 4.1	Deleted age cap ensuring at least 25% enrolled participants were ≥65 years of age.	Due to enrollment difficulties in finding previously unvaccinated elderly	Substantial
Section 7.1	Inserted laboratory-confirmed SARS-CoV-2 infection as discontinuation of study intervention	To explicitly state this criterion (which is implicitly included in criteria 2) as a discontinuation of treatment criterion.	Non-substantial
Section 9.2	Section on immunogenicity comparisons and previous Table 16 and Table 17 were moved up	Had been placed under Secondary Objective in error	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	under the Primary Objective sub-heading		
Section 9.4.3.1.1 Table 19 Table 20 Table 21 Table 22 Table 23	Analysis key (abbreviations) revised	Improvements in abbreviations for clarity	Non-substantial
Section 9.4..3.1.1	Description of statistical approach to be used with historical control comparisons added.	Inclusion of historical controls requires description of statistical methodology to be used.	Substantial

In addition, the protocol has been revised with minor rewordings, corrections, and clarifications which are all considered to be non-substantial.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A phase II/III partially double-blinded, randomised, multinational, active-controlled study in both previously vaccinated and unvaccinated adults to determine the safety and immunogenicity of AZD2816, a vaccine for the prevention of COVID-19 caused by variant strains of SARS-CoV-2.

Short Title: Phase II/III study of AZD2816, a vaccine for the prevention of COVID-19 in adults.

Rationale: Recently, several variants of the SARS-CoV-2 virus with increased transmissibility have emerged, including B.1.1.7, first identified in the UK, P.1, first identified in Brazil, and B.1.351, first identified in South Africa. In an ongoing clinical trial of AZD1222 in South Africa, interim results failed to show protection against mild to moderate disease caused by the B.1.351 variant; protection against severe disease could not be determined as no severe cases were identified (Madhi et al 2021).

Based on available evidence about vaccine effectiveness and molecular epidemiology of emerging variants, B.1.351 is estimated to have a potential to escape vaccine-elicited immunity. B.1.351 carries sequence mutations in common with other variants of concerns; immunity to B.1.351 therefore has the potential to provide some cross-immunity against other emerging strains. Development of candidate vaccines that include the B.1.351 S-protein variant is underway. AstraZeneca is developing AZD2816, a vaccine against the B.1.351 SARS-CoV-2 variant using the same ChAdOx1 platform and manufacturing processes used for AstraZeneca's currently available COVD-19 vaccine, AZD1222.

Objectives and Endpoints:

The purpose of this study is to characterize the safety and immunogenicity of AZD2816, AstraZeneca's candidate ChAdOx1 vector vaccine against SARS-CoV-2 variant strain B.1.351, when administered:

- As a single dose to SARS-CoV-2 seronegative participants who previously received a 2-dose primary vaccination against SARS-CoV-2 with AZD1222 or an mRNA COVID-19 vaccine
- As a 2-dose primary homologous vaccination to SARS-CoV-2 seronegative participants who are unvaccinated
- As the second dose of 2-dose primary heterologous vaccination (with AZD1222 as first dose) to SARS-CoV-2 seronegative participants who are unvaccinated.

The following table lists the primary and secondary endpoints:

<table>
<tr><th>Objectives</th><th colspan="2">Endpoints</th></tr>
<tr><td colspan="3">Safety Objectives: Previously unvaccinated participants</td></tr>
<tr><td colspan="3">- Primary</td></tr>
<tr><td>To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in previously unvaccinated seronegative participants</td><td colspan="2">• Incidence of local and systemic solicited AEs for 7 days post-dose
• Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose
• The change from baseline for safety laboratory measures for 28 days post-dose</td></tr>
<tr><td colspan="3">- Secondary</td></tr>
<tr><td>To characterize the safety and tolerability of a 2-dose primary heterologous vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in previously unvaccinated seronegative participants</td><td colspan="2">• Incidence of local and systemic solicited AEs for 7 days post-dose
• Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose</td></tr>
<tr><td>To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in previously unvaccinated seronegative participants</td><td colspan="2">• Incidence of local and systemic solicited AEs for 7 days post-dose
• Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose</td></tr>
<tr><td>To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in previously unvaccinated seronegative participants</td><td colspan="2">• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination</td></tr>
<tr><td>To characterize the extended safety and tolerability of a heterologous primary vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in previously unvaccinated seronegative participants</td><td colspan="2">• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination</td></tr>
<tr><td>To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in unvaccinated seronegative participants</td><td colspan="2">• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination</td></tr>
<tr><td colspan="3">Immunogenicity objectives: Previously unvaccinated participants</td></tr>
<tr><td colspan="3">To determine if the pseudoneutralizing antibody GMT response elicited by a 2-dose AZD2816 primary vaccination is non-inferior to the response elicited by a 2-dose AZD1222 primary vaccination
Estimand:</td></tr>
<tr><td>Treatment</td><td>AZD2816 vaccination</td><td>AZD1222 vaccination</td></tr>
<tr><td>Population</td><td>Seronegative participants with no prior COVID-19 vaccination</td><td>Seronegative participants with no prior COVID-19 vaccination</td></tr>
<tr><td>Dosing interval</td><td>4 weeks</td><td>4 weeks</td></tr>
<tr><td>Timepoint</td><td>28 days after second vaccination dose</td><td>28 days after second vaccination dose</td></tr>
<tr><td>Objective Level:</td><td colspan="2">Serotype comparison:</td></tr>
<tr><td>Primary</td><td>B.1.351</td><td>Wuhan-Hu-1</td></tr>
<tr><td>Key Secondary 2.2</td><td>B.1.351</td><td>B.1.351</td></tr>
<tr><td>Key Secondary 2.4</td><td>Wuhan-Hu-1</td><td>Wuhan-Hu-1</td></tr>
</table>

Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD2816 vaccination/AZD1222 vaccination	
To determine if the seroresponse rate elicited by a 2-dose AZD2816 primary vaccination is non-inferior to the seroresponse rate elicited by a 2-dose AZD1222 primary vaccination Estimand:		
Treatment	AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Key Secondary 2.1	B.1.351	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥ 4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 vaccination - AZD1222 vaccination	
To determine if the neutralizing antibody GMT response elicited by a 2-dose AZD1222+AZD2816 heterologous primary vaccination is non-inferior to the response elicited by a 2-dose AZD1222 primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Key Secondary 2.3	B.1.351	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD1222+AZD2816 vaccination/AZD1222 vaccination	
To determine if the seroresponse rate elicited by a 2-dose AZD1222+AZD2816 heterologous primary vaccination is non-inferior to the seroresponse rate elicited by a 2-dose AZD1222 primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥ 4-fold increase from baseline in pseudoneutralizing antibodies) for AZD1222+AZD2816 vaccination - AZD1222 vaccination	
To determine if the neutralizing antibody GMT response against the B.1.351 variant is non-inferior to the response against the original Wuhan-Hu-1 strain following a 2-dose AZD2816 primary vaccination Estimand:		
Treatment	AZD2816 vaccination	AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	

Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-Hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following a 2-dose AZD2816 primary vaccination Estimand:		
Treatment	AZD2816 vaccination	AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥ 4-fold increase from baseline in pseudoneutralizing antibodies) against B.1.351 versus Wuhan-Hu-1	
To determine if the neutralizing antibody GMT response against the B.1.351 variant is non-inferior to the response against the original Wuhan-Hu-1 strain following a 2-dose AZD1222+AZD2816 heterologous primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222+AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-Hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following a 2-dose AZD1222+AZD2816 heterologous primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222+AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥ 4fold increase from baseline in pseudoneutralizing antibodies) against B.1.351 versus Wuhan-Hu-1	
To also determine non-inferiority of the s-protein binding antibody response for the above comparisons as other secondary objectives		
To also determine the neutralizing antibody GMT responses 28 days after first vaccination dose in the above primary and key secondary objectives		
Safety Objectives: Previously vaccinated participants		
- Primary		
To characterize the safety and tolerability of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Incidence of local and systemic solicited AEs for 7 days post dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose	

- Secondary	•
To characterize the safety and tolerability of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination

Immunogenicity objectives: previously vaccinated participants		
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Primary	B.1.351	Wuhan-Hu-1
Key Secondary 2.1	B.1.351	B.1.351
Key Secondary 2.3	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 vaccination	
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose is non-inferior to response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Key Secondary 2.2	B.1.351	B.1.351
Key Secondary 2.5	Wuhan-Hu-1	Wuhan-Hu-1

Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 booster	
To determine if the neutralizing antibody GMT response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 is non-inferior to the response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD1222 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective Level:	Serotype comparison:	
Key Secondary 2.4	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD1222 booster/AZD1222 vaccination	
To determine if the seroresponse elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other secondary	B.1.351	Wuhan-Hu-1
Other secondary	B.1.351	B.1.351
Other secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥ 4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 primary vaccination	
To determine if the seroresponse elicited by an AZD2816 booster dose is non-inferior to response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥ 4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 booster	
To determine if the seroresponse elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD1222 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥ 4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 primary vaccination	
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose in participants previously vaccinated with an mRNA-based vaccine is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD2816 booster	AZD1222 primary vaccination

Population	mRNA vaccine vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 vaccination	
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with an mRNA-based vaccine Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	mRNA vaccine vaccinated seronegative participants	mRNA vaccine vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 booster	
To determine if the seroresponse elicited by an AZD2816 booster dose in participants previously vaccinated with an mRNA-based vaccine is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	mRNA vaccine vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥ 4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 primary vaccination	
To determine if the seroresponse elicited by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with an mRNA-based vaccine Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	mRNA vaccine vaccinated seronegative participants	mRNA vaccine vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Endpoint	Difference in seroresponse (≥ 4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 booster	
To determine if the neutralizing antibody GMT response rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following an AZD2816 booster dose. Estimand:		
Treatment	AZD2816 booster	AZD2816 booster

Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster version
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-Hu-1	
To determine if the neutralizing antibody GMT response against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following an AZD1222 booster dose. Estimand:		
Treatment	AZD1222 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-Hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following an AZD2816 booster dose. Estimand:		
Treatment	AZD2816 booster	AZD2816 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥ 4-fold increase from baseline in pseudoneutralizing antibodies) for B.1.351/Wuhan-Hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following an AZD1222 booster dose. Estimand:		
Treatment	AZD1222 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥ 4-fold increase from baseline in pseudoneutralizing antibodies) for B.1.351/Wuhan-Hu-1	
To also determine non-inferiority of the s-protein binding antibody response for the above comparisons as other secondary objectives.		

SAEs: serious adverse events; MAAEs: medically attended adverse events; AESIs: adverse events of special interest.

[a] At least a 4-fold increase in geometric mean titre from baseline

Overall Design: This is a phase II/III, multinational, randomised, partially double-blind, controlled study in two distinct cohorts: previously vaccinated and previously unvaccinated participants.

Disclosure Statement: This is a parallel-group preventive study with 8 treatment arms.

Number of Participants: Approximately 2590 SARS-CoV-2 nucleocapsid seronegative participants will be assigned to study intervention to support the primary and secondary objectives of this study. In addition, participants that are SARS-Cov-2 nucleocapsid seropositive at screening will be enrolled and assigned to study intervention for an exploratory analysis, with a cap of 10% of the seronegative population (ie, approximately 259 total participants).

Intervention Groups and Duration: Previously vaccinated participants will receive 1 dose of AZD1222 or AZD2816 on Day 1. Previously unvaccinated participants will receive one of the following 2-dose vaccinations:

- 1 dose of AZD2816 on Day 1 and on Day 29
- 1 dose of AZD1222 on Day1 and on Day 29
- 1 dose of AZD1222 on Day 1 and 1 dose of AZD2816 on Day 29
- 1 dose of AZD2816 on Day 1 and on Day 85.

Participants will be followed up for safety for 180 days after last study vaccine administration.

Data Monitoring Committee: A Data Safety Monitoring Board will provide oversight to ensure safe and ethical conduct of the study.

Statistical Methods:

Sample sizes of 300-380 seronegative participants per group are deemed appropriate based upon available immunogenicity data from previous clinical studies with AZD1222 for the primary and secondary objectives of this study.

Owing to national vaccine rollout in the recruitment countries, including the prioritization of elderly populations, it is anticipated that there will be critical differences between the previously vaccinated and previously unvaccinated cohorts that may confound the interpretation of the results. Consequently, the primary and key secondary non-inferiority analyses across these two cohorts will compare the previously vaccinated participants that received a booster dose in this study with a subset of matched participants from the previously unvaccinated participants that received the 2-dose AZD1222 primary vaccine series in the AZD1222 Phase 3 trial, Study D8110C00001.

The safety analysis set for adverse events consists of all participants who have received at least one dose of study intervention. The immunogenicity analysis set includes all participants in the safety analysis set who have no protocol deviations or intercurrent events judged to have the potential to interfere with the generation or interpretation of an immune response.

An initial interim analysis will be performed on a subset of previously AZD1222 vaccinated participants that have received a booster dose to consider unblinded sample size adjustment.

A second interim analysis will be performed when all previously AZD1222 vaccinated participants have completed their Day 29 visit to support registration of a booster dose. A third interim analysis will be performed on a subset of previously unvaccinated participants that have received their second dose to consider blinded sample size adjustment in this population. The primary analysis will be performed when there are data from all previously unvaccinated participants, 28 days after the second dose of the 4-week dosing intervals to support assessment of these 2-dose primary vaccinations to support registration of the booster dose and a 2-dose primary vaccination. A secondary analysis will be performed on data from 28 days after the second dose of the 12-week dosing interval to support assessment of this 2-dose primary vaccination. The final analysis will be performed on data from 6 months follow-up after participant's vaccination.

1.2 Schema

Figure 1 Study Design for Unvaccinated Seronegative/Seropositive Participants Receiving a 2-Dose Primary Vaccination

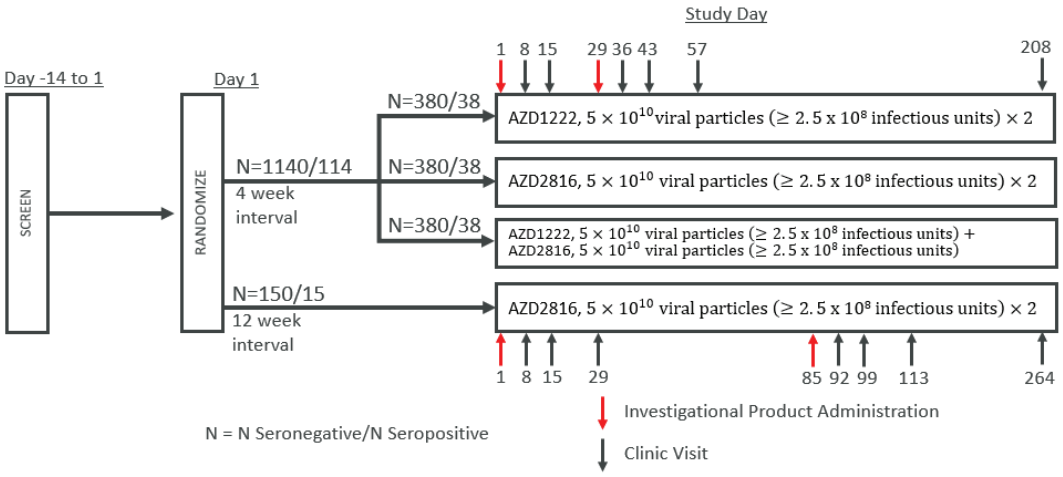
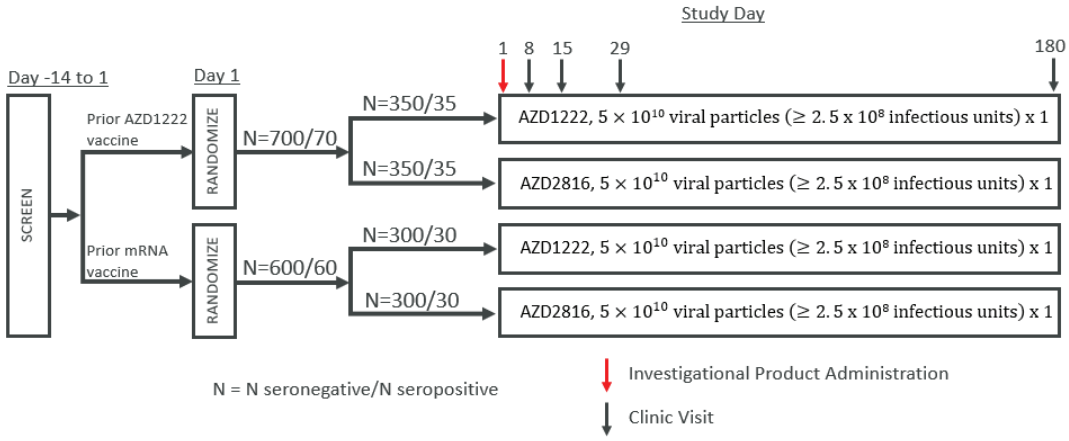


Figure 2 Study Design for Previously Vaccinated Seronegative/Seropositive Participants Receiving a 1-Dose Booster



Note: In addition to the planned 2590 seronegative participants enrolled to support the primary/secondary objectives, seropositive participants will also be enrolled in the study to support exploratory objectives in this population, with a cap of 10% of the planned seronegative participants (ie, a maximum of 259 seropositive participants, bringing total planned enrollment to 2849).

1.3 Schedule of Activities

Table 1 Schedule of Activities: Screening

Procedure	Day -14 to Day 1	See Section
Informed consent	X	5.1, Appendix A 3
Demography	X	-
Medical and surgical history	X	-
Prior and concomitant medications	X	6.5
Complete physical examination, including height and weight	X	8.2.1
Vital signs	X	8.2.2
Urine pregnancy test (for women of childbearing potential only)	X	8.2.3
Clinical safety laboratory assessments	X	8.2.3
Assessment of serious adverse events	X	8.3, Appendix B
Blood sample for SARS-CoV-2 antibody testing (lateral flow test)	X	8.5.2
Verify eligibility criteria	X	5.1, 5.2

Note: Screening activities can occur at same visit as initial vaccination with investigational product (ie, Visit 1 in Table 2, Table 3, and Table 4).

Table 2 Schedule of Activities: Treatment/Follow-up Period for Participants Previously Vaccinated with 2 Doses of AZD1222 or an mRNA Vaccine

Procedure	Treatment and Follow-up Period					Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	
Day	**1**	**8**	**15**	**29**	**180**	
Window (days)	**-**	**±2**	**±2**	**±3**	**±14**	
Medical and surgical history	X	-	-	-	-	-
Urine pregnancy test (women of childbearing potential)	X	-	-	-	-	8.2.3
Concomitant medications/vaccinations	X	X	X	X	X	6.5
Verify eligibility criteria	X	-	-	-	-	5.1, 5.2
Monitoring of COVID-19	X	X	X	X	X	8.3.8
Vaccine administration (after screening activities, the activities listed above, and the pre-dose sampling activities listed below)	X	-	-	-	-	6.1.1
Immunological assessments						
Serum sample to assess SARS-CoV-2 serology/neutralising antibodies	X (pre-dose)	-	X	X	X	8.5.2
Serum sample to assess additional immunogenicity	X (pre-dose)	-	X	X	X	8.5.2
Blood sample to assess B-cell and T-cell responses in a sub-group of participants	X (pre-dose)	-	X	X	X	8.5.2.3
Blood sample for B-cell and T-cell response sequencing in a sub-group of participants	X (pre-dose)	-	X	X	X	8.5.2.3
Safety assessments						
Targeted physical examination	X	-	-	-	-	8.2.1
Vital signs	X	X	X	X	X	8.2.2
e-Diary provided with training	X	-	-	-	-	8.3.7
e-Diary collected	-	X	-	-	-	8.3.7
Unsolicited AEs	X (post-dose)	X	X	X	-	8.3
MAAEs, SAEs, and AESIs	X[a]	X	X	X	X	8.3.8, 8.3.8
Clinical safety laboratory assessments	X (pre-dose)[b]	X	-	X	X	8.2.3

[a] Only SAEs pre-dose
[a] Not required to be repeated if performed on screening day prior to Day 1.
AE: adverse event; AESI: adverse event of special interest; MAAE: medically-attended adverse event; SAE: serious adverse event

Table 3 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 4-Week Dosing Interval

Procedure	Treatment and Follow-up Period								Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	
Day	**1**	**8**	**15**	**29**	**V4+7**	**V4+14**	**V4+28**	**V4+180**	
Window (days)	**-**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
Medical and surgical history	X	-	-	-	-	-	-	-	-
Urine pregnancy test (women of childbearing potential)	X	-	-	X	-	-	-	-	8.2.3
Concomitant medications/vaccinations	X	X	X	X	X	X	X	X	6.5
Verify eligibility criteria	X	-	-	-	-	-	-	-	5.1, 5.2
Monitoring of COVID-19	X	X	X	X	X	X	X	X	8.3.8
Vaccine administration (after screening activities, the activities listed above, and the pre-dose sampling activities listed below)	X	-	-	X	-	-	-	-	6.1.1
Immunogenicity assessments									
Serum sample for SARS-CoV-2 serology/neutralising antibodies	X (pre-dose)	-	X	X (pre-dose)	-	X	X	X	8.5.2
Serum sample for additional immunogenicity	X (pre-dose)	-	X	X (pre-dose)	-	X	X	X	8.5.2
Blood sample to assess B-cell and T-cell responses in a sub-group of participants	X (pre-dose)	-	X	X (pre-dose)	-	-	X	X	8.5.2.3
Blood sample for B-cell and T-cell response sequencing in a sub-group of participants	X (pre-dose)	-	X	X (pre-dose)	-	-	X	X	8.5.2.3
Safety assessments									
Targeted physical examination	X	-	-	X	-	-	-	-	8.2.1
Vital signs	X	X	X	X	X	X	X	X	8.2.2
e-Diary provided with training	X	-	-	X	-	-	-		8.3.7

Table 3 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 4-Week Dosing Interval

Procedure	**Treatment and Follow-up Period**								**Section**
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	
Day	**1**	**8**	**15**	**29**	**V4+7**	**V4+14**	**V4+28**	**V4+180**	
Window (days)	**-**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
e-Diary collected	-	X	-	-	X	-	-		8.3.7
Unsolicited AEs	X (post-dose)	X	X	X	X	X	X		8.3
MAAEs, SAEs, and AESIs	X[a]	X	X	X	X	X	X	X	8.3.8
Clinical safety laboratory assessments	X (pre-dose)	X	-	X (pre-dose)	X	-	X	X	8.2.3

[b] Only SAEs pre-dose

AE: adverse event; AESI: adverse event of special interest; MAAE: medically-attended adverse event; SAE: serious adverse event

Table 4 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 12-Week Dosing Interval

Procedure	Treatment and Follow-up Period									Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	
Day	**1**	**8**	**15**	**29**	**85**	**V5+7**	**V5+14**	**V5+28**	**V5+180**	
Window (days)	**-**	**±2**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
Medical and surgical history	X	-	-	-	-	-	-	-	-	-
Urine pregnancy test (women of childbearing potential)	X	-	-	-	X	-	-	-	-	8.2.3
Concomitant medications/vaccinations	X	X	X	X	X	X	X	X	X	6.5
Verify eligibility criteria	X	-	-	-	-	-	-	-	-	5.1, 5.2
Monitoring of COVID-19	X	X	X	X	X	X	X	X	X	8.3.8
Vaccine administration (after screening activities, the activities listed above, and the pre-dose sampling activities listed below)	X	-	-	-	X	-	-	-	-	6.1.1
Immunogenicity assessments										
Serum sample to assess SARS-CoV-2 serology/neutralising antibodies	X (pre-dose)	-	X	X	X (pre-dose)	-	X	X	X	8.5.2
Serum sample to assess additional immunogenicity	X (pre-dose)	-	X	X	X (pre-dose)	-	X	X	X	8.5.2
Blood sample to assess B-cell and T-cell responses in a sub-group of participants	X (pre-dose)	-	X	X	X (pre-dose)	-	-	X	X	8.5.2.3
Blood sample for B-cell and T-cell response sequencing in a sub-group of participants	X (pre-dose)	-	X	X	X (pre-dose)	-	-	X	X	8.5.2.3
Safety assessments										
Targeted physical examination	X	-	-	-	X	-	-	-	-	8.2.1
Vital signs	X	X	X	X	X	X	X	X	X	8.2.2
e-Diary provided with training	X	-	-	-	X	-	-	-		8.3.7

Table 4 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 12-Week Dosing Interval

Procedure	Treatment and Follow-up Period									Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	
Day	**1**	**8**	**15**	**29**	**85**	**V5+7**	**V5+14**	**V5+28**	**V5+180**	
Window (days)	**-**	**±2**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
e-Diary collected	-	X	-	-	-	X	-	-	-	8.3.7
Unsolicited AEs	X (post-dose)	X	X	X	X	X	X	X	-	8.3
MAAEs, SAEs, and AESIs	X[a]	X	X	X	X	X	X	X	X	8.3.8, 8.3.8
Clinical safety laboratory assessments	X (pre-dose)	X	-	X	X (pre-dose)	X	-	X	X	8.2.3

[a] Only SAEs pre-dose

AE: adverse event; AESI: adverse event of special interest; MAAE: medically-attended adverse event; SAE: serious adverse event

2 INTRODUCTION

AZD2816 is being developed for the prevention of COVID-19. It is a modified version of the current AstraZeneca SARS-CoV-2 vaccine (referred to as AZD1222 in clinical documentation) that has been modified to also provide immunity against the newly emerging SARS-CoV-2 variant strain B.1.351. Like AZD1222, AZD2816 is a recombinant replication-defective chimpanzee adenovirus vector (ChAdOx1) expressing the SARS-CoV-2 S surface glycoprotein driven by the human cytomegalovirus major immediate early promoter that includes intron A with a human tissue plasminogen activator leader sequence at the N terminus. AZD2816 differs from AZD1222 in that the S glycoprotein gene sequence used is from the B.1.351 variant strain instead of the original Wuhan-Hu-1 variant.

2.1 Study Rationale

The aim of the study is to assess the safety and immunogenicity of AZD2816 for prevention of COVID-19 as both a 2-dose primary vaccination in previously unvaccinated participants and a 1-dose booster vaccination in participants previously vaccinated against the original Wuhan-Hu-1 strain of SARS-CoV-2 by either AZD1222 or an mRNA-based vaccine. A safe and effective vaccine for COVID-19 prevention, including against the B.1.351 variant, would have significant global public health impact.

The study will also investigate the safety and immunogenicity of 1) a heterologous 2-dose vaccination with AZD1222 as first dose and AZD2816 as the second dose and 2) a single dose of AZD1222 as a booster vaccination in participants that have been previously vaccinated with an mRNA COVID-19 vaccine targeting the original Wuhan-Hu-1 strain.

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, which was named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (Zhou et al 2020). The disease these patients contracted was subsequently named Coronavirus Disease 2019 (COVID-19). The World Health Organization declared the novel coronavirus a pandemic on 11 March 2020. The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has resulted in significant global morbidity and mortality as well as major disruption to healthcare systems. Measures to change the course of the pandemic have included the accelerated development vaccines against the original Wuhan-Hu-1 strain.

Coronaviruses are spherical, enveloped viruses with positive-sense single-stranded RNA genomes. SARS-CoV-2 belongs to the phylogenetic lineage B of the genus *Betacoronavirus*, and it is the seventh corona virus known to cause human infections and the third known to cause severe disease after SARS-CoV and MERS-CoV. One fourth of the viral genome is

responsible for coding structural proteins, such as the S glycoprotein, envelope, membrane, and nucleocapsid proteins. Envelope, membrane, and nucleocapsid proteins are mainly responsible for virion assembly while the S protein is involved in cellular receptor binding, mediating fusion of virus and cell membranes and virus entry into host cells during infection. The SARS-CoV-2 spike (S) glycoprotein is a type I trimeric, transmembrane protein that is located at the surface of the viral envelope forming spike-shaped protrusions. The S protein's subunits are responsible for cellular receptor angiotensin-converting enzyme 2 binding via the receptor binding domain and subsequent fusion of virus and cell membranes, thereby mediating the entry of SARS-CoV-2 into the target cells. The S protein has an essential role in virus entry and determines tissue and cell tropism, as well as host range. The roles of the S-protein in receptor binding and membrane fusion have made it a desirable target for vaccine and antiviral development. The AstraZeneca vaccine AZD1222 expresses a codon-optimized coding sequence for S protein from the SARS-CoV-2 genome sequence accession MN908947 (ie, the Wuhan-Hu-1 isolate).

To date, 5 vaccines that rely upon the expression of the SARS CoV-2 S glycoprotein to stimulate/prime a protective immune response against the virus have demonstrated safety and efficacy in phase III clinical trials. Four of these, AZD1222 (also referred to as ChAdOx1 nCoV-19, a recombinant replication-defective chimpanzee adenoviral vectored), BNT162b2 (Pfizer-BioNTech, mRNA), mRNA-1273 (Moderna, mRNA), and Ad26.COV2-S (Janssen, adenovirus serotype 26 vectored) have received Emergency Use Authorization or Conditional Marketing Approval in the United States and/or the European Union, and elsewhere, and NVX-CoV2373 (Novavax; recombinant 86 protein) has also shown efficacy and is likely to be in use in the near future. These vaccines have been designed based upon the initial reported genetic sequence of the S protein from Wuhan in January 2020 (Lu et al 2020).

The immunogenicity and efficacy of AZD1222 has been shown in clinical trials (Ramasamy et al 2020, Voysey et al 2021a, Voysey et al 2021b). Immunogenicity data indicate that a single dose of AZD1222 elicits both humoral and cellular immunogenicity responses and that antibody responses are boosted after a second dose. In a pooled analysis of the 4 studies conducted in the United Kingdom, Brazil, and South Africa (database lock 7 December 2020), the vaccine was highly immunogenic; seroresponse of S binding antibody was > 98% after a single dose of AZD1222. Seroresponse of live neutralising antibody was 82.4% after 1 dose, which rose to 99.4% after a second dose. Efficacy analyses of the pooled DCO2 data demonstrated effective protection of AZD1222 against COVID-19 with a vaccine efficacy of 66.73% (95.84% CI: 57.41%, 74.01%) ($p < 0.001$) from 15 days after the second dose in seronegative participants receiving 2 doses. The DCO2 data also demonstrated that the standard dose of AZD1222 (5×10^{10} viral particles) provides complete protection against COVID-19 hospital admission ≥ 22 days after the first dose in the seronegative analysis set (0 versus 14 cases in the control group, 2 of which were severe, including one with a fatal outcome). Vaccine efficacy was similar in participants with pre-existing comorbidities, being

those at greatest risk of severe outcomes of COVID-19, compared to that in the general population. Recently available primary analysis data from a Phase III study performed in the United States and Latin America showed primary endpoint vaccine efficacy of 76% (95% CI: 67.60%, 82.22%; p-value < 0.001).

A sharp rise in COVID-19 cases was reported in late 2020, which was attributed to the emergence of new SARS-CoV-2 variant strains: B.1.1.7 in the United Kingdom, B.1.351 in South Africa, and P.1 in Brazil. These variant strains carry a number mutations in the S protein sequence: 9 amino acids in B.1.1.7, 10 amino acids in B.1.351, and 12 amino acids in P.1 compared with the Wuhan-Hu-1 sequence. These mutations may result in an increase of transmissibility and/or reduced vaccine effectiveness. Variant B.1.351 was first identified in South Africa in October 2020. Its attributes include approximately 50% increased transmission and moderate impact of neutralization by monoclonal antibody therapeutics, convalescent plasma and vaccine sera. In vitro neutralization assays suggest that the B.1.351 lineage viruses may be the most antigenically distinct from the original Wuhan-like strains (Zhou et al 2021). In addition, evidence suggests that AZD1222 may afford diminished protection against mild-moderate COVID-19 disease arising from the B.1.351 variant (Madhi et al 2021).

The development of candidate vaccines that would be effective against the B.1.351 variant strain is underway. AZD2816 is being developed as an updated ChAdOx-nCov19 (AZD1222) vaccine designed to provide protective immunity against the newly arising B.1.351 variant strain, using the same ChAdOx1 platform and manufacturing processes used for AstraZeneca's currently approved COVID-19 vaccine, AZD1222. The purpose of this Phase II/III, multinational, randomised, partially double-blind, active-controlled study is to demonstrate the safety and characterize the immunogenicity of AZD2816, AstraZeneca's candidate ChAdOx1 vector vaccine against B.1.351, when administered:

- As a single booster dose to SARS-CoV-2 seronegative participants who have previously received a 2-dose primary vaccination series against the original SARS-CoV-2 Wuhan-Hu-1 strain (AZD1222 or an mRNA vaccine).
- As a 2-dose homologous primary vaccination to SARS-CoV-2 seronegative participants who have not been vaccinated previously.

The immunogenicity of a 2-dose primary heterologous vaccination (with AZD1222 as first dose and AZD2816 as second dose) to SARS-CoV-2 seronegative participants who are unvaccinated and a single booster dose of AZD1222 to SARS-CoV-2 seronegative participants who have previously received a 2-dose primary vaccination series against the original Wuhan-Hu-1 strain will also be investigated.

SARS-CoV-2 seropositive participants will also be enrolled to support a parallel exploratory analysis in these participants.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD1222 and AZD2816 is provided in the respective Investigator's Brochures.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of AZD2816 and AZD1222 can be found in the respective Investigator's Brochures.

2.3.1 Risk Assessment

AZD2816 has been developed using the same vaccine vector, ChAdOx1, as AZD1222 and only differs in the sequence for SARS-CoV-2 S glycoprotein that is inserted in the vector. The anticipated safety profile of AZD2816 is the same as the observed safety profile of AZD1222. Risks associated with AZD2816 are thus the same as the risks associated with AZD1222, and no additional risks are anticipated due to the change in the targeted sequence.

A number of essentially mild and moderate adverse reactions to AZD1222 have been identified and resemble reactions frequently observed after many vaccines. Based on pooled clinical data from studies with AZD1222, the most commonly expected local solicited AEs for participants in this study are vaccination site pain and tenderness. The most commonly expected systemic solicited AEs are fatigue, headache, and malaise. The majority of reported events have been 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.

Post-authorisation hypersensitivity reactions, including anaphylaxis and angioedema, have occurred following administration of AZD1222 and are considered an identified risk.

A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with COVID-19 Vaccine (ie, AZD1222) during post-authorisation use. No events have been observed in the AZD1222 clinical development programme. Thrombosis in combination with thrombocytopenia is thus considered to be an important identified risk. This includes cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. Considering the frequency of this rare event and the size of this study, the risk for participants in this trial is considered to be low. The protocol includes exclusion criteria and instructions for heightened vigilance and thorough investigations for suspected cases to mitigate against further the risk for these rare event.

Important potential risks are 1) neurologic events and potential immune-mediated neurologic conditions and 2) vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease.

2.3.2 Benefit Assessment

All participants will receive active treatment: either AZD1222, which has been shown to be effective in providing protection against SARS-CoV-2, or AZD2816, which as a modified form of AZD1222 designed to be effective against the emergent B.1.351 variant strain and may also provide participants with protection. The information gained from this study will inform development decisions with regard to the efficacy of AZD2816 as both a primary 2-dose vaccination in participants that have not been previously vaccinated and a 1-dose booster vaccination in participants previously vaccinated against SARS-CoV-2.

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 and close monitoring of participants to minimize known and potential risks.

An independent Data Safety Monitoring Board will provide study oversight, evaluating cumulative safety and other clinical data at regular intervals.

Taking these measures into account, the potential risks identified in association with the administration of AZD2816 and AZD1222 are justified by the anticipated benefit that may be afforded to participants for the prevention of COVID-19.

3 OBJECTIVES AND ENDPOINTS

3.1 Previously unvaccinated cohort receiving a 2-dose primary vaccination

The primary safety objective for the cohort of previously unvaccinated participants receiving a 2-dose dose primary vaccination is to characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in previously unvaccinated seronegative participants.

The primary and key secondary immunogenicity objectives for this cohort are as follows:

Primary:

1: To determine if the neutralizing antibody GMT response against the B.1.351 variant elicited by a 2-dose AZD2816 vaccination is non-inferior to the response against the original Wuhan-Hu-1 strain elicited by a 2-dose AZD1222 vaccination.

Key secondary:

2.1: To determine if seroresponse against the B.1.351 variant elicited by a 2-dose AZD2816 vaccination is non-inferior to seroresponse against the original Wuhan-Hu-1 strain elicited by a 2-dose AZD1222 vaccination**.**

2.2: To determine if the neutralizing antibody GMT response against the B.1.351 variant elicited by a 2-dose AZD2816 vaccination is non-inferior to the response elicited by a 2-dose AZD1222 vaccination.

2.3: To determine if the neutralizing antibody GMT response against the B.1.351 variant elicited by a 2-dose heterologous AZD1222 + AZD2816 vaccination is non-inferior to the response against the original Wuhan-Hu-1 strain elicited by a 2-dose AZD1222 vaccination

2.4: To determine if the neutralizing antibody GMT response against the original Wuhan-Hu-1 elicited by a 2-dose AZD2816 vaccination is non-inferior to the response elicited by a 2-dose AZD1222 vaccination

The above primary and the key secondary immunogenicity objectives will be supported by other secondary immunogenicity objectives (see below) for which there will be no formal hypothesis testing.

Table 5 further describes the objectives and endpoints for this cohort of participants, including estimands for the immunogenicity objectives.

Table 5 Study Objectives and Endpoints for Previously Unvaccinated Participants Receiving a 2-Dose Primary Vaccination

Safety Objectives	**Endpoints**
- Primary	
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose
- Secondary	
To characterize the safety and tolerability of a heterologous primary vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in previously unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety and tolerability of a heterologous primary vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in previously unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
Immunogenicity Objectives	
To determine if the pseudoneutralizing antibody GMT response elicited by a 2-dose AZD2816 primary vaccination is non-inferior to the response elicited by a 2-dose AZD1222 primary vaccination Estimand:	

Treatment	AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Primary	B.1.351	Wuhan-Hu-1
Key Secondary 2.2	B.1.351	B.1.351
Key Secondary 2.4	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD2816 vaccination/AZD1222 vaccination	

To determine if the seroresponse rate elicited by a 2-dose AZD2816 primary vaccination is non-inferior to the seroresponse rate elicited by a 2-dose AZD1222 primary vaccination Estimand:

Treatment	AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Key Secondary 2.1	B.1.351	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥ 4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 vaccination - AZD1222 vaccination	
To determine if the neutralizing antibody GMT response elicited by a 2-dose AZD1222+AZD2816 heterologous primary vaccination is non-inferior to the response elicited by a 2-dose AZD1222 primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Key Secondary 2.3	B.1.351	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD1222+AZD2816 vaccination/AZD1222 vaccination	
To determine if the seroresponse rate elicited by a 2-dose AZD1222+AZD2816 heterologous primary vaccination is non-inferior to the seroresponse rate elicited by a 2-dose AZD1222 primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥ 4-fold increase from baseline in pseudoneutralizing antibodies) for AZD1222+AZD2816 vaccination - AZD1222 vaccination	
To determine if the neutralizing antibody GMT response against the B.1.351 variant is non-inferior to the response against the original Wuhan-Hu-1 strain following a 2-dose AZD2816 primary vaccination Estimand:		
Treatment	AZD2816 vaccination	AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-Hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following a 2-dose AZD2816 primary vaccination Estimand:		

Treatment	AZD2816 vaccination	AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥ 4-fold increase from baseline in pseudoneutralizing antibodies) against B.1.351 versus Wuhan-Hu-1	
To determine if the neutralizing antibody GMT response against the B.1.351 variant is non-inferior to the response against the original Wuhan-Hu-1 strain following a 2-dose AZD1222+AZD2816 heterologous primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222+AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-Hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following a 2-dose AZD1222+AZD2816 heterologous primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222+AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥ 4-fold increase from baseline in pseudoneutralizing antibodies) against B.1.351 versus Wuhan-Hu-1	
To also determine non-inferiority of the s-protein binding antibody response for the above comparisons as other secondary objectives		
To also determine the neutralizing antibody GMT responses 28 days after first vaccination dose in the above primary and key secondary objectives		
To explore anti-vector responses to the ChAdOx-1 adenovirus vector following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in sub-groups of seronegative and seropositive participants	• GMT of ChAdOx1 neutralizing antibody titres • Seroresponse rate of ChAdOx1 neutralizing antibody titres • Pairwise correlations between anti-S, pseudo-neutralization, and ChAdOx1 neutralizing antibody titres, 28 days after both Dose 1 and Dose 2	
Exploratory Objectives		
Objective	Endpoints	
To explore the immune response elicited by a 2-dose AZD2816 primary vaccination with a 12-week dosing interval compared to the response elicited by a 2-dose AZD2816 primary vaccination with a 4-week dosing interval	• GMT ratio of pseudoneutralizing antibodies • Seroresponse	

To explore antibody response to selected SARS-CoV-2 variants of interest/variants of concern following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in a sub-group of seronegative participants	• GMT of SARS-CoV-2 anti-S binding antibodies for selected variants of concern/variants of interest • Seroresponse rate of SARS-CoV-2 specific binding antibody titres for selected variants of concern/variants of interest • GMT of SARS-CoV-2 pseudoneutralizing antibody responses against the B.1.617.2 (delta) variant • Seroresponse rate of SARS-CoV-2 pseudoneutralizing antibody responses against the B.1.617.2 (delta) variant
To explore B-cell and T-cell responses following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in a sub-group of seronegative participants	• Intracellular cytokine staining and flow cytometry for T-cell responses over time • Quantification of (IFN-γ) ELISpot responses to SARS-CoV-2 B.1.351 or Wuhan-Hu-1 S protein from day of dosing baseline over time • Breadth and depth of peripheral blood B-cell and T-cell repertoire over time through immunosequencing
To monitor the incidence of SARS-CoV-2 infection following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in previously unvaccinated seronegative participants	• The incidence of SARS-CoV-2 infection defined by the seroresponse to nucleocapsid antibodies occurring post-second dose of study intervention
To monitor the incidence of COVID-19 following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in previously unvaccinated seronegative participants	• Incidence of COVID-19, defined as SARS-CoV-2 RT-PCR-positive symptomatic illness.
To explore the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in sub-groups of seronegative and seropositive participants	• Geometric mean titre of SARS-CoV-2 neutralization as determined by a live virus neutralization assay • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres as determined by a live virus neutralization assay
To explore additional immune responses following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in sub-groups of seronegative and seropositive participants	• Other exploratory assays for humoral and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data
To explore the immunogenicity objectives in seropositive participants	• GMT of pseudoneutralizing antibodies • Seroresponse rates

MAAEs: medically attended adverse events; SAEs: serious adverse events; AESIs: adverse events of special interest

[a] Seroresponse: An at least 4-fold increase in geometric mean titre from baseline.

3.2 Previously vaccinated cohort receiving a 1-dose booster vaccination

The primary safety objective for the cohort of seronegative previously vaccinated participants receiving a booster dose is to characterize the safety and tolerability of 1 booster dose of AZD2816 in participants previously vaccinated with AZD1222.

The primary and key secondary immunogenicity objectives for this cohort are as follows:

Primary:

1: To determine if the humoral immune response against the B.1.351 variant elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to the response against the original Wuhan-Hu-1 strain elicited by 2-dose AZD1222 vaccination administered to previously unvaccinated participants.

Key secondary:

2.1: To determine if the humoral immune response against the B.1.351 variant elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to the response elicited by 2-dose AZD1222 vaccination administered to previously unvaccinated participants.

2.2: To determine if the humoral immune response elicited against the B.1.351 variant by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222.

2.3: To determine if the humoral immune response against the original Wuhan-Hu-1 strain elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to the response elicited by 2-dose AZD1222 vaccination administered to previously unvaccinated participants.

2.4: To determine if the humoral immune response against the original Wuhan-Hu-1 strain elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 is non-inferior to the response elicited by a 2-dose AZD1222 vaccination

2.5: To determine if the humoral immune response against the original Wuhan-Hu-1 strain elicited by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222.

The primary and key secondary immunogenicity objectives will be supported by other secondary objectives for which there will be no formal hypothesis testing. Table 6 further describes the objectives and endpoints for this cohort of participants, including estimands for the primary and secondary immunogenicity objectives.

Table 6 Study Objectives and Endpoints for Previously Vaccinated Participants Receiving a 1-Dose Booster Vaccination

Safety Objectives	Endpoints
- Primary	
To characterize the safety and tolerability of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose
- Secondary	
To characterize the safety and tolerability of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
Immunogenicity objectives	
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:	

Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Primary	B.1.351	Wuhan-Hu-1

Key Secondary 2.1	B.1.351	B.1.351
Key Secondary 2.3	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 vaccination	
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose is non-inferior to response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Key Secondary 2.2	B.1.351	B.1.351
Key Secondary 2.5	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 booster	
To determine if the neutralizing antibody GMT response elicited by an AZD1222 booster dose in patients previously vaccinated with AZD1222 is non-inferior to the response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD1222 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective Level:	Serotype comparison:	
Key Secondary 2.4	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD1222 booster/AZD1222 vaccination	
To determine if the seroresponse elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other secondary	B.1.351	Wuhan-Hu-1
Other secondary	B.1.351	B.1.351
Other secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥ 4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 primary vaccination	
To determine if the seroresponse elicited by an AZD2816 booster dose is non-inferior to response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥ 4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 booster	

To determine if the seroresponse elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD1222 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥ 4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 primary vaccination	
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose in participants previously vaccinated with an mRNA-based vaccine is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	mRNA vaccine vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for AZD2816 booster/ AZD1222 vaccination	
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with an mRNA-based vaccine Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	mRNA vaccine vaccinated seronegative participants	mRNA vaccine vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 booster	
To determine if the seroresponse elicited by an AZD2816 booster dose in participants previously vaccinated with an mRNA-based vaccine is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	mRNA vaccine vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1

Endpoint	Difference in seroresponse (≥ 4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 primary vaccination	
To determine if the seroresponse elicited by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with an mRNA-based vaccine Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	mRNA vaccine vaccinated seronegative participants	mRNA vaccine vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Endpoint	Difference in seroresponse (≥ 4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 booster	
To determine if the neutralizing antibody GMT response rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following an AZD2816 booster dose. Estimand:		
Treatment	AZD2816 booster	AZD2816 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster vaccination
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-Hu-1	
To determine if the neutralizing antibody GMT response against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following a AZD1222 booster dose. Estimand:		
Treatment	AZD1222 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-Hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following an AZD2816 booster dose. Estimand:		
Treatment	AZD2816 booster	AZD2816 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥ 4-fold increase from baseline in pseudoneutralizing antibodies) for B.1.351/Wuhan-Hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following a AZD1222 booster dose. Estimand:		

Treatment	AZD1222 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥ 4-fold increase from baseline in pseudoneutralizing antibodies) for B.1.351/Wuhan-Hu-1	
To also determine non-inferiority of the s-protein binding antibody response for the above comparisons as other secondary objectives.		
To explore anti-vector responses to the ChAdOx-1 adenovirus vector following a booster dose of AZD2816 in sub-groups of seronegative and seropositive participants	• Magnitude of ChAdOx1 nAb titres (geometric mean titre) • Seroresponse rate of ChAdOx1 neutralizing antibody titres • Pairwise correlations between anti-S, pseudo-neutralization, and ChAdOx1 neutralizing antibody titres, 28 days after both Dose 1 and Dose 2	
Exploratory objectives		
Objective	Endpoints	
To explore antibody response to selected SARS-CoV-2 variants of interest/variants of concern following a booster dose of AZD2816 and in a sub-group of seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding titres (geometric mean titre) for selected variants of concern/variants of interest • Seroresponse rate of SARS-CoV-2 specific antibody binding titres for selected variants of concern/variants of interest • GMT of SARS-CoV-2 pseudoneutralizing antibody responses against the B.1.617.2 (delta) variant • Seroresponse rate of SARS-CoV-2 pseudoneutralizing antibody responses against the B.1.617.2 (delta) variant	
To explore B-cell and T-cell responses following a booster dose of AZD2816 in a sub-group of seronegative participants	• Intracellular cytokine staining and flow cytometry for T-cell responses over time • Quantification of (IFN-γ) ELISpot responses to SARS-CoV-2 B.1.351 or Wuhan-Hu-1 S protein from day of dosing baseline over time • Breadth and depth of peripheral blood B-cell and T-cell repertoire over time through immunosequencing	
To monitor the incidence of SARS-CoV-2 infection following a booster dose of AZD2816 in previously vaccinated seronegative participants	• The incidence of SARS-CoV-2 infection defined by the presence of nucleocapsid antibodies occurring post-dose of study intervention	
To monitor the incidence of COVID-19 following a booster dose of AZD2816 in previously vaccinated seronegative participants	• Incidence of COVID-19, defined as SARS-CoV-2 RT-PCR-positive symptomatic illness.	
To explore the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by a booster dose of AZD2816 or AZD1222 in sub-groups of seronegative and seropositive participants	• Geometric mean titre of SARS-CoV-2 neutralization as determined by a live virus neutralization assay • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres as determined by a live virus neutralization assay	
To explore additional immune responses following a booster dose of AZD2816 or AZD1222 in sub-groups of seronegative and seropositive participants	• Other exploratory assays for humoral and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data	

To explore the immunogenicity objectives in seropositive participants	• GMT of pseudoneutralizing antibodies • Seroresponse rates

MAAEs: medically attended adverse events; SAEs: serious adverse events; AESIs: adverse events of special interest.

[a] Seroresponse: An at least 4-fold increase in geometric mean titre from baseline.

4 DESIGN

4.1 Overall Design

This is a multi-country Phase II/III study to evaluate the safety and immunogenicity of AZD2816 as single-dose vaccination in previously vaccinated adult participants and as a 2-dose primary vaccination in previously unvaccinated adult participants.

A total of approximately 2590 SARS-CoV-2 nucleocapsid seronegative participants that have been screened and judged to be eligible for the study will be enrolled across these 2 populations with the goal of 1300 previously vaccinated participants receiving single-dose vaccination and 1290 unvaccinated participants receiving 2-dose primary vaccination. In addition, seropositive participants will be enrolled (with a cap of 10% of the seronegative population or 259 participants) to support exploratory analysis is these participants.

The enrollment and randomization strategy is intended to minimize group differences in terms of age, gender and the presence of comorbidities.

In both the single-dose booster treatment regimen and the 2-dose primary vaccination treatment regimen, participants will receive study intervention consisting of intramuscular administration of either AZD1222 (5×10^{10} viral particles) or AZD2816 (5×10^{10} viral particles).

Approximately 700 seronegative participants previously vaccinated with AZD1222 will be randomised 1:1 to receive a single intramuscular dose of either AZD1222 or AZD2816 in a double-blinded fashion.

Approximately 600 seronegative participants previously vaccinated with an approved mRNA based vaccination against the original Wuhan-Hu-1 strain will be randomised 1:1 to receive a single intramuscular dose of AZD2816 or AZD1222 in a double-blinded fashion.

Approximately 1290 seronegative, previously unvaccinated participants will be randomised approximately 5:5:5:2 to receive a 2-dose primary vaccination of the following:

- 2 doses of AZD1222 with a 4-week dosing interval
- 2 doses of AZD2816 with a 4-week dosing interval
- 1 dose of AZD1222 followed by 1 dose of AZD2816 with a 4-week dosing interval

- 2 doses of AZD2816 with a 12-week dosing interval.

The 3 treatments with a 4-week dosing interval will be double-blinded while the treatment with the 12-week interval will be open-label due to the difference in dosing interval.

In addition, a smaller population seropositive participants (up to 10% of the seronegative population), will be randomised to treatment in a similar manner as above.

Owing to national vaccine rollout in the recruitment countries, including the prioritization of elderly populations, it is anticipated that there will be critical differences between the previously vaccinated and previously unvaccinated cohorts that may confound the interpretation of the results. Consequently, the primary and key secondary non-inferiority analyses across these two cohorts will compare the previously vaccinated participants that received a booster dose in this study with a subset of matched participants from the previously unvaccinated participants that received the 2-dose AZD1222 primary vaccine series in the AZD1222 Phase 3 trial, Study D8110C00001.

Immunogenicity (ie, anti-Wuhan-Hu-1 and anti-B.1.351 immune responses including S-binding antibody titres and neutralizing antibody levels [pseudo-neutralization]) will be assessed in serum samples collected pre-dose on the day of each vaccination (baseline levels before vaccination), 14 and 28 days after each vaccination, and 180 days after the last vaccination.

All participants will be given a thermometer, tape measure or ruler, and a proprietary e-diary application designed for use with a smart device with instructions for use. All participants will be asked to report on solicited signs and symptoms for 7 days following vaccination (Days 1-8 for all participants and Days 29-36 for the 4-week dosing interval and Days 85-92 for the 12-week dosing interval). An e-diary will be used to collect information on the timing and severity of the solicited signs and symptoms.

Follow-up visits will take place as per the schedule of assessment within respective windows. All participants will be assessed for local and systemic AE, physical examination, review of e-diaries at these time points as detailed in the schedule of assessment. Blood will also be taken for safety assessments and immunology purposes.

All study participants will be followed for safety for 180 days after administration of their last vaccination dose. In every participant, solicited local and systemic events will be reported for up to 7 days after each dose, all unsolicited AEs will be reported for up to 28 days after each dose, and SAEs and AEs of special interest will be evaluated through study completion (up to 180 days after the last study vaccination).

An independent COVID-19 Vaccine Data Safety Monitoring Board will provide oversight, to ensure safe and ethical conduct of the study.

4.1.1 COVID-19 Assessments

Occurrence of COVID-19 in the trial will be reported as safety events, including monitoring of the potential risk of vaccine-elicited enhanced disease as an AE of special interest (see Appendix E). COVID-19 will be diagnosed and treated as per standard medical practice. In addition, experimental treatments are permitted. Detailed information will be collected in a standard way and reported on a specific case report form.

4.1.2 Screening

All potential participants will be screened, which may take place at a visit up to 14 days prior to Day 1 or on Day 1 itself.

Informed consent will be obtained before screening/enrollment. If written consent is obtained, the screening procedures specified in the Schedule of Activities (Section 1.3) will be undertaken including a medical history, physical examination, height and weight, a SARS-CoV-2 screening test and clinical safety laboratory assessments. Baseline information collected in the previously vaccinated participants will include which vaccine was received, immunization dose interval, and time since last vaccination.

For women of childbearing potential, it will be recorded that they verbally confirmed use of one highly effective form of birth control for at least 28 days prior to the planned vaccination and a urine pregnancy test will be performed that must be negative for the participant to be enrolled. (Note: Women with urine test results that are positive or undetermined will not be enrolled and should be advised to seek medical attendance outside the context of the trial if pregnancy is suspected.)

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 enrollment or to withdraw a participant from the study will be at the discretion of the Investigator.

4.1.3 Vaccination Visit

Participants will be considered enrolled at the point of vaccination. Before vaccination, the eligibility of the participant will be reviewed. Body temperature will be observed and a medical history and physical examination will be undertaken before the first vaccination to determine need to postpone vaccination or screen fail the participant. A negative pregnancy test (urine test) will need to be obtained from women of childbearing potential before vaccination. Baseline blood samples will be obtained before the first vaccination.

Participants will receive 1 dose of AZD2816 or AZD1222 at vaccination visits, administered by intramuscular injection. Previously immunized participants will have a single vaccination visit, Day 1. Participants that have not been previously vaccinated at baseline will have a second vaccination visit on Day 29 (4-week interval) or Day 85 (12-week interval).

All participants will be given a thermometer, tape measure or ruler, and a proprietary e-diary application designed for use with a smart device with instructions for use. All participants will be asked to report on solicited signs and symptoms for 7 days following vaccination (Days 1 to 8 and Days 29 to 36 or Days 85 to 92 when applicable).

4.1.4 Follow-up visits

Follow-up visits will take place as specified in the Schedule of Activities (Section 1.3). All participants will be assessed for local and systemic AE, physical examination, review of the e-diary and blood tests at these time points as detailed in the Schedule of Activities. Blood will also be taken for safety and immunogenicity assessments.

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 the last study visit in order to collect information on any SAEs/AE of special interest.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Study Design and Participant Population

The participant population includes adults ≥ 18 years of age. Persons who are healthy or have medically stable underlying conditions will be eligible. Adults with medically-stable chronic diseases may participate if, according to the judgement of the investigator, hospitalization within the study period is not anticipated and the participant appears likely to be able to remain on study through the end of protocol-specified follow-up.

For the primary and secondary objectives, those enrolled in the study must test negative for SARS-CoV-2 nucleocapsid protein antibody during screening. Some seropositive participants (capped at 10% of the seronegative participant population) will be enrolled to support an exploratory analysis.

Those enrolled in the single-dose vaccination part of the study must have received 2 doses of AZD1222 (with a dosing interval of 4-12 weeks) or 2 doses of an approved mRNA-based COVID-19 vaccine (with a dosing interval of 3-12 weeks for the BNT162b2 mRNA vaccine [Pfizer-BioNTech] and 4-12 weeks for the mRNA-1273 vaccine [Moderna]) with the second doses administered at least 90 days prior to first study intervention administration.

Pregnant/breastfeeding women, persons with severe immunodeficiency or severe underlying disease will be excluded from participation in the study. Persons previously vaccinated with

AZD1222 in the context of an AZD1222 vaccine trial are eligible for enrollment as previously vaccinated participants in the trial. Persons who have previously received any other investigational product for the prevention of COVID-19 will be excluded from participation in this study.

Participants with known risk factors for thrombosis and thrombocytopenia (excluding contraceptive hormonal therapy or replacement hormonal therapy) are excluded.

4.2.2 Rationale for Study Endpoints

The primary safety analysis includes:

- Incidence of local and systemic solicited AEs for 7 days following each vaccination will be summarized by day and overall.
- Incidence of unsolicited AEs for 28 days following each vaccination will be summarized by system organ class and preferred term, and by relationship to vaccination as assessed by the investigator.
- SAEs and AEs of special interest following the first vaccination and throughout the study duration will be summarized by system organ class and preferred term and by relationship to vaccination as assessed by the investigator.

Solicited AEs will be collected for 7 days after each dose of study intervention, a period that has proven adequate to describe reactogenicity events in previous vaccine studies. For all participants, AEs will be collected through 28 days after each dose of study intervention. SAEs, medically-attended AEs, and AEs of special interest and will be collected from Day 1 through end of the study. AEs of special interest include terms identified by the Brighton Collaboration involving events associated with vaccination in general.

The immunogenicity endpoints of interest in this study are:

- Geometric mean titre
- Seroresponse, defined as ≥ 4-fold increase in the geometric mean titre from baseline

Geometric mean titre ratios and differences in seroresponses with 95% confidence intervals will be presented to support selected comparisons of immunogenicity across groups of interest.

Immunogenicity against SARS-CoV-2 Wuhan-Hu-1 and B.1.351 strains will be characterized through the quantification of Spike-binding antibodies, pseudo-neutralization and, in a subset of participants, live neutralization. Exploratory analysis of immunogenicity against other strains and induction of other immune effectors including cell-mediated immunity will be conducted.

4.3 Justification for Dose

The AZD2816 nominal dose of 5×10^{10} viral particles is the same dose as the approved dose for AZD1222, which was based on the accumulated non-clinical data and clinical data from the AZD1222 clinical studies, as well as from other SARS-CoV-2 vaccines in development. Safety and immunogenicity data from an additional clinical study, MERS001(NCT03399578), using the same ChAdOx1 vector, also helped inform dose selection. MERS001 was the first clinical study of a ChAdOx1-vectored vaccine expressing the full-length S protein from a separate, but related, beta-coronavirus. ChAdOx1 MERS has been given to 31 participants to date at doses ranging from 5×10^9 viral particles to 5×10^{10} viral particles. Despite higher reactogenicity observed at the 5×10^{10} viral particles, this dose was safe, with self-limiting AEs and no serious adverse reactions recorded. The 5×10^{10} viral particles was the most immunogenic, in terms of inducing neutralizing antibodies 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} viral particles dose was chosen for AZD1222.

Based on accumulating nonclinical and clinical data gathered for AZD1222, a 2-dose regimen was selected for vaccination of unvaccinated participants with AZD2816 (AZD1222 Investigators Brochure). A single dose vaccination has been selected for participants previously vaccinated in line with both FDA and EMA guidance (FDA 2021, EMA 2021).

4.4 End of Study Definition

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

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

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as a protocol waiver or exemption, is not permitted.

5.1 Inclusion Criteria

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

5.1.1 All Participants:

Age

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

COVID-19

For inclusion in the SARS-CoV-2 seronegative population supporting the primary and secondary objectives:

2 No history of laboratory-confirmed SARS-CoV-2 infection (ie, no positive nucleic acid amplification test and no positive antibody test).

3 Seronegative for SARS-CoV-2 at screening (lateral flow test to detect reactivity to the nucleoprotein).

Note, patients failing to meet criteria 2 and/or 3 may be included in the separate seropositive population supporting the seropositive exploratory objectives.

Type of Participant

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

– - A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 90 days prior to enrollment

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

6 Signed informed consent obtained before conducting any study-related procedures

Reproduction

7 Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
Female participants:

(a) Women of childbearing potential must:

- Have a negative pregnancy test on the day of screening and on days of vaccination
- 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 30 days following administration of the 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 7). Periodic abstinence, the rhythm method, and withdrawal are NOT acceptable methods of contraception.

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

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

    Until follicle-stimulating hormone is documented to be within menopausal range, the participant is to be considered of childbearing potential
  - For women aged ≥50 years, post-menopausal is defined as having a history of ≥12 months amenorrhea prior to randomization, without an alternative cause, following cessation of exogenous sex-hormonal treatment.

Table 7 Highly Effective Methods of Contraception

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

[a] This is also considered a hormonal method
[b] Provided that partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success
[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse from 28 days prior to Day 1 through 30 days following administration of the second dose of study intervention, and if it is the preferred and usual lifestyle of the participant

5.1.2 Previously COVID-19 Vaccinated Participants

8 Prior completion of a 2-dose primary homologous vaccination regimen against the original SARS-CoV-2 Wuhan-Hu-1 strain with either AZD1222 (2 standard doses as authorized vaccine or as investigational product in a clinical trial with a 4- to 12-week

dosing interval) or with an mRNA vaccine approved for emergency or conditional use (eg, BNT162b2 vaccine [Pfizer-BioNTech] with a 3- to 12-week dosing interval or mRNA-1273 vaccine [Moderna] with a 4- to 12-week dosing interval). The second dose in all cases should have been administered at least 90 days prior to first administration of study intervention.

5.2 Exclusion Criteria

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

Medical Conditions

1 History of allergy to any component of AZD1222/AZD2816.

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

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

4 Any confirmed or suspected immunosuppressive or immunodeficient state, including asplenia or HIV/AIDS.

5 Recurrent severe infections and use of immunosuppressant medication within the past 6 months (≥ 20 mg per day of prednisone or its equivalent, given daily or on alternate days for ≥ 15 days within 30 days prior to administration of study intervention)
The following exceptions are permitted:
- Topical/inhaled steroids or short-term oral steroids (course lasting ≤ 14 days)

6 History of primary malignancy except for:
(a) Malignancy with low potential risk for recurrence after curative treatment (for example, history of childhood leukaemia) or for metastasis (for example, indolent prostate cancer) in the opinion of the site investigator.
(b) Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
(c) Adequately treated uterine cervical carcinoma in situ without evidence of disease
(d) Localized prostate cancer

7 History of thrombocytopenia and/or thrombosis, including participants who have experienced major venous and/or arterial thrombosis in combination with thrombocytopenia following vaccination with any COVID-19 vaccine

8 History of heparin-elicited thrombocytopenia, congenital thrombophilia (ie, factor V Leiden, prothrombin G20210A, antithrombin III deficiency, protein C deficiency and protein S deficiency, factor XIII mutation, familial dysfibrinogenemia), auto-immune thrombophilia (antiphospholipid syndrome, anti-cardiolipin antibodies, anti-β_2-glycoprotein 1 antibodies), or paroxysmal nocturnal haemoglobinuria.

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

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

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

12 Any autoimmune conditions, except mild psoriasis and vitiligo

Note: The AEs of special interest as outlined in Appendix E (including Table 28) should be considered when evaluating a participant for exclusion criteria as the presence of these AEs of special interest, especially if untreated or uncontrolled, may be a safety risk to the participant, affect the ability of the participant to participate in the study, and/or impair interpretation of the study data. Investigators should review and consider the list of conditions in Appendix E. If any of these conditions are present in a participant, the Investigator is asked to utilize his/her clinical judgment in determining the participant's eligibility for the study. Should the participant have conditions as outlined in Appendix E and the participant is enrolled, the Investigator is asked to document notes on site regarding the final rationale for enrollment.

Prior/Concomitant Therapy

13 Receipt of or planned receipt of investigational products indicated for the treatment or prevention of SARS-CoV-2 or COVID-19 with the exception of prior vaccination with AZD1222 or an mRNA COVID-10 vaccine (2 doses of the same vaccine within an approved dosing interval, see Section 5.1.2), which is allowed for participants in the previously vaccinated cohort
Note: For participants who develop COVID-19, receipt of licensed treatment options and/or participation in investigational treatment studies is permitted

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

15 Receipt of any influenza vaccine (licensed or investigational) within 7 days prior to and after administration of AZD1222/AZD2816.

16 Receipt of immunoglobulins and/or any blood products within 90 days prior to administration of study intervention or expected receipt during the period of study follow-up

Other Exclusions

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

18 Women who are currently pregnant (confirmed with positive pregnancy test), breastfeeding, having given birth less than 90 days before or planning pregnancy during the study.

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

20 Participants with a history of chronic alcohol or drug abuse or any condition associated with poor compliance.

21 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements or if vaccination would interfere with the participant's ongoing treatment.

22 Previous enrollment in the present study.

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 assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

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

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention, marketed product, or placebo intended to be administered to or medical device utilized by a study participant according to the study protocol. Study intervention is defined as AZD2816 or AZD1222 (Table 8).

6.1 Study Interventions Administered

6.1.1 Investigational Products

Table 8 Investigational Products

Intervention Name	AZD2816	AZD1222
Type	Vaccine	Vaccine
Dose Formulation	CCI [redacted]	CCI [redacted]
Unit Dose Strength	1×10^{11} viral particles/mL	1×10^{11} viral particles/mL
	$\geq 5 \times 10^{8}$ infectious units/mL	$\geq 5 \times 10^{8}$ infectious units/mL
Dosage Level	5×10^{10} viral particles (nominal, $\pm 1.5 \times 10^{10}$ viral particles)	5×10^{10} viral particles (nominal, $\pm 1.5 \times 10^{10}$ viral particles)
	$\geq 2.5 \times 10^{8}$ infectious units	$\geq 2.5 \times 10^{8}$ infectious units
Route	Intramuscular	Intramuscular
Use	Experimental	Experimental
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labelling	Will be provided in vials within a carton. Each carton and vial will be labelled as required per country requirement	Will be provided in vials within a carton. Each carton and vial will be labelled as required per country requirement
Current/Former Name	-	Previous clinical documentation: ChAdOx1 nCoV-19 Current tradename: Vaxzevria

IMP: investigational medicinal product; NIMP: non-investigational medical product; w/v: weight/volume.

AZD2816 will be supplied by the Sponsor as a vial solution for injection. It is a sterile, clear to slightly opaque solution, practically free from visible particles. Each vial of AZD2816 has a label-claim volume of 5 mL and can provide up to ten 0.5 mL doses.

AZD1222 will be supplied by the Sponsor as a vial solution for injection. It is a sterile, clear to slightly opaque solution, practically free from visible particles. Each vial of AZD1222 has a label-claim volume of 4 mL and can provide up to eight 0.5 mL doses.

Unopened vials of AZD2816 and AZD1222 must be stored at 2-8 ºC (36-46 ºF) for the duration of the assigned shelf-life and must not be frozen. Both investigational products must be kept in original packaging until use to prevent prolonged light exposure.

6.1.2 Dosing Instructions

Previously unvaccinated participants will receive 2 doses of either AZD1222, AZD2816, or AZD1222 plus AZD2816, with the first dose administered on Day 1 and the second dose on Day 29 (for a 4-week dosing interval) (Table 3) or Day 85 (for a 12-week dosing interval) (Table 4).

Previously vaccinated participants will receive 1 dose of either AZD1222 or AZD2816 (Table 2).

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

All study participants will be observed in the clinic for at least 15 minutes after vaccination. Allergic reactions to vaccines are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

6.2 Preparation/Handling/Storage/Accountability

The procedures for preparation, handling, storage, and accountability are identical for AZD2816 and AZD1222.

1 The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2 Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
3 The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4 Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual or specified handling instructions.

6.2.1 Dose Preparation and Administration

Doses of AZD2816 and 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 AZD2816 or AZD1222 in a sterile syringe.

AZD2816 and AZD1222 do not contain preservatives. Each vial must be assigned a beyond-use-date of 6 hours at 2-30 °C (36-86 °F) from first needle puncture of the vial, after which any unused portion must be discarded.

Once an AZD2816 or AZD1222 dose is drawn into a syringe for administration, the dose must be administered within the beyond-use-date of the vial. If dose administration is not completed within the 6-hour vial beyond-use-date, a new dose must be prepared from a new vial.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization

The study contains 3 cohorts that are randomised to a total of 8 treatments:

- Participants that have previously been vaccinated with 2 doses of AZD1222 will be randomised 1:1 to 1 dose of AZD2816 or 1 dose of AZD1222.
- Participants that have been previously vaccinated with an mRNA COVID-19 vaccine will be randomised 1:1 to 1 dose of AZD2816 or AZD1222.
- Previously unvaccinated participants that will be randomised 5:5:5:2 to 2 doses of AZD2816 with a 4-week dosing interval, 2 doses of AZD1222 with a 4-week dosing interval, 1 dose of AZD1222 followed by 1 dose of AZD216 with a 4-week dosing interval, or 2 doses of AZD2816 with a 12-week dosing interval.

Separate populations of SARS-CoV-2 seronegative participants (supporting the primary and secondary objectives) and SARS-CoV-2 seropositive participants (supporting exploratory objectives) will be randomised/included in the above cohorts.

Randomization will be stratified based on age (less than 65, 65 and above), gender, and presence of at least one of the following comorbidities that are known risk factors for severe illness from COVID-19 (based on the participant's past and current medical history):

- Obesity (BMI $\geq$ 30 kg/m^2 at baseline)
- Significant cardiovascular disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, or pulmonary hypertension)
- Chronic lung disease (eg, chronic obstructive pulmonary disease, idiopathic pulmonary disease, cystic fibrosis, or moderate to severe asthma)
- Diabetes.

The randomised participants will be centrally assigned to randomised study intervention using an Interactive Response Technology (IRT)/Randomisation and Trial Supply Management. Before the study is initiated, the telephone number and call-in directions for the IRT and/or

the log in information & directions for the Randomisation and Trial Supply Management will be provided to each site.

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

6.3.2 Blinding

Treatment will be double-blinded for previously vaccinated participants randomised to a single dose of either AZD2816 or AZD1222. Treatment will also be double-blind for previously unvaccinated participants randomised to 2 dose vaccinations with a 4-week dosing interval (ie, homologous AZD2816 or AZD1222 vaccination or heterologous AZD1222/AZD2816 vaccination). Previously unvaccinated participants randomised to a homologous AZD2816 vaccination with a 12-week dosing interval will receive treatment in an open-label fashion due to the different dosing interval.

For the double-blinded treatments, neither the participant nor any of the investigators or Sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the study intervention received. Since AZD2816 and AZD1222 are visually distinct prior to dose preparation (due to differences in container closure), all investigational 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, AZD2816 and AZD1222 are not visually distinct from each other.

The IRT will provide the investigators with a dose tracking number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IRT user manual that will be provided to each study site.

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

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

6.3.3 Procedures for Unblinding

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

In the event that a study participant is contacted about receiving a licensed and/or authorized COVID-19 vaccine outside of this clinical study, unblinding instructions are being provided to the sites. If the participant is unblinded, the Sponsor needs to be notified within 24 hours, and this should be documented in the site source documents.

6.4 Study Intervention Compliance

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

6.5 Concomitant Therapy

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

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

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

6.5.1 Permitted Concomitant Medications

- Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance.
- Primary care providers, or where appropriate investigators, should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study.

- Participants who develop COVID-19 after receiving study intervention should be treated with licensed medications and interventions according to standard of care. All routine vaccinations other than influenza are permitted beginning > 30 days after last dose of study intervention. Licensed influenza vaccines are permitted 7 days before and 7 days after administration of study intervention.
- Topical/inhaled steroids or short-term oral steroids (course lasting ≤ 14 days) are permitted

6.5.2 Prohibited Concomitant Medications

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

- Primary or booster vaccinations, other than AZD2816 or AZD1222, for prevention of SARS-CoV-2 or COVID-19**.**

  Note: Participants choosing to receive a licenced and/or authorized COVID-19 vaccine should inform the Investigator so it can be properly documented. Participants, who receive a licenced and/or authorized COVID-19 vaccine outside the study, should be encouraged to continue study conduct to be followed for safety reporting and all assessments.
- Receipt of any vaccine (licensed or investigational) other than licensed influenza vaccines within 30 days prior to and after administration of study intervention. Thirty days after the second vaccination, other routine vaccinations are permitted as clinically indicated.
- Glucocorticoids at a dose ≥ 20 mg/day of prednisone or equivalent given daily or on alternate days for ≥ 14 consecutive days between randomization and the participant's scheduled final visit
- Other systemically administered drugs with significant immunosuppressive activity, such as azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy between randomization and the participant's scheduled final visit
- Immunoglobulins and/or any blood product.

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

6.6 Dose Modification

Study intervention will be administered as described in Section 6.1. Dose modification is not permitted.

6.7 Intervention After the End of the Study

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

An individual participant will not receive the first or second dose (if applicable) of study intervention if any of the following occur in the participant in question:

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

Each participant who has received at least 1 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.

In the event that a study participant receives a licensed and/or authorized COVID-19 vaccine during the study, AstraZeneca needs to be notified within 24 hours and this should be documented in the site source documents. Participants who have received study intervention, regardless of reason, will be followed for the full study period.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Sponsor Study Team. If the participant does not specifically request withdrawal of consent for use of samples, then the samples collected prior to the consent withdrawal will be destroyed once per protocol analysis is complete.

7.3 Lost to Follow-up

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

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

- The study site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Schedule of Activities (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 Schedule of Activities (Section 1.3) is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities.

8.1 Efficacy Assessments

Not applicable.

8.2 Safety Assessments

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

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

8.2.2 Vital Signs

Vital signs, including heart rate, pulse oximetry, blood pressure, and body temperature, will be performed as specified in the Schedule of Activities (Section 1.3). The participant should be resting prior to the collection of vital signs. On vaccination days, vital signs should be assessed prior to vaccine administration.

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

8.2.3 Clinical Laboratory Assessments

Blood samples for determination of clinical chemistry and haematology will be taken at the visits indicated in the Schedule of Activities (Section 1.3). Additional unscheduled safety samples may be collected if clinically indicated at the discretion of the investigator, with the date and time of collection recorded in the appropriate eCRF.

The standard clinical chemistry and haematology analysis will be performed at a local laboratory at or near to the investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The following laboratory variables will be measured:

Table 9 Laboratory Safety Variables

Blood	Serum/Plasma
Haemoglobin	Activated partial thromboplastin time
Leukocyte count	Prothrombin time
Leukocyte differential count (absolute count)	Fibrinogen
Platelet count	D-dimer
-	Creatinine
-	Bilirubin, total
-	Alkaline phosphatase
-	Aspartate aminotransferase
-	Alanine aminotransferase

In case a participant shows an aspartate aminotransferase **or** alanine aminotransferase ≥ 3 × upper limit of normal together with total bilirubin ≥ 2 × the upper limit of normal, please refer to Section 8.3.6

For women participants of childbearing potential, a urine sample for pregnancy testing will be collected according to the Schedule of Activities (Section 1.3). Urine pregnancy tests for β-human chorionic gonadotropin may be performed at the site using a licensed dipstick test.

8.3 Adverse Events and Serious Adverse Events

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

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

Solicited AEs are local or systemic predefined events for assessment of reactogenicity. Solicited AEs will be collected in a e-diary (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 the reporting of solicited AEs via e-diary unless otherwise noted..

All other AEs are considered to be unsolicited AEs (collected by 'open question' at study visits).

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

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

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

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

Solicited AEs will be recorded for 7 days after each dose of study intervention (ie, Day 1 through Day 8). If a solicited AE is not resolved within the e-diary reporting period, the event will be reported as a non-solicited adverse event in the eCRF, with a start date of when started and the actual stop date.

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

Medically-attended AEs and AEs of special interest will be recorded from Day 1 through the last participant contact.

See the Schedule of Activities for the scheduled timepoints (Section 1.3).

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 Adverse Events and Serious Adverse Events

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. The Sponsor retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

AE variables

The following variables will be collected for each AE:

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

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

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

A revised toxicity grading scale from US FDA guidance for healthy volunteers enrolled in a preventive vaccine clinical study (FDA 2007) will be utilized for all unsolicited events.

8.3.3 Causality Collection

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

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

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

8.3.4 Adverse Events Based on Signs and Symptoms

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

8.3.5 Adverse Events Based on Examinations and Tests

The results from the Clinical Study Protocol-mandated vital signs and laboratory safety assessments will be summarized in the Clinical Study Report.

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

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

8.3.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation. Any occurrences of aspartate aminotransferase or alanine aminotransferase $\geq 3 \times$ the upper limit of normal together with total bilirubin $\geq 2 \times$ upper limit of normal at any point during the study following the administration of study medication should be reported to the Sponsor as a potential Hy's Law SAE within 1 day with a serious criteria of 'Important medical event' and causality assessment 'yes/related'.

The study physician will contact the investigator to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.

8.3.7 Solicited Adverse Events

Local and systemic predefined solicited AEs for reactogenicity assessment (Table 10) will be collected in a Solicited AE e-Diary for 7 days following administration of each dose of study intervention via e-diary collection. If a solicited AE is not resolved within the e-diary reporting period, the event will be also reported as a non-solicited adverse event in the eCRF, with a start date of when started and the actual stop date.

Solicited AEs should not be reported as unsolicited AEs unless they fulfil the criteria for SAEs or medically-attended AEs(see Sections 8.3 and 8.3.8, respectively).

Table 10 Predefined Solicited Adverse Events for Reactogenicity Assessment

Local	Systemic
Pain at the site of the injection	Fever (> 100 °F/37.8 °C)
Redness/erythema at the site of the injection	Chills
Tenderness at the site of the injection	Muscle pains
Induration/swelling at the site of the injection	Fatigue (physical or mental tiredness/exhaustion)
-	Headache
-	Malaise (general feeling of discomfort or uneasiness)
-	Nausea
-	Vomiting

Solicited AE e-Diary

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

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

Severity Assessment of Solicited AEs

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

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

8.3.8 COVID-19 Assessment

This study will describe the incidence of COVID-19 adverse events reported from Day 1 to 180 days after the participant's last/only dose of vaccine.

COVID-19 is defined as SARS-CoV 2-RT-PCR positive symptomatic illness. At all clinic visits following the initial vaccination, participants will be asked if they have had a diagnosis of COVID-19 since their last clinic visit (see Schedule of Activities in Section 1.3). Medical records will be obtained for confirmation of a participant-reported diagnoses of COVID-19. Qualifying symptoms are fever, shortness of breath, difficulty breathing, chills, cough, fatigue, muscle/body aches, headache, new loss of taste or smell, sore throat, congestion, runny nose, nausea, vomiting, or diarrhoea. Events will be reported as AEs/SAEs.

If a participant presents at clinic visit with COVID symptoms, diagnosis will be confirmed using RT-PCR.

8.3.9 Medically-Attended Adverse Events

Medically-attended AEs will be collected according to the timepoints specified in the Schedule of Activities (Section 1.3).

Medically-attended AEs are defined as AEs leading to medically-attended visits that were not routine visits for physical examination or vaccination, such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. AEs, including abnormal vital signs, identified on a routine study visit or during the scheduled illness visits will not be considered medically-attended AEs.

8.3.10 Adverse Events of Special Interest

AEs of special interest will be collected according to the timepoints specified in the Schedule of Activities (Section 1.3).

AEs of special interest 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. AEs of special interest are based on Brighton Collaboration case definitions (SPEAC 2020), clinical experience, and scientific interest. A list of events is provided in Appendix E.

An AE of special interest can be serious or non-serious. All AEs of special interest will be recorded in the eCRF. If any AE of special interest occurs in the course of the study, investigators or other site personnel will inform the appropriate Sponsor representatives within

1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it. Serious AEs of special interest will be recorded and reported as per Section 8.3.11.

8.3.10.1 Vascular/Hematologic Adverse Events of Special Interest

Both thrombotic, thromboembolic, and neurovascular events and thrombocytopenia events are considered to be adverse events of special interest. The investigator should remain vigilant for the occurrence of thrombotic events with thrombocytopenia and/or bleeding. If a participant experiences new onset thromboembolic events with thrombocytopenia, there should be prompt evaluation with a thorough haematological investigation. COVID-19 testing, including PCR and serology (nucleoprotein antibodies), should also be performed. See Appendix F for further guidance on investigation and management of suspected events.

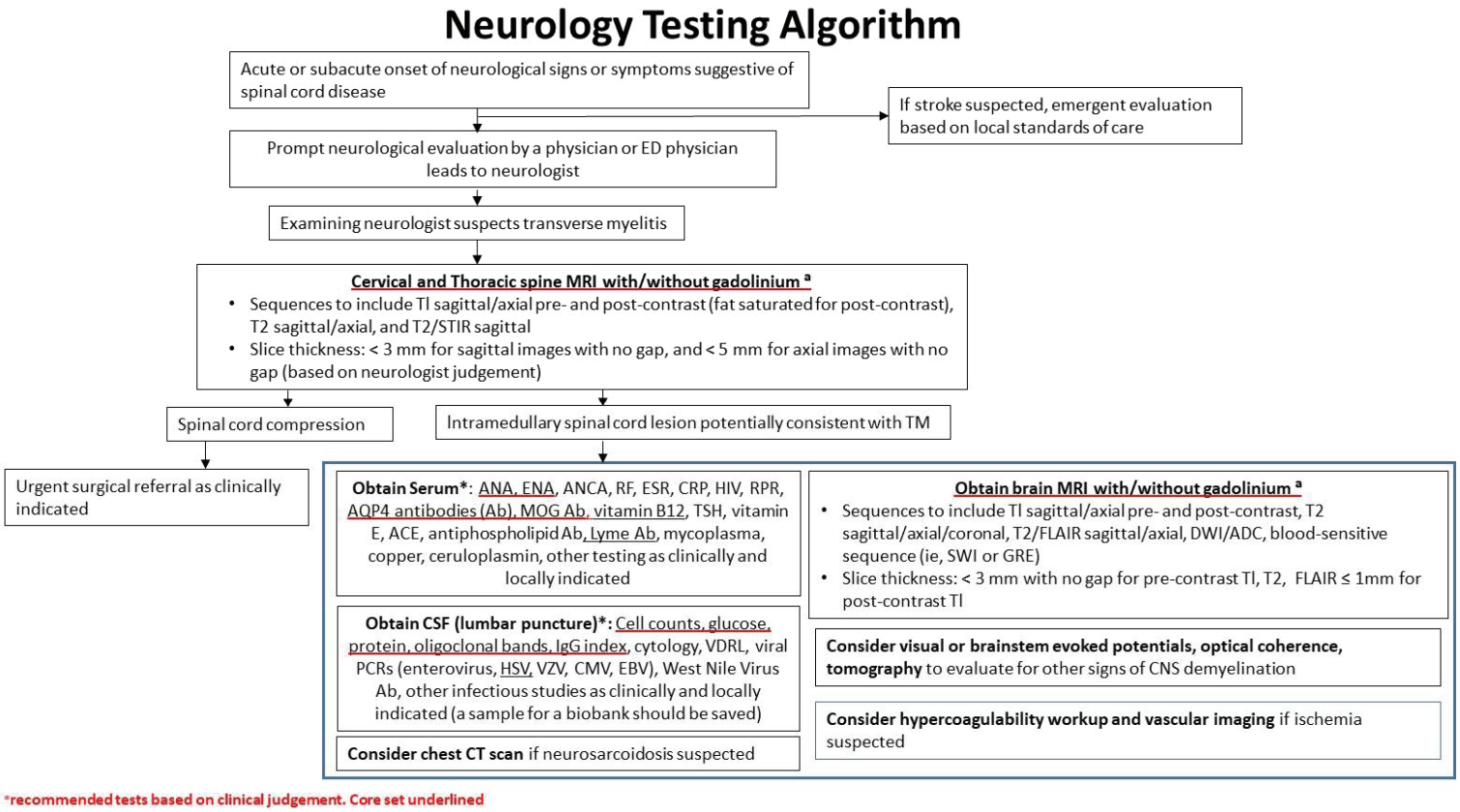
In the event of such a case of thrombosis and in accordance with local laws and ethical procedures, one blood sample may be taken from the participant and whole genome sequencing performed in order to enable investigations into the possible role of genetic polymorphisms as risk factors for these events.

8.3.10.2 Potential Neurological Adverse Events of Special Interest

If a participant experiences new onset (acute or subacute) motor and sensory disturbances (eg, weakness, numbness, paraesthesia, 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, including referral to a neurology specialist for further evaluation and testing, as clinically indicated. Testing can include evaluation for peripheral demyelinating conditions (eg, electromyography). In cases of concern for spinal cord disease, see Figure 3 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 AEs of special interest occurring in the AZD1222 clinical development program (see Appendix A 5).

Figure 3 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.

8.3.11 Reporting of Serious Adverse Events

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

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

The designated Sponsor representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform Sponsor representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but no later than 24 hours of when he or she becomes aware.

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 Sponsor representative.

If the Electronic Data Capture system is not available, then the investigator or other study site staff reports an SAE to the appropriate Sponsor representative by telephone or other method and the event is entered into the Electronic Data Capture system when available.

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

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

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

8.3.12 Pregnancy

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

8.3.12.1 Maternal Exposure

Female participants who are pregnant or have a confirmed positive pregnancy test at screening or Day 1 will be excluded from the study (see Section 5.2). Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and

spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the participant was discontinued from the study.

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

The designated Sponsor representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.11) and **within 30 days** for all other pregnancies that are not associated with an SAEs.

The same timelines apply when outcome information is available.

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

8.3.13 Medication Error

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

The designated Sponsor representative works with the investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) **or 5** (other serious initial and follow up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.11) and **within 30 days** for all other medication errors.

The definition of a Medication Error can be found in Appendix B 3.

8.4 Overdose

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

There is no specific treatment for an overdose with AZD2816 or AZD1222. If overdose occurs, the participant should be treated supportively with appropriate monitoring as necessary.

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

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

The designated Sponsor representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.11) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

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

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

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

8.5.1 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5.2 Immunogenicity Assessments

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

8.5.2.1 SARS-CoV-2 Serology Assessments

Serum samples will be collected to assess SARS-CoV-2 antigen-specific antibody levels from all participants according to the Schedule of Activities (Section 1.3). Authorized laboratories will assess serologic responses to AZD1222 and AZD2816 using validated (or qualified, where appropriate) assays. Serologic assessment to the S protein from different SARS-CoV-2 variants (which include Wuhan-Hu-1, B.1.351, B.1.1.7, and P.1) will be assessed quantitatively using a validated multiplexed ECL based immunoassay. Additionally, seroresponse will be assessed for each antigen over time. The rate of SARS-CoV-2 infection in participants receiving AZD2816 versus AZD1222 will be determined by seroresponse in a SARS-CoV-2 nucleocapsid antigen in a multiplexed electrochemiluminescence-based assay performed at an authorized laboratory. Additional exploratory assessments may be performed to measure binding antibodies to SARS-CoV-2 variants of interest (which may include B.1.429, B.1.525, B.1.526, P.2, P.3, B.1.617, and the Q677H mutation observed in multiple variants).

8.5.2.2 CCI

CCI

8.5.2.3 CCI

CCI

CCI [redacted]

8.5.2.4 CCI

CCI [redacted]

8.5.3 Pharmacodynamics

Pharmacodynamics are not evaluated in this study.

8.6 Human Biological Sample Biomarkers

Already collected samples may be analysed for biomarkers thought to play a role in COVID-19 severity or outcomes based upon emerging immunogenicity and pharmacodynamic analysis from this or other studies involving the study interventions. These analyses include but are not limited to serum or plasma cytokines, quantification of RNA, micro-RNA, and/or non-coding RNA using quantitative reverse transcriptase polymerase chain reaction (RT-PCR), microarray, sequencing, or other technologies in blood, or peripheral blood mononuclear cells to evaluate their association with AZD1222/2816 and observed clinical responses to these study interventions.

8.7 Optional Genomics Initiative Sample

Not applicable.

8.8 Medical Resource Utilization and Health Economics

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

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The overall hypothesis for this 8-armed study is that 28 days after vaccination (ie, following a single booster dose for the previously vaccinated participants or a second vaccination dose for previously unvaccinated participants), AZD2816 will be non-inferior to AZD1222 in terms of immunogenicity (ie, neutralising antibodies GMT ratio and difference in seroresponse rates). The specific null and alternative hypotheses for each objective are presented in Section 9.4.3.

9.2 Sample Size Determination

Immunogenicity response

Historical data were available for the immunogenicity responses (ie, pseudovirus neutralising antibodies, live virus neutralising antibodies, and spike protein binding antibodies) to AZD1222 from the pooled COV001/002/003/005 studies. Table 11 presents the log transformed immunogenicity responses (ie, geometric mean titres) by assay for participants that received 2 standard doses of AZD1222. These results indicate that the pseudo-neutralising antibodies exhibited the largest variation (standard deviation of 1.20 and 1.10 for the 4-week and 12-week dosing intervals respectively), while live-neutralising antibodies had the lowest (standard deviation of 0.72 for the 4-week dosing interval).

Table 11 Historic Immunogenicity Responses by Dosing Interval (Geometric Mean Antibody Titres, Standard Dose Immunogenicity Analysis Set)

	Post-1st Dose			Post-2nd dose with a 4-week dosing interval[a]			Post-2nd dose with a 12-week dosing interval[b]		
Assay	**N**	**Mean**	**Std Dev**	**N**	**Mean**	**Std Dev**	**N**	**Mean**	**Std Dev**
Pseudo	476	4.3	1.34	166	5.3	1.20	113	5.4	1.10
Live	51	4.9	1.15	42	6.2	0.72	0	-	-
Spike protein	1139	9.1	1.14	293	10.1	0.96	302	10.7	0.83

[a] Estimates from pooled COV001/002/003/005 study data from participants with 2- to 6-week dosing interval
[b] Estimates from pooled COV001/002/003/005 study data from participants with 10- to 14-week dosing interval

Table 12 presents the seroresponse (ie, ≥ 4 fold increase from baseline) by assay. These results indicate that the pseudo-neutralising antibodies exhibited the lowest proportion of seroresponse (59.7% and 85.5% for the 4-week and 12-week dosing intervals respectively), while both live-neutralising and spike-binding seroresponse rates exceeded 95%.

Table 12 Historic Seroresponse Rates by Dosing Interval (≥4-fold Increase from Baseline, Standard Dose Immunogenicity Analysis Set)

	Post-1st Dose		Post-2nd dose with a 4-week dosing interval[a]		Post-2nd dose with a 12-dose week interval[b]	
Assay	**N**	**Proportion**	**N**	**Proportion**	**N**	**Proportion**
Pseudo	499	32%	382	59.7%	117	85.5%
Live	96	75%	95	96.8%	-	-
Spike protein	940	96.6%	636	95.9%	304	99.3%

[a] Estimates from pooled COV001/002/003/005 study data from participants with 2- to 6-week dosing interval
[b] Estimates from pooled COV001/002/003/005 study data from participants with 10- to 14-week dosing interval

Under the assumption that the immunogenicity responses (ie, geometric mean antibody titres) associated with AZD2816 will be similar to the responses associated with AZD1222 in participants that received 2 standard doses in the pooled COV001/002/003/005 studies, in which standard deviations ranged from 0.72 to 1.2 (Table 11), 150 participants will provide a 95% confidence interval half-width between 0.115 and 0.192 (see Table 13). Similarly, 380 participants will provide a 95% confidence interval half-width between 0.072 and 0.120.

Under the assumption that the seroresponse rates associated with AZD2816 will be similar to the response rates in adults that received 2 standard doses of AZD1222 in the pooled COV001/002/003/005 studies (Table 12), 150 participants will provide a 95% confidence interval half-width between 1.33% and 7.85%, and 380 participants will provide a 95% confidence interval half-width between 0.84% and 4.93% (Table 14).

Table 13 Estimated Half-width of the 95% Confidence Intervals for Immunogenicity Responses (Geometric Mean Titres) Based on Historic Immunogenicity Assay Variances and the Proposed Sample Sizes

Standard Deviation	Number of participants	Estimated half-width of the 95% confidence interval (natural log scale)
0.72	150	0.115
	300	0.081
	350	0.075
	380	0.072
0.83	150	0.133
	300	0.094
	350	0.087
	380	0.084
0.96	150	0.154
	300	0.109
	350	0.101
	380	0.097
1.1	150	0.176
	300	0.124
	350	0.115
	380	0.111
1.2	150	0.192
	300	0.136
	350	0.126
	380	0.120

Table 14 Estimated Half-Width of the 95% Confidence Interval for the Seroresponse Rates based on Historic Seroresponse Rates and Proposed Sample Sizes

Observed seroresponse rate	Participants (N)	Estimated half-width of the 95% confidence interval
59.7%	150	7.85%
	300	5.55%
	350	5.14%
	380	4.93%
85.5%	150	5.63%
	300	3.98%
	350	3.69%
	380	3.54%
95.9%	150	3.17%
	300	2.24%
	350	2.08%
	380	1.99%
96.8%	150	2.82%
	300	1.99%
	350	1.84%
	380	1.77%
99.3%	150	1.33%
	300	0.94%
	350	0.87%
	380	0.84%

For a fixed sample size, the precision with which the 95% confidence interval of the binary seroresponse rate can be estimated is a function of the response rate. Table 14 provides the lower bounds of the 95% confidence interval for selected response proportions for alternate sample sizes. For a given response rate, we can be 95% confident that the true seroresponse rate is at least as large as the lower bound of the confidence interval.

Immunogenicity Comparisons: Non-inferiority

Under the assumption that there is no difference between treatment arms of interest (ie, a ratio of 1, difference on the log scale of 0), the power conferred by 150 to 380 participants for the

comparison of geometric mean titre ratio using a noninferiority margin of 1.5 (equivalent to a difference on the log scale of 0.405) is presented in .

Table 15 Power for Non-inferiority Using 1.5 as the Upper Bound of the Geometric Mean Titre Ratio

and for the comparison of seroresponse rate using the non-inferiority margin of -15% as the upper bound of the difference is presented in Table 16.

If there is no difference between treatment arms of interest (ie, a ratio of 1) in the proportion of seroresponders, 380 participants provides 98% power to establish non-inferiority to within margin of -15% if the seroresponse rate is > 50%. The observed pseudo-neutralising response rates (≥ 4 fold increase from baseline) from the COV001/002/003/005 studies for AZD1222 were 59.7% and 85.5% for the 4-week and 12-week dosing interval respectively (Table 12). A population of 380 participants provides 99% power to detect non-inferiority (using a non-inferiority margin of -15%) if the observed response rate is 59.7%.

Table 15 Power for Non-inferiority Using 1.5 as the Upper Bound of the Geometric Mean Titre Ratio

Sides	Null difference	Assumed mean treatment difference	Assumed standard deviation	Number in comparator group	Number in reference group	Alpha	Power
Upper	ln1.5 = 0.405	0	0.72	150	300	0.025	>.999
				150	350		>.999
				150	380		>.999
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999
			0.83	150	300		0.998
				150	350		0.999
				150	380		>.999
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999
			0.96	150	300		0.988
				150	350		0.991
				150	380		0.992
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999
			1.10	150	300		0.957
				150	350		0.965
				150	380		0.968
				300	300		0.994
				300	350		0.997
				300	380		0.997
				350	380		0.999
				350	350		0.998
				380	380		>.999
			1.20	150	300		0.920
				150	350		0.932
				150	380		0.937
				300	300		0.985
				300	350		0.990
				300	380		0.992
				350	380		0.995
				350	350		0.994
				380	380		0.996

Table 16 Power for Non-inferiority Using -15% as the Upper Bound of the Difference in Seroresponse Rate

Sides	Null proportion difference	Assumed difference in proportion of seroresponders	Assumed proportion of seroresponders in both groups	Number in comparator group	Number in reference group	Alpha	Power
Lower	-0.15	0	0.597	150	300	0.025	0.878
				150	350		0.894
				150	380		0.902
				300	300		0.964
				300	350		0.975
				300	380		0.979
				350	380		0.986
				350	350		0.982
				380	380		0.989
			0.855	150	300		0.993
				150	350		0.995
				150	380		0.996
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999
			0.959	150	300		>.999
				150	350		>.999
				150	380		>.999
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999
			0.968	150	300		>.999
				150	350		>.999
				150	380		>.999
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999
			0.993	150	300		>.999
				150	350		>.999
				150	380		>.999
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999

Safety

Table 17 indicates the probability of observing 1 or more safety events, such as solicited injection site or systemic reactogenicity events or an unsolicited non-serious AE of a particular type for participants in each treatment arm. With the sample size of 300 participants, at least 1 participant with an AE of incidence rate of 1% can be detected with probability of about 95%.

Table 17 Probability of detecting 1 or more safety events (N = 300)

Event Frequency	Probability (> 1 event)
≥ 10% (Very Common)	> 99%
≥ 1% (Common)	95%
≥ 0.1% (Uncommon)	26%
≥ 0.01% (Rare)	3%

9.3 Populations for Analyses

The following populations are defined:

Table 18 Populations for Analysis

Population	Description
All participants analysis set	All participants screened for the study, to be used for reporting disposition and screening failures.
Full analysis set	All randomised participants who received study treatment, irrespective of their protocol adherence and continued participation in the study. Participants will be analysed according to their randomised treatment, irrespective of whether or not they have prematurely discontinued, according to the intent-to-treat principle. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination.
Safety analysis set	The safety analysis set consists of all participants who have received study treatment. Erroneously-treated participants (eg, those randomised to AZD2816, but were actually given treatment AZD12222) are accounted for in this analysis set by assigning them to the treatment they actually received.
Immunogenicity analysis set	The vaccine immunogenicity analysis set will include all randomised participants, received at least 1 dose of planned study treatment (ie, 1 dose of either AZD2816 or 1 dose of AZD1222), had baseline and post-dose antibody measurements, have at least 1 post-dose quantifiable serum titre, and had no protocol deviations judged to have the potential to interfere with the generation or interpretation of an antibody response. The analyses conducted using this analysis set will be based on the actual treatment received.

Table 18 Populations for Analysis

Population	Description
Seronegative immunogenicity analysis set	The subset of the immunogenicity analysis set who were seronegative at baseline.
Seropositive immunogenicity analysis set	The subset of the immunogenicity analysis set who were seropositive at baseline.

Participants that are SARS-CoV-2 seropositive at screening will be included in seropositive analysis sets analogous to the above seronegative analysis sets. Further definition is provided in the Statistical Analysis Plan.

9.4 Statistical Analyses

This section provides a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints. A more technical and detailed description of the statistical analyses will be described in the Statistical Analysis Plan, and an approved version will be finalized prior to the interim analyses.

9.4.1 General Considerations

An initial interim analysis will occur when a subset of participants previously vaccinated with AZD1222 have completed their Day 29 visit (ie, 28 days after booster dose). This sample will include both participants randomised to receive a booster dose of AZD2816 as well as a those randomised to receive a booster dose of AZD1222. Analyses presenting treatment arm summaries of both the raw and model adjusted immunogenicity will be reviewed by an unblinded team within AstraZeneca to make a decision regarding the potential need for sample size re-estimation. Full details of this analyses are provided in the Interim Analysis Charter to be finalized prior to any interim analysis.

A second interim analysis will occur when all participants previously vaccinated with AZD1222 have completed their Day 29 visit (ie, 28 days after booster dose). It is estimated that this early analysis has the potential to provide clear signals about whether AZD2816 provides a strong neutralizing response against the B.1.351 strain while retaining immunogenicity against the Wuhan strain, and thereby influence programmatic decisions early. Analyses results will present treatment arm specific summaries of both the raw and model adjusted (baseline age and co-morbidities). The raw data outputs will be stratified by age group (<65, ≥ 65) while the model adjusted summaries will pool data across age groups. Full details of this analyses are provided in the Interim Analysis Statistical analysis Plan to be finalized prior to any interim analysis.

A third interim analysis may be performed when a subset of previously unvaccinated participants have completed their Day 57 visit (ie, 56 days after first dose). The participant

sample will include both participants randomised to AZD2816 as well as those randomised to AZD1222. This analysis is intended to assess immunogenicity variability. The number of previously unvaccinated participants per treatment arm may be increased based upon the results of this analysis. The details of this interim analysis, including the trigger and methods, will be specified in the Interim Analysis Charter.

The primary analysis will occur when all participants have completed their Day 29 visit and safety and immunogenicity data from all unvaccinated participants randomised to a 4-week dosing interval are available through completion of their visit 28 days after the second priming dose.

A secondary analysis will occur when all participants have completed their Day 29 visit and safety and immunogenicity data from all unvaccinated participants (including those randomised to a 12-week dosing interval) are available through completion of the visit 28 days after the second dose.

The final analysis will occur when data from all vaccinated participants is available through completion of the last study visit (180 days after the single dose for previously vaccinated participants / 180 days after the second dose for unvaccinated participants).

Further details of the primary analysis, secondary analysis and final analysis are contained within the Statistical Analysis Plan

To maintain trial integrity sponsor roles with direct input into participant management and safety monitoring will not have access to unblinded participant level data or associated outputs from the interim analyses until end of study.

Further details on the tools and processes to maintain the blind will be presented in the Study Integrity Plan.

9.4.2 Safety

9.4.2.1 Primary Endpoints

Overview

Descriptive analyses will support evaluation of safety, reactogenicity and immunogenicity. The primary safety analysis includes:

- Incidence of local and systemic solicited AEs for 7 days following each vaccination will be summarised by day and overall.
- Incidence of unsolicited AEs for 28 days following each vaccination will be summarised by system organ class and preferred term, and by relationship to vaccination as assessed by the investigator.

- MAAEs, SAEs, and AESIs following the first vaccination and throughout the study duration will be summarised by system organ class and preferred term and by relationship to vaccination as assessed by the investigator.
- The change from baseline for safety laboratory measures at 7 and 28 days after vaccination.

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

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

A listing will cover details for each individual AE. Full details of all AE analyses will be provided in the Statistical Analysis Plan, including intercurrent events for safety due to potential unblinding of participants for administration of licensed and/or approved SARS-CoV-2 or COVID-19 vaccine.

At the time of the interim analyses, group assignment will not be presented when safety event data has the potential to unblind participant's study group attribution.

9.4.2.2 Other Safety Endpoints

Vital Signs

Vital sign measurements will be performed as specified in the Schedule of Activities (Section 1.3). The set of assessments will include pulse oximetry, blood pressure, and body temperature.

Details of all vital sign analyses will be provided in the Statistical Analysis Plan, which will include descriptive statistics presented for observed values for all vital sign parameters.

COVID-19

This study will describe the incidence of COVID-19 adverse events from the first dose of the vaccine to study end (180 days post-vaccination). Descriptive statistics will be produced based on the safety analysis set. Full details will be documented in the statistical analysis plan.

9.4.3 Immunogenicity

9.4.3.1 Immunogenicity Endpoints

The immunogenicity endpoints of interest in this study are:

- Geometric mean antibody titre.
- Seroresponse, defined as ≥ 4-fold increase in the geometric mean antibody titre from baseline

Both the geometric mean antibody titre and seroresponse of participants will be summarized descriptively by strain, treatment arm, and timepoint for the immunogenicity population.

9.4.3.1.1 Estimand framework for immunogenicity descriptions and comparisons

Target populations:

1) Previously unvaccinated participants

    a. Seronegative Analysis Set: and with no evidence of prior or current infection

2) Participants who previously received SARS-CoV-2 vaccination with either AZD1222 or a licensed mRNA vaccine according to the authorized dose and dosing regimen at least 90 days prior to first study intervention (see Section 5.1.2).

Outcome variable: neutralizing antibody and binding titres to SARS-CoV-2 at 28 days after each treatment administration (1 treatment administration for the previously vaccinated population and 2 planned treatment administrations for the unvaccinated population).

Treatment conditions:

Previously unvaccinated population

- 2 doses of AZD1222 given on Day 1 and on Day 29 (4-week dosing interval)
- 2 doses of AZD2816 given on Day 1 and on Day 29 (4-week dosing interval)
- 1 dose of AZD1222 given on Day 1 and 1 dose of AZD2816 on Day 29 (4-week dosing interval)
- 2 doses of AZD2816 given on Day 1 and on Day 85 (12-week dosing interval)

Previously vaccinated population

- 1 dose of AZD1222 given on Day 1.

- 1 dose of AZD2816 given on Day 1.

Intercurrent events: the following intercurrent events could impact the antibody levels achieved:

- missing the second vaccination (for the unvaccinated population)
- receiving of immune-modifying drugs or vaccines
- subsequent infection with SARS-CoV-2.

All immunogenicity descriptions and comparisons will use the principal stratum strategy, ie, all analyses will exclude participants who experience any of the above intercurrent events.

Population-level summary:

Descriptive Analyses (see Table 20 and Table 21)

- geometric means of the antibody titres
- seroresponse proportions

Comparative Analyses (see Table 22 and Table 23**Error! Reference source not found.**)

- ratio of geometric means of the antibody titres.
- difference in seroresponse proportion

Planned Descriptive Analyses:

Table 20 and Table 21 present planned descriptive immunogenicity analyses for the unvaccinated and previously vaccinated populations respectively (each one exploring an individual treatment arm at a specific timepoint against a particular strain).

The tables show that without introduction of further variants, there are 24 planned descriptive analyses for the unvaccinated population and 16 planned descriptive analyses for the previously immunised population (index). Within each table there is an analysis key which describes the population (see Table 19). The descriptive analyses presented in Tables 19 and 20 will be repeated for the subset of participants who are seropositive at screening.

Table 19 Description of the Analysis Keys for Tables 19 and 20

Population	Analysis Key	Example
Previously unvaccinated	Vaccination treatment received: V1222: (2 doses of AZD1222) or V2816: (2 doses of AZD2816) or V1222/2816: (1 dose of AZD1222 followed by 1 dose of AZD2816) or HV1222: ([historical] 2 doses of AZD1222 from study D8110C00001) Dosing interval: (4): 4-week dosing interval or (12): 12-week dosing interval Strain: Wuhan: Wuhan-Hu-1 or Beta: Variant B.1.351 Analysis Timepoint: D1: 28 days post-dose 1 D2: 28 days post-dose 2	[V1222 (4):Wuhan:D2] = Immunogenicity following primary vaccination with 2 doses of AZD1222 using a 4-week dosing interval against Wuhan-Hu-1 28 days post-dose 2
Previously vaccinated	Pre-study primary vaccination: V1222: 2 doses of AZD1222 or VmRNA: 2 doses of an mRNA vaccine Treatment received: B1222: 1 booster dose of AZD1222 or B2816: 1 booster dose of AZD2816 Strain: Wuhan: Wuhan-Hu-1 or Beta: VarianteB.1.351 Note: analysis timepoint is 28 days post-booster dose	[V1222:B1222:Beta] = Immunogenicity in participants who were previously vaccinated with 2 doses of AZD1222 as primary vaccination series and received a single boost dose of AZD1222 against the B.1.351 variant

Table 20 Immunogenicity Descriptive Analysis for Previously Unvaccinated Treatment Groups (with Separate Seronegative and Seropositive Analyses)

Treatment	Interval	Strain	Timepoint	Endpoint	Index	Analysis Key
AZD1222	4 weeks	Wuhan-Hu-1	28 days after 1st dose	GMT	1	[V1222(4):Wuhan:D1]†
				Seroresponse	2	
			28 days after 2nd dose	GMT	3	[V1222(4):Wuhan:D2]
				Seroresponse	4	
		B.1.351	28 days after 1st dose	GMT	5	[V1222(4):Beta:D1] †
				Seroresponse	6	
			28 days after 2nd dose	GMT	7	[V1222(4):Beta:D2]
				Seroresponse	8	
AZD2816	4 weeks	Wuhan-Hu-1	28 days after 1st dose	GMT	9	[V2816(4):Wuhan:D1] ‡
				Seroresponse	10	
			28 days after 2nd dose	GMT	11	[V2816(4):Wuhan:D2]
				Seroresponse	12	
		B.1.351	28 days after 1st dose	GMT	13	[V2816(4):Beta:D1] ‡
				Seroresponse	14	
			28 days after 2nd dose	GMT	15	[V2816(4):Beta:D2]
				Seroresponse	16	
AZD1222/ AZD2816	4 weeks	Wuhan-Hu-1	28 days after 2nd dose	GMT	17	[V1222/2816(4):Wuhan:D2]
				Seroresponse	18	
		B.1.351	28 days after 2nd dose	GMT	19	[V1222/2816(4):Beta:D2]
				Seroresponse	20	
AZD2816	12 weeks	Wuhan-Hu-1	28 days after 2nd dose	GMT	21	[V2816(12):Wuhan:D2]
				Seroresponse	22	
		B.1.351	28 days after 2nd dose	GMT	23	[V2816(12):Beta:D2]
				Seroresponse	24	

† descriptive summaries for 28 days after 1st dose will pool all treatment groups who received AZD1222 as their first dose (ie, homologous and heterologous series).
‡ descriptive summaries for 28 days after 1st dose will pool all treatment groups who received AZD2816 as their first dose (4-week interval and 12-week interval treatment arms).

GMT: Geometric mean titre

Table 21 Immunogenicity Descriptive Analysis for Previously Vaccinated Treatment Groups (with Separate Seronegative and Seropositive Analyses)

Primary vaccination	Booster Treatment	Strain	Timepoint	Endpoint	Index	Analysis Key
AZD1222	AZD1222	Wuhan-Hu-1	28 days after booster dose	GMT	1	[V1222:B1222:Wuhan]
				Seroresponse	2	
		B.1.351	28 days after booster dose	GMT	3	[V1222:B1222:Beta]
				Seroresponse	4	
	AZD2816	Wuhan-Hu-1	28 days after booster dose	GMT	5	[V1222:B2816:Wuhan]
				Seroresponse	6	
		B.1.351	28 days after booster dose	GMT	7	[V1222:B2816:Beta]
				Seroresponse	8	
mRNA	AZD2816	Wuhan-Hu-1	28 days after booster dose	GMT	9	[VmRNA:B2816:Wuhan]
				Seroresponse	10	
		B.1.351	28 days after booster dose	GMT	11	[VmRNA:B2816:Beta]
				Seroresponse	12	
	AZD1222	Wuhan-Hu-1	28 days after booster dose	GMT	13	[VmRNA:B1222:Wuhan]
				Seroresponse	14	
		B.1.351	28 days after booster dose	GMT	15	[VmRNA:B1222:Beta]
				Seroresponse	16	

GMT: Geometric mean titre

Immunogenicity comparisons:

Immunogenicity analysis

A number of comparisons of geometric mean titres and seroresponse rates between vaccine regimens and vaccine types are intended to be made.

All non-inferiority comparisons of geometric mean titre ratios will be made utilizing the lower bound of two-sided score-based confidence intervals ($\alpha = 0.05$) with non-inferiority margin 0.67

All non-inferiority comparisons of seroresponse rates will be made utilizing the lower bound of two-sided score-based confidence intervals ($\alpha = 0.05$) with non-inferiority margin 15%, and superiority comparisons of seroresponse rates will be made using one-sided Fisher's exact test ($\alpha = 0.025$). Comparisons of antibody titres between treatment groups will be conducted using geometric mean titre (GMT) ratios and seroresponse rates, facilitated by an analysis of covariance (ANCOVA) model of the log2 titre, which adjusts for the baseline level, time since previous vaccination (for previously vaccinated individuals), baseline co-morbidities and gender as fixed effects. All analyses of antibody titres (GMT ratios and differences in seroresponse) will be repeated using the unadjusted (raw observed) concentration values.

Geometric Mean Titres

The statistical methodology will be based on a 2-sided 95% CI of the ratio of the GMTs. Non-inferiority will be demonstrated if the lower limit of the 2-sided 95% CI of the GMT ratio of the reference group and comparator group is > 0.67 (see Table 22 and Table 23). The 2-sided 95% CI for the ratio of GMTs will be calculated using normal approximation of log-transformed concentrations.

The 95% CI for the GMT ratio between 2 groups will be constructed as follows:

Logarithm transformation of the individual concentrations will be calculated.

The 95% CI for the difference in log(GMT) between 2 groups: $Group_C$ and $Group_R$ will be in the form:

$$\bar{X}_C - \bar{X}_R \pm t\left(1 - {}^{\alpha}/_{2}, n_C + n_R - 2\right) \times S\sqrt{{}^{1}/_{n_C} + {}^{1}/_{n_R}}$$

Where $\bar{X}_C$ and $\bar{X}_R = \log(GMT)$ are the means of the log-transformed concentration for $Group_C$ and $Group_R$, respectively,

$S^2 = {}^{[(n_C - 1)S_C^2 + (n_R - 1)S_R^2]}/_{(n_C + n_R - 2)}$ is the pooled sample variance,

n_C and n_R are the sample sizes for $Group_C$ and $Group_R$, respectively,

S_C and S_R are the sample variances for $Group_C$ and $Group_R$, respectively,

$t\left(1 - {}^{\alpha}/_{2}, n_C + n_R - 2\right)$ is the $100\left(1 - \frac{\alpha}{2}\right)$ percentile of the t-distribution with degrees of freedom $df = n_C + n_R - 2$

To test this hypothesis, a 2- sided 95% CI will be constructed around the ratio $\frac{GMT_C}{GMT_R}$, where GMT_C and GMT_R are the geometric mean of the antibody titres in the comparator and reference groups respectively, at the timepoints post vaccination for which the groups are being compared.

The hypothesis will be supported by the data, if the lower bound of the calculated of the calculated 95% CI is > 0.67. This is equivalent to testing the null hypothesis using a 1-sided type-I error rate of 0.025.

$$H_0: {}^{GMT_C}/_{GMT_R} \leq 0.67$$

$$H_A: {GMT_C}/{GMT_R} > 0.67$$

Or equivalently

$$H_0: \log(GMT_C) - \log(GMT_R) \leq \log(0.67)$$

$$H_A: \log(GMT_C) - \log(GMT_R) > \log(0.67)$$

For the separately considered GMT hypotheses, if the null hypothesis is rejected, then the alternative hypothesis of non-inferiority will be supported.

Seroresponse

The statistical methodology will be based on a 2-sided 95% CI of the difference in seroresponse rates. Non-inferiority will be demonstrated if the upper bound of the 2-sided 95% CI rate difference in seroresponse between the reference group and comparator group is <15%. The 95% CI of the difference in proportions $P_C - P_R$ will be computed using the Wilson score without continuity correction.

To test this hypothesis, a 2- sided 95% CI will be constructed around the difference $P_C - P_R$, whereP_C and P_R are the proportions of participants in the comparator and reference groups respectively who are classified as seroresponders (≥ 4 fold increase from baseline) at the timepoints post vaccination for which the groups are being compared.

The hypothesis will be supported by the data, if the lower bound of the calculated of the calculated 95% CI is ≥ 15%. This is equivalent to testing the null hypothesis using a 1-sided type-I error rate of 0.025.

$$H_0: P_C - P_R < -15\%$$

$$H_A: P_C - P_R \geq 15\%$$

If the null hypothesis is rejected, then the alternative hypothesis of non-inferiority will be supported.

Comparisons

The primary and secondary immunogenicity objectives and the GMT and seroresponse comparisons for the previously unvaccinated participants receiving a 2-dose primary vaccination are presented in Table 22

The immunogenicity objectives and the GMT and seroresponse comparisons for the previously vaccinated participants receiving a 1-dose booster vaccination are presented in Table 23.

Owing to national vaccine rollout in the recruitment countries, including the prioritization of elderly populations, it is anticipated that there will be critical differences between the previously vaccinated and previously unvaccinated cohorts with respect to age and presence of important underlying comorbidities that may confound the interpretation of the results. Consequently, the primary and key secondary non-inferiority analyses across these two cohorts will compare the previously vaccinated participants that received a booster dose in this study with a subset of matched participants from the previously unvaccinated participants that received the 2-dose AZD1222 primary vaccine series in the AZD1222 Phase 3 study D8110C00001, which was performed in the US, Chile, and Peru.

This historical control group will be matched, at a minimum, to the previously vaccinated AZD1222 booster cohort in the D7220C00001 study based on age, gender, and presence of baseline comorbidities. These matched samples will then serve as the control arm for all planned non-inferiority analyses (both geometric mean titre [GMT] ratio and difference in seroresponse) of the previously vaccinated cohort treatment arms to the primary series vaccination. Comparisons of antibody titres between the previously vaccinated cohort in this study and the historical controls from Study D8110C00001 will be conducted using the immunogenicity analysis described above (ie, using an adjusted ANCOVA model to calculated adjusted means and standard errors for the historical comparators).

For immunogenicity data not already available, preserved sera samples from the matched controls will be used to generate immune response by the primary series parent vaccine against variant strains. AstraZeneca confirms that study D8110C00001 utilizes the same validated pseudovirus neutralising antibody assay for the Wuhan-Hu-1 strain and that residual sera are available from these study participants that will be tested in a pseudovirus neutralising antibody assay against the beta (B.1.351) variant (Monogram Biosciences, South San Francisco, USA).

Further details on the matching procedures and reporting of historical samples are provided in the statistical analysis plan.

Table 22 Immunogenicity Comparisons for Previously Unvaccinated Groups

Objective	$\frac{[\![\mathbf{[GMT]}]\!]_{\mathbf{comparator}}]}{[\![\mathbf{[GMT]}]\!]_{\mathbf{reference}}]}$	$[\![\mathbf{[Seroresponse]}]\!]_{\mathbf{comparator}}] - [\![\mathbf{[Seroresponse]}]\!]_{\mathbf{reference}}]$
To determine if the neutralizing antibody GMT response/seroresponse elicited by a 2-dose AZD2816 primary vaccination is non-inferior to the response elicited by a 2-dose AZD1222 primary vaccination	[V2816(4): Beta: D2]/[V1222(4): Wuhan: D2] (Primary)	[V2816(4): Beta: D2] − [V1222(4): Wuhan: D2] (Key Secondary 2.1)
	[V2816(4): Beta: D1]/[V1222(4): Wuhan: D1]	[V2816(4): Beta: D1] − [V1222(4): Wuhan: D1]
	[V2816(4): Beta: D2]/[V1222(4): Beta: D2] (Key Secondary 2.2)	[V2816(4): Beta: D2] − [V1222(4): Beta: D2] (Other Secondary)
	[V2816(4): Beta: D1]/[V1222(4): Beta: D1]	[V2816(4): Beta: D1] − [V1222(4): Beta: D1]
	[V2816(4): Wuhan: D2]/[V1222(4): Wuhan: D2] (Key Secondary 2.4)	[V2816(4): Wuhan: D2] − [V1222(4): Wuhan: D2] (Other Secondary)
	[V2816(4): Wuhan: D1]/[V1222(4): Wuhan: D1]	[V2816(4): Wuhan: D1] − [V1222(4): Wuhan: D1]
To determine if the neutralizing antibody GMT response/seroresponse elicited by a 2-dose AZD1222 + AZD2816 heterologous primary vaccination is non-inferior to the response elicited by a 2-dose AZD1222 primary vaccination	[V1222/2816(4): Beta: D2]/[V1222(4): Wuhan: D2] (Key Secondary 2.3)	[V1222/2816(4): Beta: D2] − [V1222(4): Wuhan: D2] (Other Secondary)
	[V1222/2816(4): Wuhan: D2] /[V1222(4): Wuhan: D2] (Other Secondary)	[V1222/2816(4): Wuhan: D2] − [V1222(4): Wuhan: D2] (Other Secondary)
	[V1222/2816(4): Wuhan: D2] /[V1222(4): Wuhan: D2] (Other Secondary)	[V1222/2816(4): Wuhan: D2] − [V1222(4): Wuhan: D2] (Other Secondary)

Table 22 Immunogenicity Comparisons for Previously Unvaccinated Groups

Objective	$\frac{[\![\mathbf{[GMT]}]\!]_{\mathbf{comparator}}]}{[\![\mathbf{[GMT]}]\!]_{\mathbf{reference}}]}$	$[\![\mathbf{[Seroresponse]}]\!]_{\mathbf{comparator}}] - [\![\mathbf{[Seroresponse]}]\!]_{\mathbf{reference}}]$
To determine if the neutralizing antibody GMT response/seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following a 2-dose AZD2816 primary vaccination	[V2816(4): Beta: D2]/[V2816(4): Wuhan: D2] (Other Secondary)	[V2816(4): Beta: D2] − [V2816(4): Wuhan: D2] (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following a 2-dose AZD1222/AZD2816 primary heterologous vaccination	[V1222/2816(4): Beta: D2]/[V1222 /2816(4): Wuhan: D2] (Other Secondary)	[V1222/2816(4): Beta: D2] − [V1222/2816(4): Wuhan: D2] (Other Secondary)

Table 23 Immunogenicity Comparisons for Previously Vaccinated Group

Objective	$\frac{[\![\mathbf{[GMT]}]\!]_{\mathbf{comparator}}]}{[\![\mathbf{[GMT]}]\!]_{\mathbf{reference}}]}$	$[\![\mathbf{[Seroresponse]}]\!]_{\mathbf{comparator}}] - [\![\mathbf{[Seroresponse]}]\!]_{\mathbf{reference}}]$
To determine if the neutralizing antibody GMT response/seroresponse elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination	[V1222: B2816: Beta]/[HV1222(4): Wuhan: D2] (Primary)	[V1222: B2816: Beta] − [HV1222(4): Wuhan: D2] (Other Secondary)
	[V1222: B2816: Beta]/[HV1222(4): Beta: D2] (Key Secondary 2.1)	[V1222: B2816: Beta] − [HV1222(4): Beta: D2] (Other Secondary)
	[V1222: B2816: Wuhan]/[HV1222(4): Wuhan: D2] (Key Secondary 2.3)	[V1222: B2816: Wuhan] − [HV1222(4): Wuhan: D2] (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse elicited by an AZD2816 booster dose is non-inferior to response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222	[V1222: B2816: Beta]/[V1222: B1222: Beta] (Key Secondary 2.2)	[V1222: B2816: Beta] − [V1222: B1222: Beta] (Other Secondary)
	[V1222: B2816: Wuhan]/[V1222: B1222: Wuhan] (Key Secondary 2.5)	[V1222: B2816: Wuhan] − [V1222: B1222: Wuhan] (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse elicited by an AZD1222 booster dose in patients previously vaccinated with AZD1222 is non-inferior to the response elicited by a 2-dose AZD1222 vaccination	[V1222: B1222: Wuhan]/[HV1222(4): Wuhan: D2] (Key Secondary 2.4)	[V1222: B1222: Wuhan] − [HV1222(4): Wuhan: D2] (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse elicited by an AZD2816 booster dose in participants previously vaccinated	[VmRNA: B2816: Beta]/[HV1222(4): Wuhan: D2] (Other Secondary)	[VmRNA: B2816: Beta] − [HV1222(4): Wuhan: D2] (Other Secondary)
	[VmRNA: B2816: Beta]/[HV1222(4): Beta: D2] (Other Secondary)	[VmRNA: B2816: Beta] − [HV1222(4): Beta: D2] (Other Secondary)

Table 23 Immunogenicity Comparisons for Previously Vaccinated Group

Objective	$\frac{[\![\mathbf{GMT}]\!]_{\mathbf{comparator}}]}{[\![\mathbf{GMT}]\!]_{\mathbf{reference}}]}$	$[\![\mathbf{Seroresponse}]\!]_{\mathbf{comparator}}] - [\![\mathbf{Seroresponse}]\!]_{\mathbf{reference}}]$
with an mRNA-based vaccine is non-inferior to response elicited by a 2-dose AZD1222 vaccination	[VmRNA: B2816: Wuhan]/[HV1222(4): Wuhan: D2] (Other Secondary)	[VmRNA: B2816: Wuhan] − [HV1222(4): Wuhan: D2] (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse elicited by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with an mRNA-based vaccine	[VmRNA: B2816: Wuhan])/[VmRNA: B1222: Wuhan] (Other Secondary)	[VmRNA: B2816: Wuhan] − [VmRNA: B1222: Wuhan] (Other Secondary)
	[VmRNA: B2816: Beta])/[VmRNA: B1222: Beta] (Other Secondary)	[VmRNA: B2816: Beta] − [VmRNA: B1222: Beta] (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following an AZD2816 booster dose	[V1222: B2816: Beta]/[V1222: B2816: Wuhan] (Other Secondary)	[V1222: B2816: Beta] − [V1222: B2816: Wuhan] (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following an AZD1222 booster dose	[V1222: B1222: Beta]/[V1222: B1222: Wuhan] (Other Secondary)	[V1222: B1222: Beta] − [V1222: B1222: Wuhan] (Other Secondary)

9.4.4 Multiple Comparisons

A hierarchical approach will be used to control for multiplicity of the primary and key secondary immunogenicity endpoints. That is, the null hypotheses for the immunogenicity endpoints will be tested in a hierarchical order, and the subsequent null hypothesis will be tested only if the prior null hypothesis is rejected. Consequently, no adjustment to alpha for multiplicity will be made in the analysis of immune response. The primary statistical comparisons of safety data will not be adjusted for multiple comparisons. Further details are provided in the statistical analysis plan.

9.4.5 Data Safety Monitoring Board

An independent COVID-19 Vaccine Data Safety Monitoring Board will provide oversight, to ensure safe and ethical conduct of the study. During the study, the benefit/risk assessment will be continuously monitored by the Board to ensure that the balance remains favourable. Further details, composition, and operation of the COVID-19 Vaccine Data Safety Monitoring Board will be described in a separate charter. For further details, see Appendix A 5.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Not applicable.

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

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

Regulatory Reporting Requirements for SAEs

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

A 2 Financial Disclosure

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

A 3 Informed Consent Process

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

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

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

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

A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

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

A 5 Committee Structure

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

A COVID-19 Vaccine Data Safety Monitoring Board comprised of independent experts will be convened to provide oversight and to ensure safe and ethical conduct of the study. The COVID 19 Vaccine Data Safety Monitoring Board will have the responsibility of evaluating cumulative safety and other clinical study data at regular intervals and making appropriate recommendations based on the available data. During the study, the benefit/risk assessment will be continuously monitored by the COVID-19 Vaccine Data Safety Monitoring Board to ensure that the balance remains favourable. Full details of the COVID-19 Vaccine Data Safety Monitoring Board composition and operations can be found in the COVID-19 Vaccine Data Safety Monitoring Board Charter.

An independent Neurological AESI Expert Committee will be available to review and provide on request about the diagnosis and causality assessment of selected neurological AEs of special interest occurring in the study. Details on the composition and operation of this committee are described in the Neurological AESI Expert Committee Charter.

A 6 Dissemination of Clinical Study Data

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

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

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

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A 9 Study and Site Start and Closure

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

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or ICH/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 IRB/IECs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of 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 SAEs and non-SAEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

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

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

AEs for **malignant tumours** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-SAE**. 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 hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life Threatening

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

Hospitalization

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

Important Medical Event or Medical Treatment

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

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used. Examples of important medical events include such events as listed below:

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

Intensity Rating Scale

A revised toxicity grading scale found in the US FDA guidance for healthy volunteers enrolled in a preventive vaccine clinical study (FDA 2007) will be utilized for all events.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for

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

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 investigational product.

- 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 investigational product?
- Consistency with known investigational product profile. Was the AE consistent with the previous knowledge of the suspect investigational product (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 investigational product?
- 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 investigational product was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

- Is this a recognized feature of overdose of the investigational medicinal product?
- 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 3 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 investigational product, but rather a human or process related failure while the investigational product 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 investigational product
- 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:

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

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

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

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

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

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

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

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

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

C 2 Withdrawal of Informed Consent for Donated Biological Samples

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

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

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

The investigator:

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

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

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

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

Appendix D 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 24: Clinical Abnormalities, Local Reactions to Injectable Product
- Table 25: Clinical Abnormalities, Vital Signs
- Table 26: Clinical Abnormalities, Systemic (General or Illness)

Table 24 Tables for Clinical Abnormalities: Local Reactions to Injectable Product

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

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

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

ER: emergency room.

Table 25 Tables for Clinical Abnormalities: Vital Signs

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

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

Table 26 Tables for Clinical Abnormalities: Systemic (General or Illness)

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

Appendix E Adverse Events of Special Interest

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

Table 27 Adverse Events of Special Interest

Category	Medical Concept
Neurologic	Generalized convulsion: episodes of neuronal hyperactivity most commonly resulting in sudden, involuntary muscular contractions. They may also manifest as sensory disturbances, autonomic dysfunction and behavioural abnormalities, and impairment or loss of consciousness.
	Guillain-Barré syndrome: a peripheral nerve demyelinating disease, which can present as temporary ascending paralysis.
	Acute disseminated encephalomyelitis: defined as a uniphasic syndrome of brain inflammation and demyelination occurring in temporal association with an antecedent immunologic challenge, such as infection or an immunization. ADEM most commonly occurs in the paediatric population.
	Other neurologic events: include new onset event (acute or subacute) motor and sensory disturbances (eg, weakness, numbness, paraesthesia, hypoesthesia, hyperesthesia, dysesthesias), bowel/bladder dysfunction, gait impairment, or visual disturbance, or any event of myelitis, encephalomyelitis, myelitis transverse, or other sudden neurological deficit.
Vascular	Thrombotic, thromboembolic, and neurovascular events: events that can manifest as transient or permanent vision problems, dizziness, trouble understanding, facial droop, slurred speech, unilateral weakness, deep vein thrombosis with swollen, warm or painful leg, pulmonary embolism with shortness of breath, chest pain or irregular heart rate.
Hematologic	Thrombocytopenia: a disorder in which there is an abnormally low platelet count; a normal platelet count ranges from 150 000 to 450 000 platelets per µL.
Immunologic	Vasculitides: a group of related disorders characterized by inflammation of blood vessels (vasculitis) leading to tissue or end-organ injury.
	Anaphylaxis: an acute hypersensitivity reaction with multi-organ-system involvement that can present as, or rapidly progress to, a severe life-threatening reaction requiring immediate medical attention.
	Vaccine-associated enhanced respiratory disease: pathogenicity has been linked to a vaccine immune response characterized by induction of non-neutralizing antibodies, and a T-cell response of the Th2 type with hypereosinophilia (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: 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 28.

Table 28 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

Table 28 List of Potential Immune-mediated Medical Conditions

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, Bechet's syndrome, leukocytoclastic vasculitis

Table 28 List of Potential Immune-mediated Medical Conditions

Category	Condition
Other	Antiphospholipid syndrome
	Autoimmune haemolytic anaemia
	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 anaemia
	Raynaud's phenomenon
	Sarcoidosis
	Sjögren's syndrome
	Stevens-Johnson syndrome
	Uveitis

Appendix F Actions Required in Cases of Thrombotic Events With Thrombocytopenia and/or Bleeding

F 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of thrombotic events with thrombocytopenia and/or bleeding. It is not intended to be a comprehensive guide to the management of all venous thromboembolic events.

During the course of the study, the investigator will remain vigilant for occurrence of thrombotic events with thrombocytopenia and/or bleeding. Appropriate investigations (eg, imaging) to diagnose these events should be made on a case-by-case basis. The investigator is responsible for determining whether a participant meets criteria for thrombotic events with thrombocytopenia and/or bleeding at any point during the study.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting criteria for thrombotic events with thrombocytopenia and/or bleeding. The Study Physician contacts the investigator to provide guidance, discuss, and agree an approach for the participant's follow-up and the continuous review of data. Guidance from the International Society of Thrombosis and Haemostasis for management of thrombocytopenic thromboembolism occurring after vaccination can be found at www.isth.org. Notably, participants should only be treated with heparin if a test for heparin-elicited thrombocytopenia antibodies is negative. An alternative explanation for thrombocytopenia should be considered (eg, alcohol use, liver cirrhosis, concomitant medications, exposure to toxic chemicals, viral infections).

The investigator is responsible for recording data pertaining to thrombotic events with thrombocytopenia and/or bleeding and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

F 2 Tests that Should Be Considered if Thrombotic Events With Thrombocytopenia and/or Bleeding Are Suspected

The following tests should be considered, but not limited to:

1. Measurement of platelet levels, prothrombin time, activated partial thromboplastin time, D-dimer levels, and fibrinogen levels

2. Complete blood count, reticulocyte count, blood film, haptoglobins

3. Anti-platelet factor 4 antibodies

4. Anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies, rheumatoid factor, human leucocyte antigen B27, ADAMTS13 activity, anti-cardiolipin antibodies IgG + IgM, and anti-B2GPI antibodies IgG + IgM

5. Complement (eg, C3, C4, complement complex C5b-9, C5a), autoantibodies (eg, antinuclear IgG, anti-double stranded DNA IgG, anti-Smith IgG, anti-SSA IgG, anti-SSB IgG, anti-Jo1 IgG, anti-MPO IgG, anti-PR3 IgG, anti-glomerular basement membrane IgG)

6. Factor V Leiden, Factor II (prothrombin) variant

7. Platelet activation markers and functional assays (eg: sCD40L, soluble glycoproteins, degranulation markers [PF4, vWF, P-selectin, annexin V]), anti-PF4-plasma-serotonin release assay (if anti-PF4 ELISA positive)

8. Inflammatory markers: TNFa, IL-1, IL-4, IL-6, IL-10, IL-13

9. Cell adhesion molecules: VCAM, ICAM, E-selectin

10. Adenovirus serology

11. Additional viral serology: Cytomegalovirus (IgG and IgM), Ebstein-Barr virus (IgG and IgM), HIV, Parvo virus B19

12. COVID-19 testing, including PCR and serology

13. Calculation of an International Society of Thrombosis and Haemostatis score for Disseminated Intravascular Coagulation (derived from platelet levels, fibrinogen, and D-Dimer)

Appendix G Abbreviations

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ChAdOx1 MERS	Chimpanzee adenovirus Ox1 with MERS Spike antigen
ChAdOx1 nCoV-19	AZD1222 when initially developed by the University of Oxford
COVID-19	Coronavirus disease 2019
eCRF	Electronic case report form
e-Diary	Electronic diary
GMT	Geometric mean titre
ICF	Informed consent form
ICH/GCP	International Council for Harmonisation/Good Clinical Practice
IRB/IEC	Institutional Review Board/ Independent Ethics Committee
IRT	Interactive Response Technology
MAAEs	Medically attended adverse events
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
S	Spike
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome-coronavirus-2

Appendix H Protocol Amendment History

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	11 October2021
Amendment 2	29 July 2021
Amendment 1	2 June 2021
Version 1	14 May 2021

Amendment 3: 11 October 2021

The principal reason for this amendment was to remove the age cap and revise the primary and key secondary non-inferiority analyses to included historical controls due to difficulties in recruiting the previously unvaccinated cohort

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Synopsis Section 4.1 Section 9.4..3.1.1	Inserted information on use of historical controls	Required based on anticipated confounding between previously vaccinated and previously unvaccinated cohorts.	Substantial
Section 3.2, Table 6	Inserted exploratory objectives on exploration of humoral immune response with live virus neutralization assay and exploration of additional immune response based on emerging data	Omitted in error	Non-substantial
Section 4.1	Deleted age cap ensuring at least 25% enrolled participants were ≥65 years of age.	Due to enrollment difficulties in finding previously unvaccinated elderly	Substantial
Section 7.1	Inserted laboratory-confirmed SARS-CoV-2 infection as discontinuation of study intervention	To explicitly state this criterion (which is implicitly included in criteria 2) as a discontinuation of treatment criterion.	Non-substantial
Section 9.2	Section on immunogenicity comparisons and previous Table	Placed under Secondary Objective in error	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	16 and Table 17 were moved up under the Primary Objective sub-heading		
Section 9.4.3.1.1 Table 19 Table 20 Table 21 Table 22 Table 23	Analysis key (abbreviations) revised	Improvements in abbreviations for clarity	Non-substantial
Section 9.4..3.1.1	Description of statistical approach to be used with historical control comparisons added.	Inclusion of historical controls requires description of statistical methodology to be used.	Substantial

In addition, the protocol has been revised with minor rewordings, corrections, and clarifications which are all considered to be non-substantial.

Amendment 2: 15 July 2021

The principal reason for this amendment was to

1) add an additional interim analysis to evaluate immunogenicity in a subset of AZD1222 previously vaccinated subjects boosted with AZD1222 or AZD2816

2) revise Objectives/Endpoints from descriptive to comparative, with ranking of primary, key secondary, other secondary, and exploratory objectives

3) add non-inferiority margins to primary analysis and add additional participants to maintain power

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.1 Synopsis (Objectives and Endpoints)	Revised this section from primarily descriptive to primarily comparative. Comparative immunogenicity objectives created and ranked as primary, key secondary, other secondary.	Objectives of study changed from descriptive to comparative, testing for non-inferiority across treatment comparisons	Substantial
1.1 Synopsis (Number of Participants; Statistical Methods)	Overall size increased to 2590 participants	Adjustments made to maintain power with the added non-inferiority margins	Substantial
1.1 Synopsis (Statistical Methods)	An additional interim analysis added. Second interim analysis changed to include only the previously vaccinated with AZD1222 cohort.	Interim analysis plan was reviewed and revised.	Substantial
1.2 Schema	Figures updated with increased participant numbers	Adjustments made to maintain power with the added non-inferiority margins	Substantial
1.3 Schedule of Activities	Table 2: footnote clarification added Table 3: minor corrections	Clarification/Correction	Non-substantial
2.1 Study Rationale (and elsewhere in protocol)	Clarification on previous vaccination criteria	Clarification	Non-substantial
3 Objectives	Section completely rewritten. Divided into 2 sections: Previously unvaccinated and previously vaccinated. Immunogenicity objectives created for comparisons. Objectives ranked as primary, key secondary, other secondary, or exploratory.	Objectives of study changed to show non-inferiority across treatments.	Substantial
4.1 Overall design	Participant numbers increased	Adjustments made to maintain power with the added non-inferiority margins	Substantial
4.1 Overall design	Cap on age added	To ensure good representation across age groups	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
8.3.2	Removal of severity grade 5	Correction	Non-substantial
8.5.2.3 CCI [redacted]	Addition of information on number of patients sampled for CCI [redacted]	Clarification	Non-substantial
9.1 Statistical Hypotheses	Addition of statistical hypotheses	Include hypothesis being tested.	Substantial
9.2 Sample size determination	Confidence intervals for populations of 350 and 380 added to Table 14 and Table 15	Updated to include current populations of 350 and 380 participants	Non-substantial
9.2 Sample size determination	Power estimates for populations of 350 and 380 added to Table 17 and Table 18	Updated to include current populations of 350 and 380 participants	Non-substantial
9.4.1 General considerations	Details on the initial interim, second interim, and third interim analysis added	Include revised information on the analysis plan, including interim analyses	Substantial
9.4.3.1.1 Estimand framework for immunogenicity descriptions and comparisons	Objectives removed from descriptive analysis Table 23 and Table 24	Objectives of study changed from descriptive to comparative, showing non-inferiority across treatments	Substantial
9.4.3.1.1 Estimand framework for immunogenicity descriptions and comparisons	Section of Immunogenicity Comparisons added.	Objectives of study changed from descriptive to comparative, showing non-inferiority across treatments	Substantial
9.4.3.1.1 Estimand framework for immunogenicity descriptions and comparisons	Table 25 and Table 26 on immunogenicity comparisons revised, aligned with the revised objectives/endpoints.	Objectives of study changed from descriptive to comparative, showing non-inferiority across treatments	Substantial
9.4.4 Multiple Comparisons	Section added.	Objectives of study changed from descriptive to comparative, showing non-inferiority across treatments	Substantial

In addition, the protocol has been revised with minor corrections and clarifications.

Amendment 1: 2 June 2021

Version 1 of the protocol was amended prior to the commencement of the study (ie, prior to approval of the protocol by an ethics committee) based on feedback from internal and regulatory authority reviews. The most substantial changes were as follows:

- addition of 2 treatment arms: 1) AZD1222 as a single booster vaccination in participants previously vaccinated with an mRNA COVID-19 vaccine and 2) heterologous vaccination with AZD1222 plus AZD2816 in previously unvaccinated participants
- further definition of analysis sets
- addition of thrombotic events with thrombocytopenia as a discontinuation criteria

In addition, corrections and revisions to text to improve readability were made.

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SIGNATURE PAGE

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Clinical Study Protocol	
Study Intervention	AZD2816
Study Code	D7220C00001
Version	Amendment GBR-1
Date	3 June 2021

TITLE PAGE

A Phase II/III Partially Double-Blinded, Randomised, Multinational, Active-Controlled Study in Both Previously Vaccinated and Unvaccinated Adults Ages 30 and Above to Determine the Safety and Immunogenicity of AZD2816, a Vaccine for the Prevention of COVID-19 Caused by Variant Strains of SARS-CoV-2

Sponsor Name:	**AstraZeneca AB**
Legal Registered Address:	151 85 Södertälje, Sweden
Regulatory Agency Identifier Numbers:	EudraCT: 2021-002530-17

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: D7220C00001

Amendment Number: GBR-1

Study Intervention: AZD2816

Study Phase: II/III

Short Title: Phase II/III Study of AZD2816, a Vaccine for the Prevention of COVID-19 in Adults

Study Physician Name and Contact Information will be provided separately.

International Coordinating Investigator: Andrew J Pollard, FRCPCH PhD FMedSci
University of Oxford
Oxford, United Kingdom

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment GBR-1	3 June 2021
Amendment 1	1 June 2021
Version 1	14 May 2021

Amendment GBR-1: 2 June 2021

Prior to the commencement of the study (ie, prior to approval of the protocol by an ethics committee), the Amendment 1 version of the protocol was amended based on feedback from the UK's MHRA to restrict the study population to adults ages 30 and above and provide a risk:benefit statement for the inclusion of adults ages 30 to 39 (provided in Section 2.3.3)

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A phase II/III partially double-blinded, randomised, multinational, active-controlled study in both previously vaccinated and unvaccinated adults to determine the safety and immunogenicity of AZD2816, a vaccine for the prevention of COVID-19 caused by variant strains of SARS-CoV-2.

Short Title: Phase II/III study of AZD2816, a vaccine for the prevention of COVID-19 in adults.

Rationale: Recently, several variants of the SARS-CoV-2 virus with increased transmissibility have emerged, including B.1.1.7, first identified in the UK, P.1, first identified in Brazil, and B.1.351, first identified in South Africa. In an ongoing clinical trial of AZD1222 in South Africa, interim results failed to show protection against mild to moderate disease caused by the B.1.351 variant; protection against severe disease could not be determined as no severe cases were identified (Madhi et al 2021).

Based on available evidence about vaccine effectiveness and molecular epidemiology of emerging variants, B.1.351 is estimated to have a potential to escape vaccine-induced immunity. B.1.351 carries sequence mutations in common with other variants of concerns; immunity to B.1.351 therefore has the potential to provide some cross-immunity against other emerging strains. Development of candidate vaccines that include the B.1.351 S-protein variant is underway. AstraZeneca is developing AZD2816, a vaccine against the B.1.351 SARS-CoV-2 variant using the same ChAdOx1 platform and manufacturing processes used for AstraZeneca's currently available COVD-19 vaccine, AZD1222.

Objectives and Endpoints:

The purpose of this study is to demonstrate the safety and characterize the immunogenicity of AZD2816, AstraZeneca's candidate ChAdOx1 vector vaccine against SARS-CoV-2 variant strain B.1.351, when administered:

- As a single booster dose to SARS-CoV-2 seronegative individuals who previously received a 2-dose primary vaccination against SARS-CoV-2 with AZD1222 or an mRNA COVID-19 vaccine
- As a 2-dose primary homologous vaccination to SARS-CoV-2 seronegative individuals who are unvaccinated
- As the second dose of 2-dose primary heterologous vaccination (with AZD1222 as first dose) to SARS-CoV-2 seronegative individuals who are unvaccinated.

It is anticipated that the majority of the patients recruited in the United Kingdom will belong to the previously-vaccinated cohort that will receive a single booster dose of AZD2816 or AZD1222.

The following table lists the primary and secondary endpoints:

Objectives	Endpoints
Safety Objectives	
- Primary	
Previously vaccinated seronegative participants	
To characterize the safety and tolerability of 1 dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose
Unvaccinated seronegative participants	
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose
- Secondary	
Previously vaccinated seronegative participants	
To characterize the safety and tolerability of 1 dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of 1 dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of 1 dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of 1 dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination

To characterize the extended safety of 1 dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
Unvaccinated seronegative participants	
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of a heterologous 2-dose primary vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of a 2-dose primary heterologous vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
Immunogenicity objectives	
- Primary (descriptive)	
Previously vaccinated seronegative participants	

To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by 1 dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by 1 dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
Unvaccinated seronegative participants	
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in unvaccinated seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
- Secondary (descriptive)	
Previously vaccinated seronegative participants	
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by 1 dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by 1 dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
Unvaccinated seronegative participants	
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by a 2-dose primary vaccination with AZD1222 with a 4-week interval in unvaccinated seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by a heterologous 2-dose primary vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in unvaccinated seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by a 2-dose primary vaccination with AZD2816 with a 12-week interval in unvaccinated seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
- Secondary (comparative)	
Previously vaccinated seronegative participants receiving 1 dose versus unvaccinated seronegative participants receiving 2 doses	

To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD2816 in seronegative participants previously vaccinated with AZD1222 relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rates of SARS-CoV-2 specific antibody binding titres and neutralization titres
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rates of SARS-CoV-2 specific antibody binding titres and neutralization titres
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD1222 in seronegative participants previously vaccinated with AZD1222 relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rates of SARS-CoV-2 specific antibody binding titres and neutralization titres
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rates of SARS-CoV-2 specific antibody binding titres and neutralization titres
Previously vaccinated seronegative participants	
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD2816 relative to the response with 1 dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD2816 in seronegative participants previously vaccinated with an mRNA vaccine relative to the response with 1 dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD1222 relative to 1 dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rates of SARS-CoV-2 specific antibody binding titres and neutralization titres
Unvaccinated seronegative participants	

To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 variant strain elicited by a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week interval in previously unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 variant strain elicited by a 2-dose primary heterologous vaccination with AZD1222/AZD2816 with a 4-week dosing interval relative to the response elicited by a 2-dose primary homologous vaccination with AZD1222 with a 4-week interval in previously unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To evaluate the immune responses against the B.1.351 variant strain and the Wuhan-Hu-1 strain elicited by a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval relative to the response elicited by a 2-dose primary vaccination with AZD2816 with a 4-week interval in previously unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres

SAEs: serious adverse events; MAAEs: medically attended adverse events; AESIs: adverse events of special interest.

[a] At least a 4-fold increase in geometric mean titre from baseline

Overall Design: This is a phase II/III, multinational, randomised, partially double-blind, controlled study in both previously vaccinated and unvaccinated participants.

Disclosure Statement: This is a parallel-group preventive study with 8 treatment arms.

Number of Participants: Approximately 2250 SARS-CoV-2 nucleocapsid seronegative participants will be assigned to study intervention to support the primary and secondary objectives of this study. In addition, participants that are SARS-Cov-2 nucleocapsid seropositive at screening will be enrolled and assigned to study intervention for an exploratory analysis, with a cap of 10% of the seronegative population (ie, approximately 225 total participants).

Intervention Groups and Duration: Previously vaccinated individuals will receive 1 dose of AZD1222 or AZD2816 on Day 1. Previously unvaccinated participants will receive one of the following 2-dose vaccinations:

- 1 dose of AZD2816 on Day 1 and on Day 29
- 1 dose of AZD1222 on Day1 and on Day 29
- 1 dose of AZD1222 on Day 1 and 1 dose of AZD2816 on Day 29
- 1 dose of AZD2816 on Day 1 and on Day 85.

Participants will be followed up for safety for 180 days after last study vaccine administration.

Data Monitoring Committee: A Data Safety Monitoring Board will provide oversight to ensure safe and ethical conduct of the study.

Statistical Methods:

Sample sizes of 300 seronegative participants per group (or 150 for the AZD2816 primary vaccination with a 12-week dosing interval group) are deemed appropriate based upon available immunogenicity data from previous clinical studies with AZD1222 for the primary and secondary objectives of this study.

The safety analysis set for adverse events consists of all participants who have received at least one dose of study intervention. The immunogenicity analysis set includes all participants in the safety analysis set who have no protocol deviations or intercurrent events judged to have the potential to interfere with the generation or interpretation of an immune response.

An interim analysis will be performed when all previously vaccinated participants have completed their Day 29 visit. A primary analysis will be performed on data from 28 days after the second dose of the 4-week dosing intervals to support assessment of these 2-dose primary vaccinations. A secondary analysis will be performed on data from 28 days after the second dose of the 12-week dosing interval to support assessment of this 2-dose primary vaccination. The final analysis will be performed on data from 6 months follow-up after participant's vaccination.

1.2 Schema

Figure 1 Study Design for Previously Vaccinated Seronegative/Seropositive Participants

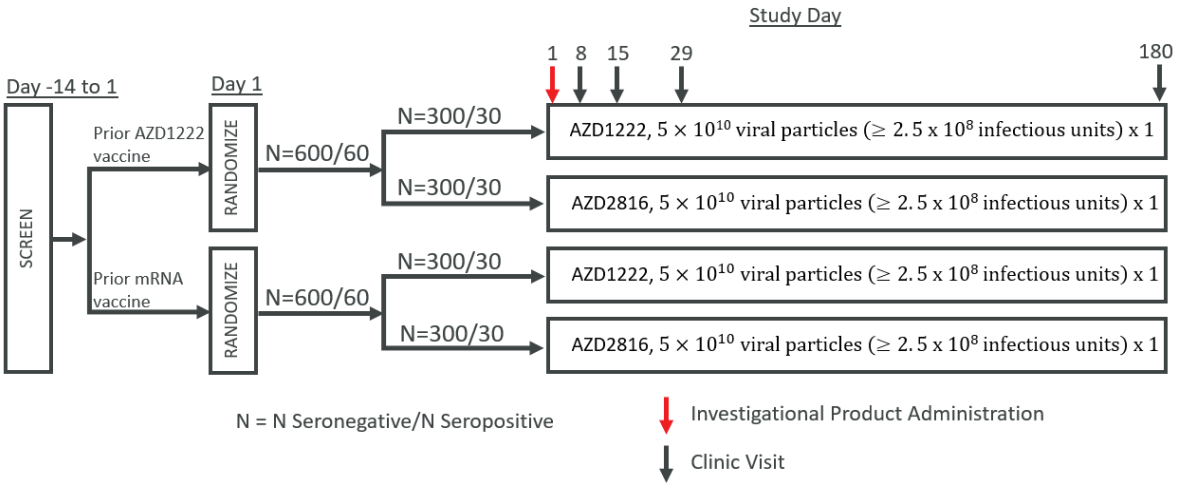
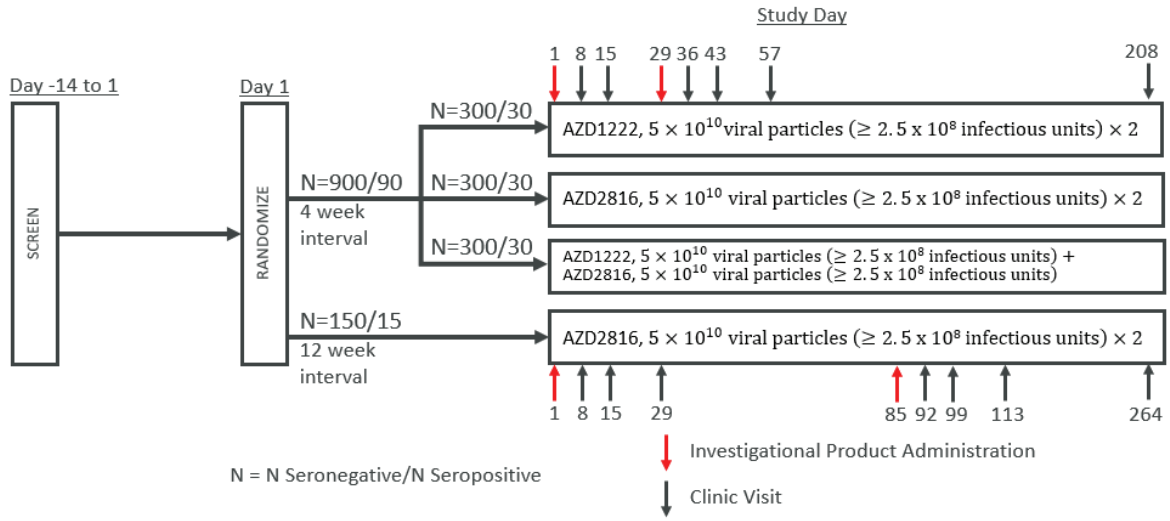


Figure 2 Study Design for Unvaccinated Seronegative/Seropositive Participants



Note: In addition to the approximately 2250 seronegative participants enrolled to support the primary/secondary objectives, seropositive participants will also be enrolled in the study to support exploratory objectives in this population, with a cap of 10% of the planned seronegative participants (ie, a maximum of 225 seropositive participants, bringing total enrollment to 2475).

1.3 Schedule of Activities

Table 1 Schedule of Activities: Screening

Procedure	Day -14 to Day 1	See Section
Informed consent	X	5.1, Appendix A 3
Demography	X	-
Medical and surgical history	X	-
Prior and concomitant medications	X	6.5
Complete physical examination, including height and weight	X	8.2.1
Vital signs	X	8.2.2
Urine pregnancy test (for women of childbearing potential only)	X	8.2.3
Clinical safety laboratory assessments	X	8.2.3
Assessment of serious adverse events	X	8.3, Appendix B
Blood sample for SARS-CoV-2 antibody testing (lateral flow test)	X	8.5.2
Verify eligibility criteria	X	5.1, 5.2

Note: Screening activities can occur at same visit as initial vaccination with investigational product (ie, Visit 1 in Table 2, Table 3, and Table 4).

Table 2 Schedule of Activities: Treatment/Follow-up Period for Participants Previously Vaccinated with 2 Doses of AZD1222 or an mRNA Vaccine

Procedure	Treatment and Follow-up Period					Section
Day	**1**	**8**	**15**	**29**	**180**	
Window (days)	**-**	**±2**	**±2**	**±3**	**±14**	
Medical and surgical history	X	-	-	-	-	-
Urine pregnancy test (women of childbearing potential)	X	-	-	-	-	8.2.3
Concomitant medications/vaccinations	X	X	X	X	X	6.5
Verify eligibility criteria	X	-	-	-	-	5.1, 5.2
Monitoring of COVID-19	X	X	X	X	X	8.3.8
Vaccine administration (after screening activities, the activities listed above, and the pre-dose sampling activities listed below)	X	-	-	-	-	6.1.1
Immunological assessments						
Serum sample to assess SARS-CoV-2 serology/neutralising antibodies	X (pre-dose)	-	X	X	X	8.5.2
Serum sample to assess additional immunogenicity	X (pre-dose)	-	X	X	X	8.5.2
Blood sample to assess B-cell and T-cell responses in a sub-group of participants	X (pre-dose)	-	X	X	X	8.5.2.3
Blood sample for B-cell and T-cell response sequencing in a sub-group of participants	X (pre-dose)	-	X	X	X	8.5.2.3
Safety assessments						
Targeted physical examination	X	-	-	-	-	8.2.1
Vital signs	X	X	X	X	X	8.2.2
e-Diary provided with training	X	-	-	-	-	8.3.7
e-Diary collected	-	X	-	-	-	8.3.7
Unsolicited AEs	X (post-dose)	X	X	X	-	8.3
MAAEs, SAEs, and AESIs	X[a]	X	X	X	X	8.3.8, 8.3.8
Clinical safety laboratory assessments	X (pre-dose)	X	-	X	X	8.2.3

[a] Only SAEs pre-dose

AE: adverse event; AESI: adverse event of special interest; MAAE: medically-attended adverse event; SAE: serious adverse event

Table 3 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 4-Week Dosing Interval

Procedure	Treatment and Follow-up Period								Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	
Day	**1**	**8**	**15**	**29**	**V4+7**	**V4+14**	**V4+28**	**V4+180**	
Window (days)	**-**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
Medical and surgical history	X	-	-	-	-	-	-	-	-
Urine pregnancy test (women of childbearing potential)	X	-	-	X	-	-	-	-	8.2.3
Concomitant medications/vaccinations	X	X	X	X	X	X	X	X	6.5
Verify eligibility criteria	X	-	-	-	-	-	-	-	5.1, 5.2
Monitoring of COVID-19	X	X	X	X	X	X	X	X	8.3.8
Vaccine administration (after screening activities, the activities listed above, and the pre-dose sampling activities listed below)	X	-	-	X	-	-	-	-	6.1.1
Immunogenicity assessments									
Serum sample for SARS-CoV-2 serology/neutralising antibodies	X (pre-dose)	-	X	X (pre-dose)	-	X	X	X	8.5.2
Serum sample for additional immunogenicity	X (pre-dose)	-	X	X (pre-dose)	-	X	X	X	8.5.2
Blood sample to assess B-cell and T-cell responses in a sub-group of participants	X (pre-dose)	-	X	X (pre-dose)	-	-	X	X	8.5.2.3
Blood sample for B-cell and T-cell response sequencing in a sub-group of participants	X (pre-dose)	-	X	X (pre-dose)	-	-	X	X	8.5.2.3
Safety assessments									
Targeted physical examination	X	-	-	X	-	-	-	-	8.2.1
Vital signs	X	X	X	X	X	X	X	X	8.2.2
e-Diary provided with training	X	-	-	X	-	-	-		8.3.7

Table 3 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 4-Week Dosing Interval

Procedure	**Treatment and Follow-up Period**								**Section**
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	
Day	**1**	**8**	**15**	**29**	**V4+7**	**V4+14**	**V4+28**	**V4+180**	
Window (days)	**-**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
e-Diary collected	-	X	-	-	X	-	-		8.3.7
Unsolicited AEs	X (post-dose)	X	X	X	-	X	X	-	8.3
MAAEs, SAEs, and AESIs	X[a]	X	X	X	-	X	X	X	8.3.8
Clinical safety laboratory assessments	X (pre-dose)	X	-	X (pre-dose)	X	-	X	X	8.2.3

[a] Only SAEs pre-dose

AE: adverse event; AESI: adverse event of special interest; MAAE: medically-attended adverse event; SAE: serious adverse event

Table 4 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 12-Week Dosing Interval

Procedure	Treatment and Follow-up Period									Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	
Day	**1**	**8**	**15**	**29**	**85**	**V5+7**	**V5+14**	**V5+28**	**V5+180**	
Window (days)	**-**	**±2**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
Medical and surgical history	X	-	-	-	-	-	-	-	-	-
Urine pregnancy test (women of childbearing potential)	X	-	-	-	X	-	-	-	-	8.2.3
Concomitant medications/vaccinations	X	X	X	X	X	X	X	X	X	6.5
Verify eligibility criteria	X	-	-	-	-	-	-	-	-	5.1, 5.2
Monitoring of COVID-19	X	X	X	X	X	X	X	X	X	8.3.8
Vaccine administration (after screening activities, the activities listed above, and the pre-dose sampling activities listed below)	X	-	-	-	X	-	-	-	-	6.1.1
Immunogenicity assessments										
Serum sample to assess SARS-CoV-2 serology/neutralising antibodies	X (pre-dose)	-	X	X	X (pre-dose)	-	X	X	X	8.5.2
Serum sample to assess additional immunogenicity	X (pre-dose)	-	X	X	X (pre-dose)	-	X	X	X	8.5.2
Blood sample to assess B-cell and T-cell responses in a sub-group of participants	X (pre-dose)	-	X	X	X (pre-dose)	-	-	X	X	8.5.2.3
Blood sample for B-cell and T-cell response sequencing in a sub-group of participants	X (pre-dose)	-	X	X	X (pre-dose)	-	-	X	X	8.5.2.3
Safety assessments										
Targeted physical examination	X	-	-	-	X	-	-	-	-	8.2.1
Vital signs	X	X	X	X	X	X	X	X	X	8.2.2
e-Diary provided with training	X	-	-	-	X	-	-	-		8.3.7

Table 4 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 12-Week Dosing Interval

Procedure	Treatment and Follow-up Period									Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	
Day	**1**	**8**	**15**	**29**	**85**	**V5+7**	**V5+14**	**V5+28**	**V5+180**	
Window (days)	**-**	**±2**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
e-Diary collected	-	X	-	-	-	X	-	-	-	8.3.7
Unsolicited AEs	X (post-dose)	X	X	X	X	X	X	X	-	8.3
MAAEs, SAEs, and AESIs	X[a]	X	X	X	X	X	X	X	X	8.3.8, 8.3.8
Clinical safety laboratory assessments	X (pre-dose)	X	-	X	X (pre-dose)	X	-	X	X	8.2.3

[a] Only SAEs pre-dose

AE: adverse event; AESI: adverse event of special interest; MAAE: medically-attended adverse event; SAE: serious adverse event

2 INTRODUCTION

AZD2816 is being developed for the prevention of COVID-19. It is a modified version of the current AstraZeneca SARS-CoV-2 vaccine (referred to as AZD1222 in clinical documentation) that has been modified to also provide immunity against the newly emerging SARS-CoV-2 variant strain B.1.351. Like AZD1222, AZD2816 is a recombinant replication-defective chimpanzee adenovirus vector (ChAdOx1) expressing the SARS-CoV-2 S surface glycoprotein driven by the human cytomegalovirus major immediate early promoter that includes intron A with a human tissue plasminogen activator leader sequence at the N terminus. AZD2816 differs from AZD1222 in that the S glycoprotein gene sequence used is from the B.1.351 variant strain instead of the original Wuhan-Hu-1 variant.

2.1 Study Rationale

The aim of the study is to assess the safety and immunogenicity of AZD2816 for prevention of COVID-19 as both a 2-dose primary vaccination in previously unvaccinated participants and a 1-dose booster vaccination in participants previously vaccinated against the original Wuhan-Hu-1 strain of SARS-CoV-2. A safe and effective vaccine for COVID-19 prevention, including against the B.1.351 variant, would have significant global public health impact.

The study will also investigate the safety and immunogenicity of 1) a heterologous 2-dose vaccination with AZD1222 as first dose and AZD2816 as the second dose and 2) a single dose of AZD1222 as a booster vaccination in participants that have been previously vaccinated with an mRNA COVID-19 vaccine.

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, which was named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (Zhou et al 2020). The disease these patients contracted was subsequently named Coronavirus Disease 2019 (COVID-19). The World Health Organization declared the novel coronavirus a pandemic on 11 March 2020. The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has resulted in significant global morbidity and mortality as well as major disruption to healthcare systems. Measures to change the course of the pandemic have included the accelerated development vaccines against the original Wuhan-Hu-1 strain.

Coronaviruses are spherical, enveloped viruses with positive-sense single-stranded RNA genomes. SARS-CoV-2 belongs to the phylogenetic lineage B of the genus *Betacoronavirus*, and it is the seventh corona virus known to cause human infections and the third known to cause severe disease after SARS-CoV and MERS-CoV. One fourth of the viral genome is responsible for coding structural proteins, such as the S glycoprotein, envelope, membrane,

and nucleocapsid proteins. Envelope, membrane, and nucleocapsid proteins are mainly responsible for virion assembly while the S protein is involved in cellular receptor binding, mediating fusion of virus and cell membranes and virus entry into host cells during infection. The SARS-CoV-2 spike (S) glycoprotein is a type I trimeric, transmembrane protein that is located at the surface of the viral envelope forming spike-shaped protrusions. The S protein's subunits are responsible for cellular receptor angiotensin-converting enzyme 2 binding via the receptor binding domain and subsequent fusion of virus and cell membranes, thereby mediating the entry of SARS-CoV-2 into the target cells. The S protein has an essential role in virus entry and determines tissue and cell tropism, as well as host range. The roles of the S-protein in receptor binding and membrane fusion have made it a desirable target for vaccine and antiviral development. The AstraZeneca vaccine AZD1222 expresses a codon-optimized coding sequence for S protein from the SARS-CoV-2 genome sequence accession MN908947 (ie, the Wuhan-Hu-1 isolate).

To date, 5 vaccines that rely upon the expression of the SARS CoV-2 S glycoprotein to stimulate/prime a protective immune response against the virus have demonstrated safety and efficacy in phase III clinical trials. Four of these, AZD1222 (also referred to as ChAdOx1 nCoV-19, a recombinant replication-defective chimpanzee adenoviral vectored), BNT162b2 (Pfizer-BioNTech, mRNA), mRNA-1273 (Moderna, mRNA), and Ad26.COV2-S (Janssen, adenovirus serotype 26 vectored) have received Emergency Use Authorization or Conditional Marketing Approval in the United States and/or the European Union, and elsewhere, and NVX-CoV2373 (Novavax; recombinant 86 protein) has also shown efficacy and is likely to be in use in the near future. These vaccines have been designed based upon the initial reported genetic sequence of the S protein from Wuhan in January 2020 (Lu et al 2020).

The immunogenicity and efficacy of AZD1222 has been shown in clinical trials (Ramasamy et al 2020, Voysey et al 2021a, Voysey et al 2021b). Immunogenicity data indicate that a single dose of AZD1222 elicits both humoral and cellular immunogenicity responses and that antibody responses are boosted after a second dose. In a pooled analysis of the 4 studies conducted in the United Kingdom, Brazil, and South Africa (DCO2 database lock 07 December 2020), the vaccine was highly immunogenic; seroresponse of S binding antibody was > 98% after a single dose of AZD1222. Seroresponse of live neutralising antibody was 82.4% after 1 dose, which rose to 99.4% after a second dose. Efficacy analyses of the pooled DCO2 data demonstrated effective protection of AZD1222 against COVID-19 with a vaccine efficacy of 66.73% (95.84% CI: 57.41%, 74.01%) ($p < 0.001$) from 15 days after the second dose in seronegative participants receiving 2 doses. The DCO2 data also demonstrated that the standard dose of AZD1222 (5×10^{10} viral particles) provides complete protection against COVID-19 hospital admission ≥ 22 days after the first dose in the seronegative analysis set (0 versus 14 cases in the control group, 2 of which were severe, including one with a fatal outcome). Vaccine efficacy was similar in participants with pre-existing comorbidities, being those at greatest risk of severe outcomes of COVID-19, compared to that in the general

population. Recently available primary analysis data from a Phase III study performed in the United States and Latin America showed primary endpoint vaccine efficacy of 76% (95% CI: 67.60%, 82.22%; p-value < 0.001).

A sharp rise in COVID-19 cases was reported in late 2020, which was attributed to the emergence of new SARS-CoV-2 variant strains: B.1.1.7 in the United Kingdom, B.1.351 in South Africa, and P.1 in Brazil. These variant strains carry a number mutations in the S protein sequence: 9 amino acids in B.1.1.7, 10 amino acids in B.1.351, and 12 amino acids in P.1 compared with the Wuhan-Hu-1 sequence. These mutations may result in an increase of transmissibility and/or reduced vaccine effectiveness. Variant B.1.351 was first identified in South Africa in October 2020. Its attributes include approximately 50% increased transmission and moderate impact of neutralization by monoclonal antibody therapeutics, convalescent plasma and vaccine sera. In vitro neutralization assays suggest that the B.1.351 lineage viruses may be the most antigenically distinct from the original Wuhan-like strains (Zhou et al 2021). In addition, evidence suggests that AZD1222 may afford diminished protection against mild-moderate COVID-19 disease arising from the B.1.351 variant which is also antigenically the most different from the Wuhan-Hu-1 virus (Madhi et al 2021).

The development of candidate vaccines that would be effective against the B.1.351 variant strain is underway. AZD2816 is being developed as an updated ChADOx-nCOv19 vaccine designed to provide protective immunity against the newly arising B.1.351 variant strain, using the same ChAdOx1 platform and manufacturing processes used for AstraZeneca's currently approved COVID-19 vaccine, AZD1222. The purpose of this Phase II/III, multinational, randomised, partially double-blind, active-controlled study is to demonstrate the safety and characterize the immunogenicity of AZD2816, AstraZeneca's candidate ChAdOx1 vector vaccine against B.1.351, when administered:

- As a single booster dose to SARS-CoV-2 seronegative individuals who have previously received a 2-dose primary vaccination series (AZD1222 or an mRNA vaccine) against SARS-CoV-2
- As a 2-dose homologous primary vaccination to SARS-CoV-2 seronegative individuals who have not been vaccinated previously.

It is anticipated that the majority of the patients recruited in the United Kingdom will belong to the previously-vaccinated cohort that will receive a single booster dose.

The immunogenicity of a 2-dose primary heterologous vaccination (with AZD1222 as first dose and AZD2816 as second dose) to SARS-CoV-2 seronegative individuals who are unvaccinated and a single booster dose of AZD1222 to SARS-CoV-2 seronegative individuals who have previously received a 2-dose primary mRNA vaccination series will also be investigated.

SARS-CoV-2 seropositive participants will be enrolled in separate cohorts to support a parallel exploratory analysis in these participants.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD1222 and AZD2816 is provided in the respective Investigator's Brochures.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of AZD2816 and AZD1222 can be found in the respective Investigator's Brochures.

2.3.1 Risk Assessment

AZD2816 has been developed using the same vaccine vector, ChAdOx1, as AZD1222 and only differs in the sequence for SARS-CoV-2 S glycoprotein that is inserted in the vector. The anticipated safety profile of AZD2816 is the same as the observed safety profile of AZD1222. Risks associated with AZD2816 are thus the same as the risks associated with AZD1222, and no additional risks are anticipated due to the change in the targeted sequence.

A number of essentially mild and moderate adverse reactions to AZD1222 have been identified and resemble reactions frequently observed after many vaccines. Based on pooled clinical data from studies with AZD1222, the most commonly expected local solicited AEs for participants in this study are vaccination site pain and tenderness. The most commonly expected systemic solicited AEs are fatigue, headache, and malaise. The majority of reported events have been 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.

Post-authorisation hypersensitivity reactions, including anaphylaxis and angioedema, have occurred following administration of AZD1222 and are considered an identified risk.

A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with COVID-19 Vaccine (ie, AZD1222) during post-authorisation use. No events have been observed in the AZD1222 clinical development programme. Thrombosis in combination with thrombocytopenia is thus considered to be an important identified risk. This includes cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. Considering the frequency of this rare event and the size of this study, the risk for participants in this trial is considered to be low. The protocol includes exclusion criteria and instructions for heightened vigilance and thorough investigations for suspected cases to mitigate against further the risk for these rare event.

Important potential risks are 1) neurologic events and potential immune-mediated neurologic conditions and 2) vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease.

2.3.2 Benefit Assessment

All participants will receive active treatment: either AZD1222, which has been shown to be effective in providing protection against SARS-CoV-2, or AZD2816, which as a modified form of AZD1222 designed to be effective against the emergent B.1.351 variant strain and may also provide participants with protection. The information gained from this study will inform development decisions with regard to the efficacy of AZD2816 as both a primary 2-dose vaccination in participants that have not been previously vaccinated and a 1-dose booster vaccination in participants previously vaccinated against SARS-CoV-2.

2.3.3 Benefit: Risk Assessment for Inclusion of Adults from 30 to 39 Years of Age

There have been reports of very rare adverse events of concurrent thrombosis and thrombocytopenia following vaccination with the first dose of AstraZeneca CoV-19 vaccine (AZD1222). There have been no safety concerns identified for thrombosis/thrombocytopenia associated with the second dose of the AstraZeneca (AZD1222) vaccine. Up to 19 May 2021, the MHRA has received reports of 332 cases of major thromboembolic events with concurrent thrombocytopenia in the United Kingdom following vaccination with COVID-19 Vaccine AstraZeneca. The estimated number of first doses of COVID-19 Vaccine AstraZeneca administered was 24.2 million, and the estimated number of second doses was 10.7 million.

Any risk for serious thromboembolic events with thrombocytopenia is expected to be similar for AZD1222 and AZD2816 due to the similarity of the investigational products.

In the context of this extremely rare adverse event, current advice from the United Kingdom's Joint Committee on Vaccination and Immunization (JCVI) recommends that unvaccinated adults aged 30 to 39 years who are not in a clinical priority group at higher risk of severe COVID-19 disease should be preferentially offered an alternative to AZD1222 where possible and only where no substantial delay or barrier in access to vaccination would arise (JCVI 2021). The recommendations are not a contra-indication in this age group but a public vaccination policy recommendation in the context of a current low incidence of disease, the availability of alternative vaccines, and current speed and uptake of the vaccination programme overall in the UK. The recommendations further advise that AZD1222 can be used in the age group 30-39 if these factors deteriorate, stating that if other vaccines are not available "the benefits of receiving the AstraZeneca (AZD1222) vaccine outweigh the risks".

The participants of the proposed study differ from the general public in that they are carefully selected, with exclusion of individuals with a wide range of risk factors for thrombosis/thrombocytopenia, to minimize this risk. The study also includes careful monitoring both pre-treatment and post-treatment to detect risk for thrombotic events with thrombocytopenia and promptly identify safety concerns at the individual participant level. The protocol and training for the investigators urges increased vigilance for these events of thrombosis with thrombocytopenia. Furthermore, Appendix F provides guidance on identifying, treating, and assessing these very rare events. The risk of these events occurring is disclosed in the Participant Information Sheet and Informed Consent Form. Furthermore, participants are advised to be alert for the following side effects in the 28 days after vaccination: severe/unusual headache, new or unexplained bruising/bleeding, shortness of breath, chest pain, leg swelling, persistent abdominal pain. The exclusion of individuals with a wide range of risk factors for thrombosis with thrombocytopenia and measures included in the study to ensure early detection of these events mitigates the risk for these rare events.

With regard to benefit, all patients enrolled in the study will receive active treatment, either with the approved AZD1222, which has a good safety profile and high efficacy in adults ages 18 and over, including protection against severe disease, or the experimental but closely related AZD2816, which is expected to have a similar safety profile with the potential to have broader efficacy than AZD1222, including against the emergent B.1.351 variant. Furthermore, the inclusion of these patients in the trial is important to investigate safety and immunogenicity of AZD2816, as both a primary vaccination and a booster vaccination, across the age groups for which it may be administered in clinical practice.

To summarise, the risk of serious harm due to vaccine-induced thrombotic thrombocytopenia is known to be small. As of 19 May 2021, the MHRA's estimate of the overall incidence after first or unknown doses is 1.3 per 100,000 doses. Thus, the risk of one of these events occurring in the sub-group of participants 30 to 39 year of age from a study population of around 2000 patients is extremely low. This risk is appropriately mitigated in the study protocol to the extent that the risk-benefit of patients 30 to 39 years of age participating in this study is considered to be small, acceptable, and justified by the potential public health benefits of the study.

2.3.4 Overall Benefit: Risk Conclusion

For the safety of participants, the protocol has incorporated various risk mitigation measures including appropriate inclusion and exclusion criteria and close monitoring of participants to minimize known and potential risks.

An independent Data Safety Monitoring Board will provide study oversight, evaluating cumulative safety and other clinical data at regular intervals.

Taking these measures into account, the potential risks identified in association with the administration of AZD2816 and AZD1222 are justified by the anticipated benefit that may be afforded to participants for the prevention of COVID-19.

3 OBJECTIVES AND ENDPOINTS

Table 5 describes the objectives and endpoints of this study. Co-primary objectives were chosen to characterise the safety and humoral immune response of AZD2816 and AZD1222 against selected strains when administered as a primary 2-dose homologous vaccination series or a primary 2-dose heterologous vaccination series in previously unvaccinated participants or as a single booster vaccination to participants who have been previously vaccinated with 2 doses of AZD1222 or an approved mRNA COVID-19 vaccine. All primary and secondary objectives/endpoints are descriptive; there will be no hypothesis testing in this study. Estimates of neutralizing antibody geometric mean titre ratio and difference in seroresponse rates (and 95% confidence interval) will be generated as secondary analyses to support the assessment of relative immune responses between selected study groups.

Table 5 Study Objectives and Endpoints

Objectives	Endpoints
Safety Objectives	
- Primary	
Previously vaccinated seronegative participants	
To characterize the safety and tolerability of 1 dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose
Unvaccinated seronegative participants	
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose
- Secondary	
Previously vaccinated seronegative participants	
To characterize the safety and tolerability of 1 dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose

To characterize the safety and tolerability of 1 dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of 1 dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of 1 dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
Unvaccinated seronegative participants	
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of a heterologous primary vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination

To characterize the extended safety and tolerability of a heterologous primary vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
Immunogenicity objectives	
- Primary (descriptive)	
Previously vaccinated seronegative participants	
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by 1 dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by 1 dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
Unvaccinated seronegative participants	
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in unvaccinated seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
- Secondary (descriptive)	
Previously vaccinated seronegative participants	
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by 1 dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by 1 dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
Unvaccinated seronegative participants	

To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by a 2-dose primary vaccination with AZD1222 with a 4-week interval in unvaccinated seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by a heterologous dose primary vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in unvaccinated seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To describe the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by a 2-dose primary vaccination with AZD2816 with a 12-week interval in unvaccinated seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre) • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
- **Secondary (comparative)**	
Previously vaccinated seronegative participants receiving 1 dose versus unvaccinated seronegative participants receiving 2 doses	
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD2816 in seronegative participants previously vaccinated with AZD1222 relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rates of SARS-CoV-2 specific antibody binding titres and neutralization titres
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rates of SARS-CoV-2 specific antibody binding titres and neutralization titres
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD1222 in seronegative participants previously vaccinated with AZD1222 relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rates of SARS-CoV-2 specific antibody binding titres and neutralization titres
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rates of SARS-CoV-2 specific antibody binding titres and neutralization titres

Previously vaccinated seronegative participants	
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD2816 relative to the response with 1 dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD2816 in seronegative participants previously vaccinated with an mRNA vaccine relative to the response with 1 dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by 1 dose of AZD1222 relative to 1 dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rates of SARS-CoV-2 specific antibody binding titres and neutralization titres
Unvaccinated seronegative participants	
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by a primary 2-dose vaccination with AZD2816 with a 4-week dosing interval relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week interval in previously unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by a heterologous dose primary vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week interval in previously unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
To evaluate the immune responses against the B.1.351 and Wuhan-Hu-1 strains elicited by a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval relative to the response elicited by a 2-dose primary vaccination with AZD2816 with a 4-week interval in previously unvaccinated seronegative participants	• Ratio of the magnitudes of SARS-CoV-2 specific antibody binding and neutralization titres (geometric mean titre ratio) • Difference in seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres
Exploratory	
Previously vaccinated and unvaccinated participants (seronegative and seropositive at screening)	

To explore antibody response to selected SARS-CoV-2 variants of interest/variants of concern following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in a sub-group of seronegative participants	• Magnitude of SARS-CoV-2 specific antibody binding titres (geometric mean titre) for selected variants of concern/variants of interest • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding titres for selected variants of concern/variants of interest
To explore B-cell and T-cell responses following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in a sub-group of seronegative participants	• Intracellular cytokine staining and flow cytometry for T-cell responses over time • Quantification of (IFN-γ) ELISpot responses to SARS-CoV-2 B.1.351 or Wuhan-Hu-1 S protein from day of dosing baseline over time • Breadth and depth of peripheral blood B-cell and T-cell repertoire over time through immunosequencing
To monitor the incidence of SARS-CoV-2 infection following 1 dose of AZD2816 or 1 dose of AZD1222 in previously vaccinated seronegative participants	• The incidence of SARS-CoV-2 infection defined by the presence of nucleocapsid antibodies occurring post-dose of study intervention
To monitor the incidence of COVID-19 following 1 dose of AZD2816 or AZD1222 in previously vaccinated seronegative participants	• Incidence of COVID-19, defined as SARS-CoV-2 RT-PCR-positive symptomatic illness.
To monitor the incidence of SARS-CoV-2 infection following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in unvaccinated seronegative participants	• The incidence of SARS-CoV-2 infection defined by the presence of nucleocapsid antibodies occurring post-second dose of study intervention
To monitor the incidence of COVID-19 following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in unvaccinated seronegative participants	• Incidence of COVID-19, defined as SARS-CoV-2 RT-PCR-positive symptomatic illness.
To explore the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in sub-groups of seronegative and seropositive participants	• Magnitude of SARS-CoV-2 neutralization titres (geometric mean titre) as determined by a live virus neutralization assay • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres as determined by a live virus neutralization assay
To explore anti-vector responses to the ChAdOx-1 adenovirus vector following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in sub-groups of seronegative and seropositive participants	• Magnitude of ChAdOx1 nAb titres (geometric mean titre) • Seroresponse rate of ChAdOx1 neutralizing antibody titres • Pairwise correlations between anti-S, pseudo-neutralization, and ChAdOx1 neutralizing antibody titres, 1 month after both Dose 1 and Dose 2
To explore additional immune responses following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in sub-groups of seronegative and seropositive participants	• Other exploratory assays for humoral and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data

MAAEs: medically attended adverse events; SAEs: serious adverse events; AESIs: adverse events of special interest

[a] Seroresponse: An at least 4-fold increase in geometric mean titre from baseline.

4 DESIGN

4.1 Overall Design

This is a multi-country Phase II/III study to evaluate the safety and immunogenicity of AZD2816 as single-dose vaccination in previously vaccinated adult participants and as a 2-dose primary vaccination in previously unvaccinated adult participants.

A total of approximately 2250 SARS-CoV-2 nucleocapsid seronegative participants that have been screened and judged to be eligible for the study will be enrolled across these 2 populations with the goal of 1200 previously vaccinated participants receiving single-dose vaccination and 1050 unvaccinated participants receiving 2-dose primary vaccination. In addition, seropositive participants will be enrolled (with a cap of 10% of the seronegative population or 225 participants) to support exploratory analysis is these participants.

The enrollment and randomization strategy is intended to minimize group differences in terms of age, gender and the presence of comorbidities.

In both the single-dose booster treatment regimen and the 2-dose primary vaccination treatment regimen, participants will receive study intervention consisting of intramuscular administration of either AZD1222 (5×10^{10} viral particles) or AZD2816 (5×10^{10} viral particles).

Approximately 600 seronegative participants previously vaccinated with AZD1222 will be randomised 1:1 to receive a single intramuscular dose of either AZD1222 or AZD2816 in a double-blinded fashion.

Approximately 600 seronegative participants previously vaccinated with an approved mRNA based vaccination will be randomised 1:1 to receive a single intramuscular dose of AZD2816 or AZD1222 in a double-blinded fashion.

It is anticipated that the majority of the patients recruited in the United Kingdom will belong to 1 of the 2 above previously-vaccinated groups.

Approximately 1050 seronegative, previously unvaccinated participants will be randomised 2:2:2:1 to receive a 2-dose primary vaccination of the following:

- 2 doses of AZD1222 with a 4-week dosing interval
- 2 doses of AZD2816 with a 4-week dosing interval
- 1 dose of AZD1222 followed by 1 dose of AZD2816 with a 4-week dosing interval
- 2 doses of AZD2816 with a 12-week dosing interval.

The 3 treatments with a 4-week dosing interval will be double-blinded while the treatment with the 12-week interval will be open-label due to the difference in dosing interval.

In addition, a smaller population seropositive participants (approximately 10% of the seronegative population), will be randomised to treatment in a similar manner as above.

Immunogenicity (ie, anti-Wuhan-Hu-1 and anti-B.1.351 immune responses including S-binding antibody titres and neutralizing antibody levels [pseudo-neutralization]) will be assessed in serum samples collected pre-dose on the day of each vaccination (baseline levels before vaccination), 14 and 28 days after each vaccination, and 180 days after the last vaccination.

All participants will be given a thermometer, tape measure or ruler, and a proprietary e-diary application designed for use with a smart device with instructions for use. All participants will be asked to report on solicited signs and symptoms for 7 days following vaccination (Days 1-8 for all participants and Days 29-36 for the 4-week dosing interval and Days 85-92 for the 12-week dosing interval). An e-diary will be used to collect information on the timing and severity of the solicited signs and symptoms.

Follow-up visits will take place as per the schedule of assessment within respective windows. All participants will be assessed for local and systemic AE, physical examination, review of e-diaries at these time points as detailed in the schedule of assessment. Blood will also be taken for safety assessments and immunology purposes.

All study participants will be followed for safety for 180 days after administration of their last vaccination dose. In every participant, solicited local and systemic events will be reported for up to 7 days after each dose, all unsolicited AEs will be reported for up to 28 days after each dose, and SAEs and AEs of special interest will be evaluated through study completion (up to 180 days after the last study vaccination).

An independent COVID-19 Vaccine Data Safety Monitoring Board will provide oversight, to ensure safe and ethical conduct of the study.

4.1.1 COVID-19 Assessments

Occurrence of COVID-19 in the trial will be reported as safety events, including monitoring of the potential risk of vaccine-induced enhanced disease as an AE of special interest (see Appendix E). COVID-19 will be diagnosed and treated as per standard medical practice. In addition, experimental treatments are permitted. Detailed information will be collected in a standard way and reported on a specific case report form.

4.1.2 Screening

All potential participants will be screened, which may take place at a visit up to 14 days prior to Day 1 or on Day 1 itself.

Informed consent will be obtained before screening/enrollment. If written consent is obtained, the screening procedures specified in the Schedule of Activities (Section 1.3) will be undertaken including a medical history, physical examination, height and weight, a SARS-CoV-2 screening test and clinical safety laboratory assessments. Baseline information collected in the previously vaccinated participants will include which vaccine was received, immunization dose interval, and time since last vaccination.

For women of childbearing potential, it will be recorded that they verbally confirmed use of one highly effective form of birth control for at least 28 days prior to the planned vaccination and a urine pregnancy test will be performed that must be negative for the participant to be enrolled. (Note: Women with urine test results that are positive or undetermined will not be enrolled and should be advised to seek medical attendance outside the context of the trial if pregnancy is suspected.)

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 enrollment or to withdraw a participant from the study will be at the discretion of the Investigator.

4.1.3 Vaccination Visit

Participants will be considered enrolled at the point of vaccination. Before vaccination, the eligibility of the participant will be reviewed. Body temperature will be observed and a medical history and physical examination will be undertaken before the first vaccination to determine need to postpone vaccination or screen fail the participant. A negative pregnancy test (urine test) will need to be obtained from women of childbearing potential before vaccination. Baseline blood samples will be obtained before the first vaccination.

Participants will receive 1 dose of AZD2816 or AZD1222 at vaccination visits, administered by intramuscular injection. Previously immunized participants will have a single vaccination visit, Day 1. Participants that have not been previously vaccinated at baseline will have a second vaccination visit on Day 29 (4-week interval) or Day 85 (12-week interval).

All participants will be given a thermometer, tape measure or ruler, and a proprietary e-diary application designed for use with a smart device with instructions for use. All participants will be asked to report on solicited signs and symptoms for 7 days following vaccination (Days 1 to 8 and Days 29 to 36 or Days 85 to 92 when applicable).

4.1.4 Follow-up visits

Follow-up visits will take place as specified in the Schedule of Activities (Section 1.3). All participants will be assessed for local and systemic AE, physical examination, review of the e-diary and blood tests at these time points as detailed in the Schedule of Activities. Blood will also be taken for safety and immunogenicity assessments.

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 the last study visit in order to collect information on any SAEs/AE of special interest.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Study Design and Participant Population

The participant population includes adults ≥ 30 years of age. Persons who are healthy or have medically stable underlying conditions will be eligible. Adults with medically-stable chronic diseases may participate if, according to the judgement of the investigator, hospitalization within the study period is not anticipated and the participant appears likely to be able to remain on study through the end of protocol-specified follow-up.

For the primary and secondary objectives, those enrolled in the study must test negative for SARS-CoV-2 nucleocapsid protein antibody during screening. Some seropositive participants (capped at 10% of the seronegative participant population) will be enrolled to support an exploratory analysis.

Those enrolled in the single-dose vaccination part of the study must have received 2 doses of AZD1222 (with a dosing interval of 4-12 weeks) or 2 doses of an mRNA COVID-19 vaccine (with a dosing interval of 3-12 weeks for the BNT162b2 mRNA vaccine [Pfizer-BioNTech] and 4-12 weeks for the mRNA-1273 vaccine [Moderna]) with the second doses administered at least 3 months prior to first study intervention administration.

Pregnant/breastfeeding women, persons with severe immunodeficiency or severe underlying disease will be excluded from participation in the study. Persons previously vaccinated with AZD1222 in the context of an AZD1222 vaccine trial are eligible for enrollment as previously vaccinated participants in the trial. Persons who have previously received any other investigational product for the prevention of COVID-19 will be excluded from participation in this study.

Participants with known risk factors for thrombosis and thrombocytopenia (excluding contraceptive hormonal therapy or replacement hormonal therapy) are excluded.

4.2.2 Rationale for Study Endpoints

There is no statistical hypothesis testing planned for this study. Descriptive statistics will support evaluation of safety, reactogenicity, and immunogenicity.

An interim analysis will occur when all previously vaccinated participants have completed their Day 29 visit. A second interim analysis may be conducted when previously unvaccinated participants have completed their Day 29 visit.

The primary analysis will occur when all participants have completed their Day 29 visit AND all previously unvaccinated participants randomised to a 4-week dosing interval have completed their Day 57 visit (ie, 28 days after their second dose).

A secondary analysis will occur when all participants have completed their Day 29 visit AND all previously unvaccinated participants (including those randomised to either a 4-week or a 12-week dosing interval) have completed their Day 57/Day 113 visit (ie, 28 days after their second dose).

The final analysis will occur when data from all vaccinated participants are available through completion of the last study visit (180 days after the single dose for previously vaccinated participants/180 days after the second dose for unvaccinated participants).

The primary safety analysis includes:

- Incidence of local and systemic solicited AEs for 7 days following each vaccination will be summarized by day and overall.
- Incidence of unsolicited AEs for 28 days following each vaccination will be summarized by system organ class and preferred term, and by relationship to vaccination as assessed by the investigator.
- SAEs and AEs of special interest following the first vaccination and throughout the study duration will be summarized by system organ class and preferred term and by relationship to vaccination as assessed by the investigator.

Solicited AEs will be collected for 7 days after each dose of study intervention, a period that has proven adequate to describe reactogenicity events in previous vaccine studies. For all participants, AEs will be collected through 28 days after each dose of study intervention. SAEs, medically-attended AEs, and AEs of special interest and will be collected from Day 1 through end of the study. AEs of special interest include terms identified by the Brighton Collaboration involving events associated with vaccination in general .

The immunogenicity endpoints of interest in this study are:

- Geometric mean titre

- Seroresponse, defined as ≥ 4-fold increase in the geometric mean titre from baseline

Geometric mean titre ratios and differences in seroresponses with 95% confidence intervals will be presented to support selected comparisons of immunogenicity across groups of interest.

Immunogenicity against SARS-CoV-2 Wuhan-Hu-1 and B.1.351 strains will be characterized through the quantification of Spike-binding antibodies, pseudo-neutralization and, in a subset of participants, live neutralization. Exploratory analysis of immunogenicity against other strains and induction of other immune effectors including cell-mediated immunity will be conducted.

4.3 Justification for Dose

The AZD2816 nominal dose of 5×10^{10} viral particles is the same dose as the approved dose for AZD1222, which was based on the accumulated non-clinical data and clinical data from the AZD1222 clinical studies, as well as from other SARS-CoV-2 vaccines in development. Safety and immunogenicity data from an additional clinical study, MERS001(NCT03399578), using the same ChAdOx1 vector, also helped inform dose selection. MERS001 was the first clinical study of a ChAdOx1-vectored vaccine expressing the full-length S protein from a separate, but related, beta-coronavirus. ChAdOx1 MERS has been given to 31 participants to date at doses ranging from 5×10^{9} viral particles to 5×10^{10} viral particles. Despite higher reactogenicity observed at the 5×10^{10} viral particles, this dose was safe, with self-limiting AEs and no serious adverse reactions recorded. The 5×10^{10} viral particles was the most immunogenic, in terms of inducing neutralizing antibodies 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} viral particles dose was chosen for AZD1222.

Based on accumulating nonclinical and clinical data gathered for AZD1222, a 2-dose regimen was selected for vaccination of unvaccinated participants with AZD2816 (AZD1222 Investigators Brochure). A single dose vaccination has been selected for participants previously vaccinated in line with both FDA and EMA guidance (FDA 2021, EMA 2021).

4.4 End of Study Definition

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

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

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as a protocol waiver or exemption, is not permitted.

5.1 Inclusion Criteria

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

5.1.1 All Participants:

Age

1 Adult, ≥ 30 years of age at the time of consent

COVID-19

For inclusion in the SARS-CoV-2 seronegative population supporting the primary and secondary objectives:

2 No history of laboratory-confirmed SARS-CoV-2 infection (ie, no positive nucleic acid amplification test and no positive antibody test).

3 Seronegative for SARS-CoV-2 at screening (lateral flow test to detect reactivity to the nucleoprotein).

Note, patients failing to meet criteria 2 and/or 3 may be included in the separate seropositive population supporting the seropositive exploratory objectives.

Type of Participant

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

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

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

6 Signed informed consent obtained before conducting any study-related procedures

Reproduction

7 Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
Female participants:

(a) Women of childbearing potential must:

- Have a negative pregnancy test on the day of screening and on days of vaccination
- 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 30 days following administration of the 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 6). Periodic abstinence, the rhythm method, and withdrawal are NOT acceptable methods of contraception.

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

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

    Until follicle-stimulating hormone is documented to be within menopausal range, the participant is to be considered of childbearing potential
  - For women aged ≥50 years, post-menopausal is defined as having a history of ≥12 months amenorrhea prior to randomization, without an alternative cause, following cessation of exogenous sex-hormonal treatment.

Table 6 Highly Effective Methods of Contraception

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

[a] This is also considered a hormonal method
[b] Provided that partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success
[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse from 28 days prior to Day 1 through 30 days following administration of the second dose of study intervention, and if it is the preferred and usual lifestyle of the participant

5.1.2 Previously COVID-19 Vaccinated Participants

8 Prior completion of a 2-dose primary homologous vaccination regimen against SARS-CoV-2 with either AZD1222 (2 standard doses as authorized vaccine or as investigational product in a clinical trial with a 4- to 12-week dosing interval) or with an mRNA vaccine approved for emergency or conditional use (eg, BNT162b2 vaccine [Pfizer-BioNTech] with a 3- to 12-week dosing interval or mRNA-1273 vaccine [Moderna] with a 4- to 12-week dosing interval). The second dose in all cases should have been administered at least 3 months prior to first administration of study intervention.

5.2 Exclusion Criteria

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

Medical Conditions

1 History of allergy to any component of AZD1222/AZD2816.

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

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

4 Any confirmed or suspected immunosuppressive or immunodeficient state, including asplenia or HIV/AIDS.

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

- Topical/inhaled steroids or short-term oral steroids (course lasting ≤ 14 days)

6 History of primary malignancy except for:

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

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

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

(d) Localized prostate cancer

7 History of thrombocytopenia and/or thrombosis, including participants who have experienced major venous and/or arterial thrombosis in combination with thrombocytopenia following vaccination with any COVID-19 vaccine

8 History of heparin-induced thrombocytopenia, congenital thrombophilia (ie, factor V Leiden, prothrombin G20210A, antithrombin III deficiency, protein C deficiency and

protein S deficiency, factor XIII mutation, familial dysfibrinogenemia), auto-immune thrombophilia (antiphospholipid syndrome, anti-cardiolipin antibodies, anti-β_2-glycoprotein 1 antibodies), or paroxysmal nocturnal haemoglobinuria.

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

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

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

12 Any autoimmune conditions, except mild psoriasis and vitiligo

Note: The AEs of special interest as outlined in Appendix E (including Table 27) should be considered when evaluating a participant for exclusion criteria as the presence of these AEs of special interest, especially if untreated or uncontrolled, may be a safety risk to the participant, affect the ability of the participant to participate in the study, and/or impair interpretation of the study data. Investigators should review and consider the list of conditions in Appendix E. If any of these conditions are present in a participant, the Investigator is asked to utilize his/her clinical judgment in determining the participant's eligibility for the study. Should the participant have conditions as outlined in Appendix E and the participant is enrolled, the Investigator is asked to document notes on site regarding the final rationale for enrollment.

Prior/Concomitant Therapy

13 Receipt of or planned receipt of investigational products indicated for the treatment or prevention of SARS-CoV-2 or COVID-19 with the exception of prior vaccination with AZD1222 or an mRNA COVID-10 vaccine (2 doses of the same vaccine within an approved dosing interval, see Section 5.1.2), which is allowed for participants in the previously vaccinated cohort
Note: For participants who develop COVID-19, receipt of licensed treatment options and/or participation in investigational treatment studies is permitted

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

15 Receipt of any influenza vaccine (licensed or investigational) within 7 days prior to and after administration of AZD1222/AZD2816.

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

Other Exclusions

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

18 Women who are currently pregnant (confirmed with positive pregnancy test), breastfeeding, having given birth less than 3 months before or planning pregnancy during the study.

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

20 Participants with a history of chronic alcohol or drug abuse or any condition associated with poor compliance.

21 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements or if vaccination would interfere with the participant's ongoing treatment.

22 Previous enrollment in the present study.

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 assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

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

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention, marketed product, or placebo intended to be administered to or medical device utilized by a study participant according to the study protocol. Study intervention is defined as AZD2816 or AZD1222 (Table 7).

6.1 Study Interventions Administered

6.1.1 Investigational Products

Table 7 Investigational Products

Intervention Name	AZD2816	AZD1222
Type	Vaccine	Vaccine
Dose Formulation	CCI [redacted]	CCI [redacted]
Unit Dose Strength	1×10^{11} viral particles/mL	1×10^{11} viral particles/mL
	$\geq 5 \times 10^{8}$ infectious units/mL	$\geq 5 \times 10^{8}$ infectious units/mL
Dosage Level	5×10^{10} viral particles (nominal, $\pm 1.5 \times 10^{10}$ viral particles)	5×10^{10} viral particles (nominal, $\pm 1.5 \times 10^{10}$ viral particles)
	$\geq 2.5 \times 10^{8}$ infectious units	$\geq 2.5 \times 10^{8}$ infectious units
Route	Intramuscular	Intramuscular
Use	Experimental	Experimental
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labelling	Will be provided in vials within a carton. Each carton and vial will be labelled as required per country requirement	Will be provided in vials within a carton. Each carton and vial will be labelled as required per country requirement
Current/Former Name	-	Previous clinical documentation: ChAdOx1 nCoV-19 Current tradename: Vaxzevria

IMP: investigational medicinal product; NIMP: non-investigational medical product; w/v: weight/volume.

AZD2816

AZD2816 will be supplied by the Sponsor as a vial solution for injection. It is a sterile, clear to slightly opaque solution, practically free from visible particles. Each vial of AZD2816 has a label-claim volume of 5 mL and can provide up to ten 0.5 mL doses.

AZD1222

AZD1222 will be supplied by the Sponsor as a vial solution for injection. It is a sterile, clear to slightly opaque solution, practically free from visible particles. Each vial of AZD1222 has a label-claim volume of 4 mL and can provide up to eight 0.5 mL doses.

Unopened vials of AZD2816 and AZD1222 must be stored at 2-8 ºC (36-46 ºF) for the duration of the assigned shelf-life and must not be frozen. Both investigational products must be kept in original packaging until use to prevent prolonged light exposure.

6.1.2 Dosing Instructions

Previously unvaccinated participants will receive 2 doses of either AZD1222, AZD2816, or AZD1222 plus AZD2816, with the first dose administered on Day 1 and the second dose on Day 29 (for a 4-week dosing interval) (Table 3) or Day 85 (for a 12-week dosing interval) (Table 4).

Previously vaccinated participants will receive 1 dose of either AZD1222 or AZD2816 (Table 2).

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

All study participants will be observed in the clinic for at least 15 minutes after vaccination. Allergic reactions to vaccines are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

6.2 Preparation/Handling/Storage/Accountability

The procedures for preparation, handling, storage, and accountability are identical for AZD2816 and AZD1222.

1 The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2 Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
3 The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4 Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual or specified handling instructions.

6.2.1 Dose Preparation and Administration

Doses of AZD2816 and 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 AZD2816 or AZD1222 in a sterile syringe.

AZD2816 and AZD1222 do not contain preservatives. Each vial must be assigned a beyond-use-date of 6 hours at 2-30 °C (36-86 °F) from first needle puncture of the vial, after which any unused portion must be discarded.

Once an AZD2816 or AZD1222 dose is drawn into a syringe for administration, the dose must be administered within the beyond-use-date of the vial. If dose administration is not completed within the 6-hour vial beyond-use-date, a new dose must be prepared from a new vial.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization

The study contains 3 cohorts that are randomised to a total of 8 treatments:

- Participants that have previously been vaccinated with 2 doses of AZD1222 will be randomised 1:1 to 1 dose of AZD2816 or 1 dose of AZD1222.
- Participants that have been previously vaccinated with an mRNA COVID-19 vaccine will be randomised 1:1 to 1 dose of AZD2816 or AZD2816.
- Vaccination naïve participants that will be randomised 2:2:2:1 to 2 doses of AZD2816 with a 4-week dosing interval, 2 doses of AZD1222 with a 4-week dosing interval, 1 dose of AZD1222 followed by 1 dose of AZD216 with a 4-week dosing interval, or 2 doses of AZD2816 with a 12-week dosing interval.

Separate populations of SARS-CoV-2 seronegative participants (supporting the primary and secondary objectives) and SARS-CoV-2 seropositive participants (supporting exploratory objectives) will be randomised/included in the above cohorts.

Randomization will be stratified based on age (less than 65, 65 and above), gender, and presence of at least one of the following comorbidities that are known risk factors for severe illness from COVID-19 (based on the participant's past and current medical history):

- Obesity (BMI $\geq$ 30 kg/m^2 at baseline)
- Significant cardiovascular disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, or pulmonary hypertension)
- Chronic lung disease (eg, chronic obstructive pulmonary disease, idiopathic pulmonary disease, cystic fibrosis, or moderate to severe asthma)
- Diabetes (Type 1 or Type 2).

The randomised participants will be centrally assigned to randomised study intervention using an Interactive Response Technology (IRT)/Randomisation and Trial Supply Management. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information & directions for the Randomisation and Trial Supply Management will be provided to each site.

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

6.3.2 Blinding

Treatment will be double-blinded for previously vaccinated participants randomised to a single dose of either AZD2816 or AZD1222. Treatment will also be double-blind for previously unvaccinated participants randomised to 2 dose vaccinations with a 4-week dosing interval (ie, homologous AZD2816 or AZD1222 vaccination or heterologous AZD1222/AZD2816 vaccination). Previously unvaccinated participants randomised to a homologous AZD2816 vaccination with a 12-week dosing interval will receive treatment in an open-label fashion due to the different dosing interval.

For the double-blinded treatments, neither the participant nor any of the investigators or Sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the study intervention received. Since AZD2816 and AZD1222 are visually distinct prior to dose preparation (due to differences in container closure), all investigational 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, AZD2816 and AZD1222 are not visually distinct from each other.

The IRT will provide the investigators with a dose tracking number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IRT user manual that will be provided to each study site.

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

The Sponsor retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational medicinal product and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken

for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

6.3.3 Procedures for Unblinding

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

In the event that a study participant is contacted about receiving a licensed and/or authorized COVID-19 vaccine outside of this clinical study, unblinding instructions are being provided to the sites. If the participant is unblinded, the Sponsor needs to be notified within 24 hours, and this should be documented in the site source documents.

6.4 Study Intervention Compliance

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

6.5 Concomitant Therapy

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

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

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

6.5.1 Permitted Concomitant Medications

- Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance.

- Primary care providers, or where appropriate investigators, should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study.
- Participants who develop COVID-19 after receiving study intervention should be treated with licensed medications and interventions according to standard of care. All routine vaccinations other than influenza are permitted beginning > 30 days after last dose of study intervention. Licensed influenza vaccines are permitted 7 days before and 7 days after administration of study intervention.
- Topical/inhaled steroids or short-term oral steroids (course lasting ≤ 14 days) are permitted

6.5.2 Prohibited Concomitant Medications

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

- Primary or booster vaccinations, other than AZD2816 or AZD1222, for prevention of SARS-CoV-2 or COVID-19**.**

  Note: Participants choosing to receive a licenced and/or authorized COVID-19 vaccine should inform the Investigator so it can be properly documented. Participants, who receive a licenced and/or authorized COVID-19 vaccine outside the study, should be encouraged to continue study conduct to be followed for safety reporting and all assessments.
- Receipt of any vaccine (licensed or investigational) other than licensed influenza vaccines within 30 days prior to and after administration of study intervention. Thirty days after the second vaccination, other routine vaccinations are permitted as clinically indicated.
- Glucocorticoids at a dose ≥ 20 mg/day of prednisone or equivalent given daily or on alternate days for ≥ 14 consecutive days between randomization and the participant's scheduled final visit
- Other systemically administered drugs with significant immunosuppressive activity, such as azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy between randomization and the participant's scheduled final visit
- Immunoglobulins and/or any blood product.

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

6.6 Dose Modification

Study intervention will be administered as described in Section 6.1. Dose modification is not permitted.

6.7 Intervention After the End of the Study

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

An individual participant will not receive the first or second dose (if applicable) of study intervention if any of the following occur in the participant in question:

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

Each participant who has received at least 1 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.

In the event that a study participant receives a licensed and/or authorized COVID-19 vaccine during the study, AstraZeneca needs to be notified within 24 hours and this should be documented in the site source documents. Participants who have received study intervention, regardless of reason, will be followed for the full study period.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Sponsor Study Team. If the participant does not specifically request withdrawal of consent for use of samples, then the samples collected prior to the consent withdrawal will be destroyed once per protocol analysis is complete.

7.3 Lost to Follow-up

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

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

- The study site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Schedule of Activities (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 Schedule of Activities (Section 1.3) is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities.

8.1 Efficacy Assessments

Not applicable.

8.2 Safety Assessments

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

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

8.2.2 Vital Signs

Vital signs, including heart rate, pulse oximetry, blood pressure, and body temperature, will be performed as specified in the Schedule of Activities (Section 1.3). The participant should be resting prior to the collection of vital signs. On vaccination days, vital signs should be assessed prior to vaccine administration.

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

8.2.3 Clinical Laboratory Assessments

Blood samples for determination of clinical chemistry and haematology will be taken at the visits indicated in the Schedule of Activities (Section 1.3). Additional unscheduled safety samples may be collected if clinically indicated at the discretion of the investigator, with the date and time of collection recorded in the appropriate eCRF.

The standard clinical chemistry and haematology analysis will be performed at a local laboratory at or near to the investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The following laboratory variables will be measured:

Table 8 Laboratory Safety Variables

Blood	Serum/Plasma
Haemoglobin	Activated partial thromboplastin time
Leukocyte count	Prothrombin time
Leukocyte differential count (absolute count)	Fibrinogen
Platelet count	D-dimer
-	Creatinine
-	Bilirubin, total
-	Alkaline phosphatase
-	Aspartate aminotransferase
-	Alanine aminotransferase

In case a participant shows an aspartate aminotransferase **or** alanine aminotransferase $\geq 3 \times$ upper limit of normal together with total bilirubin $\geq 2 \times$ the upper limit of normal, please refer to Section 8.3.6

For women participants of childbearing potential, a urine sample for pregnancy testing will be collected according to the Schedule of Activities (Section 1.3). Urine pregnancy tests for β-human chorionic gonadotropin may be performed at the site using a licensed dipstick test.

8.3 Adverse Events and Serious Adverse Events

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

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

Solicited AEs are local or systemic predefined events for assessment of reactogenicity. Solicited AEs will be collected in a e-diary (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 the reporting of solicited AEs via e-diary unless otherwise noted..

All other AEs are considered to be unsolicited AEs (collected by 'open question' at study visits).

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

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

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

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

Solicited AEs will be recorded for 7 days after each dose of study intervention (ie, Day 1 through Day 8). If a solicited AE is not resolved within the e-diary reporting period, the event will be reported as a non-solicited adverse event in the eCRF, with a start date of when started and the actual stop date.

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

Medically-attended AEs and AEs of special interest will be recorded from Day 1 through the last participant contact.

See the Schedule of Activities for the scheduled timepoints (Section 1.3).

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 Adverse Events and Serious Adverse Events

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. The Sponsor retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

AE variables

The following variables will be collected for each AE:

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

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

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

A revised toxicity grading scale from US FDA guidance for healthy volunteers enrolled in a preventive vaccine clinical study (FDA 2007) will be utilized for all unsolicited events with an assigned severity grading including Grade 5.

8.3.3 Causality Collection

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

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

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

8.3.4 Adverse Events Based on Signs and Symptoms

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

8.3.5 Adverse Events Based on Examinations and Tests

The results from the Clinical Study Protocol-mandated vital signs and laboratory safety assessments will be summarized in the Clinical Study Report.

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

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

8.3.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation. Any occurrences of aspartate aminotransferase or alanine aminotransferase $\geq 3 \times$ the upper limit of normal together with total bilirubin $\geq 2 \times$ upper limit of normal at any point during the study following the administration of study medication should be reported to the Sponsor as a potential Hy's Law SAE within 1 day with a serious criteria of 'Important medical event' and causality assessment 'yes/related'.

The study physician will contact the investigator to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.

8.3.7 Solicited Adverse Events

Local and systemic predefined solicited AEs for reactogenicity assessment (Table 9) will be collected in a Solicited AE e-Diary for 7 days following administration of each dose of study intervention via e-diary collection. If a solicited AE is not resolved within the e-diary reporting period, the event will be also reported as a non-solicited adverse event in the eCRF, with a start date of when started and the actual stop date.

Solicited AEs should not be reported as unsolicited AEs unless they fulfil the criteria for SAEs or medically-attended AEs(see Sections 8.3 and 8.3.8, respectively).

Table 9 Predefined Solicited Adverse Events for Reactogenicity Assessment

Local	Systemic
Pain at the site of the injection	Fever (> 100 °F/37.8 °C)
Redness/erythema at the site of the injection	Chills
Tenderness at the site of the injection	Muscle pains
Induration/swelling at the site of the injection	Fatigue (physical or mental tiredness/exhaustion)
-	Headache
-	Malaise (general feeling of discomfort or uneasiness)
-	Nausea
-	Vomiting

Solicited AE e-Diary

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

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

Severity Assessment of Solicited AEs

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

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

8.3.8 COVID-19 Assessment

This study will describe the incidence of COVID-19 adverse events reported from Day 1 to 180 days after the participant's last/only dose of vaccine.

COVID-19 is defined as SARS-CoV 2-RT-PCR positive symptomatic illness. At all clinic visits following the initial vaccination, participants will be asked if they have had a diagnosis of COVID-19 since their last clinic visit (see Schedule of Activities in Section 1.3). Medical records will be obtained for confirmation of a participant-reported diagnoses of COVID-19. Qualifying symptoms are fever, shortness of breath, difficulty breathing, chills, cough, fatigue, muscle/body aches, headache, new loss of taste or smell, sore throat, congestion, runny nose, nausea, vomiting, or diarrhoea. Events will be reported as AEs/SAEs.

If a participant presents at clinic visit with COVID symptoms, diagnosis will be confirmed using RT-PCR.

8.3.9 Medically-Attended Adverse Events

Medically-attended AEs will be collected according to the timepoints specified in the Schedule of Activities (Section 1.3).

Medically-attended AEs are defined as AEs leading to medically-attended visits that were not routine visits for physical examination or vaccination, such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. AEs, including abnormal vital signs, identified on a routine study visit or during the scheduled illness visits will not be considered medically-attended AEs.

8.3.10 Adverse Events of Special Interest

AEs of special interest will be collected according to the timepoints specified in the Schedule of Activities (Section 1.3).

AEs of special interest 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. AEs of special interest are based on Brighton Collaboration case definitions (SPEAC 2020), clinical experience, and scientific interest. A list of events is provided in Appendix E.

An AE of special interest can be serious or non-serious. All AEs of special interest will be recorded in the eCRF. If any AE of special interest occurs in the course of the study, investigators or other site personnel will inform the appropriate Sponsor representatives within

1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it. Serious AEs of special interest will be recorded and reported as per Section 8.3.11.

8.3.10.1 Vascular/Hematologic Adverse Events of Special Interest

Both thrombotic, thromboembolic, and neurovascular events and thrombocytopenia events are considered to be adverse events of special interest. The investigator should remain vigilant for the occurrence of thrombotic events with thrombocytopenia and/or bleeding. If a participant experiences new onset thromboembolic events with thrombocytopenia, there should be prompt evaluation with a thorough haematological investigation. COVID-19 testing, including PCR and serology (nucleoprotein antibodies), should also be performed. See Appendix F for further guidance on investigation and management of suspected events.

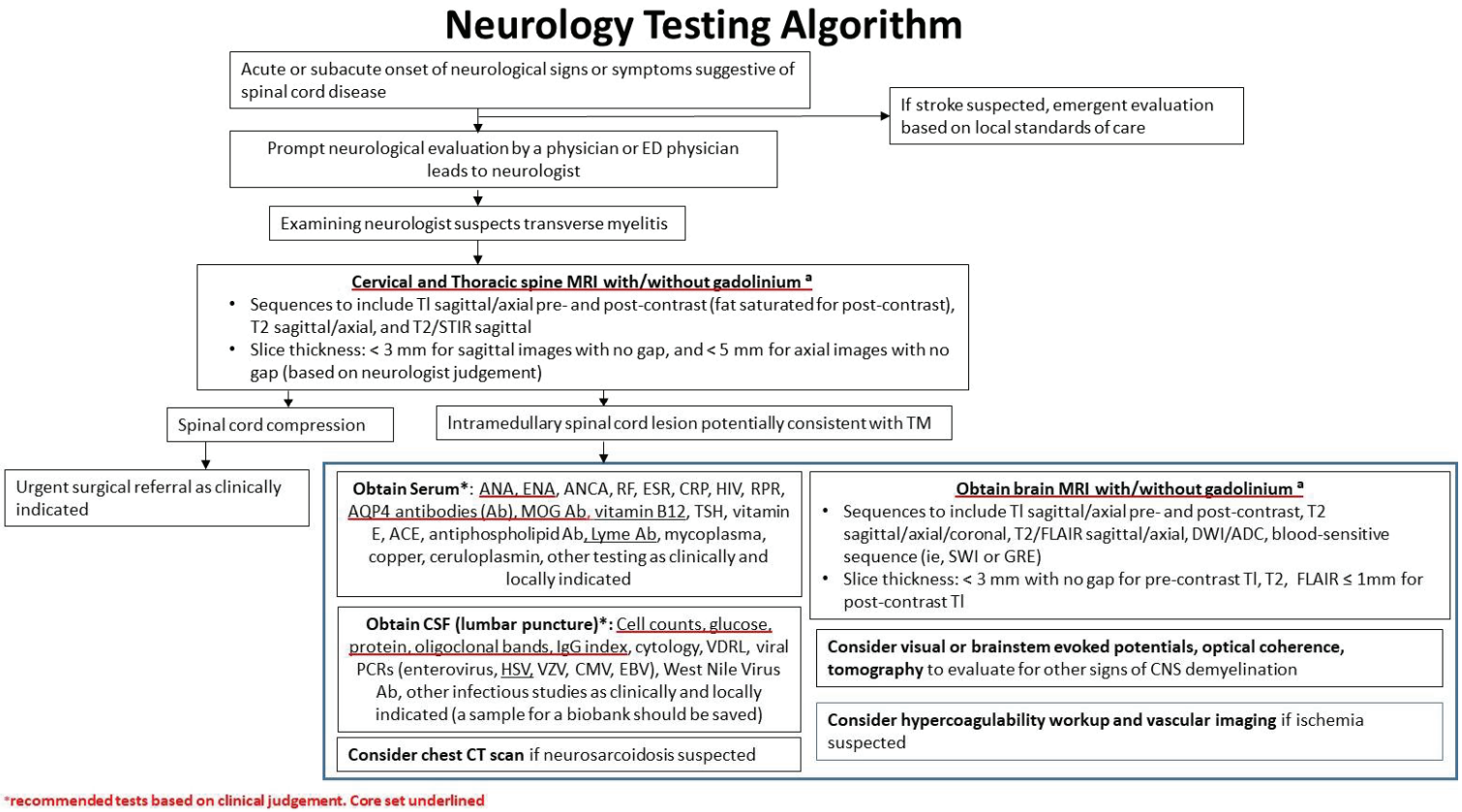
In the event of such a case of thrombosis and in accordance with local laws and ethical procedures, one blood sample may be taken from the participant and whole genome sequencing performed in order to enable investigations into the possible role of genetic polymorphisms as risk factors for these events.

8.3.10.2 Potential Neurological Adverse Events of Special Interest

If a participant experiences new onset (acute or subacute) motor and sensory disturbances (eg, weakness, numbness, paraesthesia, 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, including referral to a neurology specialist for further evaluation and testing, as clinically indicated. Testing can include evaluation for peripheral demyelinating conditions (eg, electromyography). In cases of concern for spinal cord disease, see Figure 3 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 AEs of special interest occurring in the AZD1222 clinical development program (see Appendix A 5).

Figure 3 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.

8.3.11 Reporting of Serious Adverse Events

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

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

The designated Sponsor representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform Sponsor representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but no later than 24 hours of when he or she becomes aware.

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 Sponsor representative.

If the Electronic Data Capture system is not available, then the investigator or other study site staff reports an SAE to the appropriate Sponsor representative by telephone or other method and the event is entered into the Electronic Data Capture system when available.

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

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

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

8.3.12 Pregnancy

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

8.3.12.1 Maternal Exposure

Female participants who are pregnant or have a confirmed positive pregnancy test at screening or Day 1 will be excluded from the study (see Section 5.2). Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and

spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the participant was discontinued from the study.

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

The designated Sponsor representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.11) and **within 30 days** for all other pregnancies that are not associated with an SAEs.

The same timelines apply when outcome information is available.

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

8.3.13 Medication Error

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

The designated Sponsor representative works with the investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) **or 5** (other serious initial and follow up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.11) and **within 30 days** for all other medication errors.

The definition of a Medication Error can be found in Appendix B 3.

8.4 Overdose

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

There is no specific treatment for an overdose with AZD2816 or AZD1222. If overdose occurs, the participant should be treated supportively with appropriate monitoring as necessary.

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

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

The designated Sponsor representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.11) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

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

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

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

8.5.1 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5.2 Immunogenicity Assessments

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

8.5.2.1 SARS-CoV-2 Serology Assessments

Serum samples will be collected to assess SARS-CoV-2 antigen-specific antibody levels from all participants according to the Schedule of Activities (Section 1.3). Authorized laboratories will assess serologic responses to AZD1222 and AZD2816 using validated (or qualified, where appropriate) assays. Serologic assessment to the S protein from different SARS-CoV-2 variants (which include Wuhan-Hu-1, B.1.351, B.1.1.7, and P.1) will be assessed quantitatively using a validated multiplexed ECL based immunoassay. Additionally, seroresponse will be assessed for each antigen over time. The rate of SARS-CoV-2 infection in participants receiving AZD2816 versus AZD1222 will be determined by seroconversion in a SARS-CoV-2 nucleocapsid antigen in a multiplexed electrochemiluminescence-based assay performed at an authorized laboratory. Additional exploratory assessments may be performed to measure binding antibodies to SARS-CoV-2 variants of interest (which may include B.1.429, B.1.525, B.1.526, P.2, P.3, B.1.617, and the Q677H mutation observed in multiple variants).

8.5.2.2 CCI

CCI

8.5.2.3 CCI

CCI

8.5.2.4 CCI

CCI

8.5.3 Pharmacodynamics

Pharmacodynamics are not evaluated in this study.

8.6 Human Biological Sample Biomarkers

Already collected samples may be analysed for biomarkers thought to play a role in COVID-19 severity or outcomes based upon emerging immunogenicity and pharmacodynamic analysis from this or other studies involving the study interventions. These analyses include but are not limited to serum or plasma cytokines, quantification of RNA, micro-RNA, and/or non-coding RNA using quantitative reverse transcriptase polymerase chain reaction (RT-PCR), microarray, sequencing, or other technologies in blood, or peripheral blood mononuclear cells to evaluate their association with AZD1222/2816 and observed clinical responses to these study interventions.

8.7 Optional Genomics Initiative Sample

Not applicable.

8.8 Medical Resource Utilization and Health Economics

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

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

There is no statistical hypothesis testing planned for this study. Descriptive analyses will support evaluation of safety, reactogenicity and immunogenicity.

9.2 Sample Size Determination

Primary Objective: Characterise Immunogenicity (Precision)

Historical data were available for the immunogenicity responses to AZD1222 from the pooled COV001/002/003/005 studies. Table 10 presents the log transformed immunogenicity responses (ie, geometric mean titres) by assay for participants that received 2 standard doses

of AZD1222. These results indicate that the pseudo-neutralising antibodies exhibited the largest variation (standard deviation of 1.20 and 1.10 for the 4-week and 12-week dosing intervals respectively), while live-neutralising antibodies had the lowest (standard deviation of 0.72 for the 4-week dosing interval).

Table 10 Historic Immunogenicity Responses by Dosing Interval (Geometric Mean Antibody Titres, Standard Dose Immunogenicity Analysis Set)

	Post-1st Dose			Post-2nd dose with a 4-week dosing interval[a]			Post-2nd dose with a 12-week dosing interval[b]		
Assay	**N**	**Mean**	**Std Dev**	**N**	**Mean**	**Std Dev**	**N**	**Mean**	**Std Dev**
Pseudo	476	4.3	1.34	166	5.3	1.20	113	5.4	1.10
Live	51	4.9	1.15	42	6.2	0.72	0	-	-
Spike protein	1139	9.1	1.14	293	10.1	0.96	302	10.7	0.83

[a] Estimates from pooled COV001/002/003/005 study data from participants with 2- to 6-week dosing interval
[b] Estimates from pooled COV001/002/003/005 study data from participants with 10- to 14-week dosing interval

Table 11 presents the seroresponse (ie, > 4 fold increase from baseline) by assay. These results indicate that the pseudo-neutralising antibodies exhibited the lowest proportion of seroresponse (59.7% and 85.5% for the 4-week and 12-week dosing intervals respectively), while both live-neutralising and spike-binding seroresponse rates exceeded 95%.

Table 11 Historic Seroresponse Rates by Dosing Interval (>4-fold Increase from Baseline, Standard Dose Immunogenicity Analysis Set)

	Post-1st Dose		Post-2nd dose with a 4-week dosing interval[a]		Post-2nd dose with a 12-dose week interval[b]	
Assay	**N**	**Proportion**	**N**	**Proportion**	**N**	**Proportion**
Pseudo	499	32%	382	59.7%	117	85.5%
Live	96	75%	95	96.8%	-	-
Spike protein	940	96.6%	636	95.9%	304	99.3%

[a] Estimates from pooled COV001/002/003/005 study data from participants with 2- to 6-week dosing interval
[b] Estimates from pooled COV001/002/003/005 study data from participants with 10- to 14-week dosing interval

Under the assumption that the immunogenicity responses (ie, geometric mean antibody titres) associated with AZD2816 will be similar to the responses associated with AZD1222 in participants that received 2 standard doses in the pooled COV001/002/003/005 studies, in which standard deviations ranged from 0.72 to 1.2 (Table 10), 150 participants will provide a 95% confidence interval half-width between 0.115 and 0.192 (see Table 12). Similarly, 300 participants will provide a 95% confidence interval half-width between 0.081 and 0.136.

Table 12 Estimated Half-width of the 95% Confidence Intervals for Immunogenicity Responses (Geometric Mean Titres) Based on Historic Immunogenicity Assay Variances and the Proposed Sample Sizes

Standard Deviation	Number of participants	Estimated half-width of the 95% confidence interval (natural log scale)
0.72	150	0.115
	300	0.081
0.83	150	0.133
	300	0.094
0.96	150	0.154
	300	0.109
1.1	150	0.176
	300	0.124
1.2	150	0.192
	300	0.136

Under the assumption that the seroresponse rates associated with AZD2816 will be similar to the response rates in adults that received 2 standard doses of AZD1222 in the pooled COV001/002/003/005 studies (Table 11), 150 participants will provide a 95% confidence interval half-width between 1.33% and 7.85%, and 300 participants will provide a 95% confidence interval half-width between 0.94% and 5.55% (Table 13).

Table 13 Estimated Half-Width of the 95% Confidence Interval for the Seroresponse Rates based on Historic Seroconversion Rates and Proposed Sample Sizes

Observed seroconversion rate	Number of participants	Estimated half-width of the 95% confidence interval
59.7%	150	7.85%
	300	5.55%
85.5%	150	5.63%
	300	3.98%
95.9%	150	3.17%
	300	2.24%
96.8%	150	2.82%
	300	1.99%
99.3%	150	1.33%
	300	0.94%

For a fixed sample size, the precision with which the 95% confidence interval of the binary seroresponse rate can be estimated is a function of the response rate. Table 13 provides the lower bounds of the 95% confidence interval for selected response proportions for alternate sample sizes. For a given response rate, we can be 95% confident that the true seroresponse rate is at least as large as the lower bound of the confidence interval.

Primary Objective: Safety

Table 14 indicates the probability of observing 1 or more safety events, such as solicited injection site or systemic reactogenicity events or an unsolicited non-serious AE of a particular type for participants in each treatment arm. With the sample size of 300 participants, at least 1 participant with an AE of incidence rate of 1% can be detected with probability of about 95%.

Table 14 Probability of detecting 1 or more safety events (N = 300)

Event Frequency	Probability (> 1 event)
≥ 10% (Very Common)	> 99%
≥ 1% (Common)	95%
≥ 0.1% (Uncommon)	26%
≥ 0.01% (Rare)	3%

Secondary Objective: Compare Immunogenicity

Although this study will describe and compare the immune responses between AZD2816 and AZD1222 for selected group pairs, no-formal non-inferiority margin for either the geometric mean titre ratio or the difference in seroresponse is prospectively defined.

Under the assumption that there is no difference between treatment arms of interest (ie, a ratio of 1, difference on the log scale of 0), the power conferred by 150 and 300 participants respectively for the comparison of geometric mean titre ratio using a noninferiority margin of 1.5 (equivalent to a difference on the log scale of 0.405) is presented in

Table 15.

Table 15 Power for Non-inferiority Using 1.5 as the Upper Bound of the Geometric Mean Titre Ratio

Sides	Null difference	Assumed mean treatment difference	Assumed standard deviation	N of participants in comparator group	N of participants in reference group	Alpha	Power
Upper	ln1.5 = 0.405	0	0.72	150	300	0.025	> 0.999
				300	300		> 0.999
			0.83	150	300		0.998
				300	300		> 0.999
			0.96	150	300		0.988
				300	300		> 0.999
			1.10	150	300		0.957
				300	300		0.994
			1.20	150	300		0.920
				300	300		0.985

Similarly, if there is no difference between treatment arms of interest (ie, a ratio of 1) in the proportion of seroresponders, 300 participants provides 80% power for to establish non-inferiority to within margin of -10% if the seroresponse rate is > 75%. The observed pseudo-neutralising response rates (> 4 fold increase from baseline) from the COV001/002/003/005 studies for AZD1222 were 59.7% and 85.5% for the 4-week and 12-week dosing interval respectively (Table 11). A population of 300 participants provides 70% power to detect non-inferiority (using a non-inferiority margin of -10%) if the observed response rate is 59.7% (Table 16).

Table 16 Power for Non-inferiority Using -10% as the Upper Bound of the Difference in Seroresponse Rate

Sides	Null proportion difference	Assumed proportion of seroresponders in both groups	Assumed difference in proportion of seroresponders	N in comparator group	N in reference group	Alpha	Power
Lower	-0.1	0.597	0	150	300	0.025	0.546
				300	300		0.707
		0.855		150	300		0.844
				300	300		0.929
		0.959		150	300		0.998
				300	300		> 0.999
		0.968		150	300		> 0.999
				300	300		> 0.999
		0.993		150	300		> 0.999
				300	300		> 0.999

9.3 Populations for Analyses

The following populations are defined:

Table 17 Populations for Analysis

Population	Description
All participants analysis set	All participants screened for the study, to be used for reporting disposition and screening failures.
Full analysis set	All randomised participants who received study treatment, irrespective of their protocol adherence and continued participation in the study. Participants will be analysed according to their randomised treatment, irrespective of whether or not they have prematurely discontinued, according to the intent-to-treat principle. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination.
Safety analysis set	The safety analysis set consists of all participants who have received study treatment. Erroneously-treated participants (eg, those randomised to AZD2816, but were actually given treatment AZD12222) are accounted for in this analysis set by assigning them to the treatment they actually received.

Table 17 Populations for Analysis

Population	Description
Immunogenicity analysis set	The vaccine immunogenicity analysis set will include all randomised participants, received at least 1 dose of planned study treatment (ie, 1 dose of either AZD2816 or 1 dose of AZD1222), had baseline and post-dose antibody measurements, have at least 1 post-dose quantifiable serum titre, and had no protocol deviations judged to have the potential to interfere with the generation or interpretation of an antibody response. The analyses conducted using this analysis set will be based on the actual treatment received.
Seronegative immunogenicity analysis set	The subset of the immunogenicity analysis set who were seronegative at baseline.
Seropositive immunogenicity analysis set	The subset of the immunogenicity analysis set who were seropositive at baseline.

Participants that are SARS-CoV-2 seropositive at screening will be included in seropositive analysis sets analogous to the above seronegative analysis sets. Further definition is provided in the Statistical Analysis Plan.

9.4 Statistical Analyses

This section provides a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints. A more technical and detailed description of the statistical analyses will be described in the Statistical Analysis Plan, and an approved version will be finalized prior to the interim analyses.

9.4.1 General Considerations

An interim analysis will occur when all previously vaccinated participants have completed their Day 29 visit (ie, 28 days after booster dose). It is estimated that this early analysis has the potential to provide clear signals about whether AZD2816 provides a strong neutralizing response against the B.1.351 strain while retaining immunogenicity against the Wuhan strain, and thereby influence programmatic decisions early.

A second interim analysis may be performed when previously unvaccinated participants have completed their Day 29 visit (ie, 28 days after fist dose). This analysis is intended to assess immunogenicity variability. The number of previously unvaccinated participants per treatment arm may be increased based upon the results of this analysis. The details of this interim analysis, including the trigger and methods, will be specified in the Statistical Analysis Plan to be finalized prior to any interim analysis.

The primary analysis will occur when all participants have completed their Day 29 visit and safety and immunogenicity data from all unvaccinated participants randomised to a 4-week

dosing interval are available through completion of their visit 28 days after the second priming dose.

A secondary analysis will occur when all participants have completed their Day 29 visit and safety and immunogenicity data from all unvaccinated participants (including those randomised to a 12-week dosing interval) are available through completion of the visit 28 days after the second dose.

The final analysis will occur when data from all vaccinated participants is available through completion of the last study visit (180 days after the single dose for previously vaccinated participants / 180 days after the second dose for unvaccinated participants).

To maintain trial integrity sponsor roles with direct input into participant management and safety monitoring will not have access to unblinded participant level data or associated outputs from the interim analyses until end of study.

Further details on the tools and processes to maintain the blind will be presented in the Study Integrity Plan.

9.4.2 Safety

9.4.2.1 Primary Endpoints

Overview

Descriptive analyses will support evaluation of safety, reactogenicity and immunogenicity. The primary safety analysis includes:

- Incidence of local and systemic solicited AEs for 7 days following each vaccination will be summarised by day and overall.
- Incidence of unsolicited AEs for 28 days following each vaccination will be summarised by system organ class and preferred term, and by relationship to vaccination as assessed by the investigator.
- MAAEs, SAEs, and AESIs following the first vaccination and throughout the study duration will be summarised by system organ class and preferred term and by relationship to vaccination as assessed by the investigator.
- The change from baseline for safety laboratory measures at 7 and 28 days after vaccination.

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

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

A listing will cover details for each individual AE. Full details of all AE analyses will be provided in the Statistical Analysis Plan, including intercurrent events for safety due to potential unblinding of participants for administration of licensed and/or approved SARS-CoV-2 or COVID-19 vaccine.

At the time of the interim analyses, group assignment will not be presented when safety event data has the potential to unblind participant's study group attribution.

9.4.2.2 Other Safety Endpoints

Vital Signs

Vital sign measurements will be performed as specified in the Schedule of Activities (Section 1.3). The set of assessments will include pulse oximetry, blood pressure, and body temperature.

Details of all vital sign analyses will be provided in the Statistical Analysis Plan, which will include descriptive statistics presented for observed values for all vital sign parameters.

COVID-19

This study will describe the incidence of COVID-19 adverse events from the first dose of the vaccine to study end (180 days post-vaccination). Descriptive statistics will be produced based on the safety analysis set. Full details will be documented in the statistical analysis plan.

9.4.3 Immunogenicity

9.4.3.1 Immunogenicity Endpoints

The immunogenicity endpoints of interest in this study are:

- Geometric mean antibody titre.
- Seroresponse, defined as ≥ 4-fold increase in the geometric mean antibody titre from baseline

Both the geometric mean antibody titre and seroresponse of participants will be summarized descriptively by strain, treatment arm, and timepoint for the immunogenicity population.

9.4.3.1.1 Estimand framework for immunogenicity descriptions and comparisons

Target populations:

1) Previously unvaccinated participants

a. Seronegative Analysis Set: and with no evidence of prior or current infection

2) Participants who previously received SARS-CoV-2 vaccination with either AZD1222 or a licensed mRNA vaccine according to the authorized dose and dosing regimen at least 3 months prior to first study intervention (see Section 5.1.2).

Outcome variable: neutralizing antibody and binding titres to SARS-CoV-2 at 28 days after each treatment administration (1 treatment administration for the previously vaccinated population and 2 planned treatment administrations for the unvaccinated population).

Treatment conditions:

Previously unvaccinated population

- 2 doses of AZD1222 given on Day 1 and on Day 29 (4-week interval)
- 2 doses of AZD2816 given on Day 1 and on Day 29 (4-week dosing interval)
- 1 dose of AZD1222 given on Day 1 and 1 dose of AZD2816 on Day 29 (4-week dosing interval)
- 2 doses of AZD2816 given on Day 1 and on Day 85 (12-week dosing interval)

Previously vaccinated population

- 1 dose of AZD1222 given on Day 1.
- 1 dose of AZD2816 given on Day 1.

Intercurrent events: the following intercurrent events could impact the antibody levels achieved:

- missing the second vaccination (for the unvaccinated population)
- receiving of immune-modifying drugs or vaccines
- subsequent infection with SARS-CoV-2.

All immunogenicity descriptions and comparisons will use the principal stratum strategy, ie, all analyses will exclude participants who experience any of the intercurrent events above

Population-level summary:

Descriptive Analyses (see Table 19 and Table 20)

- geometric means of the antibody titres

- seroresponse proportions

Comparative Analyses (see Table 21 and Table 22)

- ratio of geometric means of the antibody titres.
- difference in seroresponse proportion

Planned Descriptive Analyses:

Table 19 and Table 20 present planned descriptive immunogenicity analyses for the unvaccinated and previously vaccinated populations respectively (each one exploring an individual treatment arm at a specific timepoint against a particular strain).

The tables show that without introduction of further variants, there are 24 planned descriptive analyses for the unvaccinated population and 16 planned descriptive analyses for the previously immunised population (index). Within each table there is an analysis key which describes the population (see Table 18). The descriptive analyses presented in Tables 19 and 20 will be repeated for the subset of participants who are seropositive at screening.

Table 18 Description of the Analysis Keys for Tables 19 and 20

Population	Analysis Key	Example
Previously unvaccinated	Primary series dosing interval: P4 (4-week dosing interval) or P12 (12-week dosing interval) Treatment received: 1222 (2 doses of AZD1222) or 2816 (2 doses of AZD2816) or 1222/2816 (1 dose of AZD1222 followed by 1 dose of AZD2816) Strain: W (Wuhan-Hu-1) or V (Variant B.1.351) Analysis Timepoint: 1 (28 days post-dose 1) 2 (28 days post-dose 2)	[P4:1222:W:1] = Immunogenicity following primary vaccination with a 4-week dosing interval of 2 doses of AZD1222 against Wuhan-Hu-1 28 days post-dose 1
Previously vaccinated	Pre-study primary vaccination: P1222 (2 doses of AZD1222) or PmRNA (2 doses of an mRNA vaccine) Treatment received: B1222 (1 booster dose of AZD1222) or B2816 (1 booster dose of AZD2816) Strain: W (Wuhan-Hu-1) or V (Variant B.1.351)	[P1222:B1222:V] = Immunogenicity in participants who were previously vaccinated with 2 doses of AZD1222 as primary vaccination series and received a single boost dose of AZD1222 against the B.1.351 variant

Table 19 Immunogenicity Descriptive Analysis for Previously Unvaccinated Treatment Groups (with Separate Seronegative and Seropositive Analyses)

Objective	Treatment	Dosing interval	Strain	Timepoint	Endpoint	Index	Analysis Key
To describe the humoral immune responses induced by a 2-dose primary vaccination with AZD1222 with a 4-week interval in unvaccinated participants	AZD1222	4 weeks	Wuhan-Hu-1	28 days after 1st dose	GMT	1	[P4:1222:W:1]†
					Seroresponse	2	
				28 days after 2nd dose	GMT	3	[P4:1222:W:2]
					Seroresponse	4	
			B.1.351	28 days after 1st dose	GMT	5	[P4:1222:V:1]†
					Seroresponse	6	
				28 days after 2nd dose	GMT	7	[P4:1222:V:2]
					Seroresponse	8	
To describe the humoral immune responses induced by a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in unvaccinated participants	AZD2816	4 weeks	Wuhan-Hu-1	28 days after 1st dose	GMT	9	[P4:2816:W:1]‡
					Seroresponse	10	
				28 days after 2nd dose	GMT	11	[P4:2816:W:2]
					Seroresponse	12	
			B.1.351	28 days after 1st dose	GMT	13	[P4:2816:V:1]‡
					Seroresponse	14	
				28 days after 2nd dose	GMT	15	[P4:2816:V:2]
					Seroresponse	16	
To describe the humoral immune responses against induced by a 2-dose primary heterologous vaccination with AZD1222/AZD2816 with a 4-week dosing interval in unvaccinated participants	AZD1222/2816	4 weeks	Wuhan-Hu-1	28 days after 2nd dose	GMT	17	[P4:1222/2816:W:2]
					Seroresponse	18	
			B.1.351	28 days after 2nd dose	GMT	19	[P4:1222/2816:V:2]
					Seroresponse	20	
To describe the humoral immune responses induced by a 2-dose primary vaccination with AZD2816 with a 12-week interval in unvaccinated participants	AZD2816	12 weeks	Wuhan-Hu-1	28 days after 1st dose	GMT	21	[P12:2816:W:2]
					Seroresponse	22	
			B.1.351	28 days after 2nd dose	GMT	23	[P12:2816:V:2]
					Seroresponse	24	

† descriptive summaries for 28 days after 1st dose will pool all treatment groups who received AZD1222 as their first dose (ie, homologous and heterologous series).
‡ descriptive summaries for 28 days after 1st dose will pool all treatment groups who received AZD2816 as their first dose (4-week interval and 12-week interval treatment arms).

GMT: Geometric mean titre

Table 20 Immunogenicity Descriptive Analysis for Previously Vaccinated Treatment Groups (with Separate Seronegative and Seropositive Analyses)

Objective	Primary vaccination	Booster Treatment	Strain	Timepoint	Endpoint	Index	Analysis Key
To assess the humoral immune response induced by 1 dose of AZD1222 in participants previously vaccinated with AZD1222	AZD1222	AZD1222	Wuhan-Hu-1	28 days after booster dose	GMT	1	[P1222:B1222:W]
					Seroresponse	2	
			B.1.351	28 days after booster dose	GMT	3	[P1222:B1222:V]
					Seroresponse	4	
To assess the humoral immune response induced by 1 dose of AZD2816 in participants previously vaccinated with AZD1222		AZD2816	Wuhan-Hu-1	28 days after booster dose	GMT	5	[P1222:B2816:W]
					Seroresponse	6	
			B.1.351	28 days after booster dose	GMT	7	[P1222:B2816:V]
					Seroresponse	8	
To assess the humoral immune response induced by 1 dose of AZD2816 in participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	mRNA	AZD2816	Wuhan-Hu-1	28 days after booster dose	GMT	9	[PmRNA:B2816:W]
					Seroresponse	10	
			B.1.351	28 days after booster dose	GMT	11	[PmRNA:B2816:V]
					Seroresponse	12	
To assess the humoral immune response induced by 1 dose of AZD1222 in participants previously vaccinated with a SARS-CoV-2 mRNA vaccine		AZD1222	Wuhan-Hu-1	28 days after booster dose	GMT	13	[PmRNA:B1222:W]
					Seroresponse	14	
			B.1.351	28 days after booster dose	GMT	15	[PmRNA:B1222:V]
					Seroresponse	16	

GMT: Geometric mean titre

In addition to descriptive immunogenicity assessments for all treatment arms, geometric mean titre ratios and differences in seroresponse will be evaluated for the pairs of groups as detailed in Table 21 and Table 22. For each pair, the two-sided 95% confidence intervals for the ratio of the geometric mean titre and difference in seroresponse will be calculated. The geometric mean titre ratio assume a normal distribution for the natural log of the concentration. All confidence intervals will be unadjusted for multiple analyses and are provided solely as a guide to clinical and scientific judgment. It is acknowledged that the chance of falsely concluding that one or more differences in immunogenicity outcomes exist will be greater than the nominal two-sided 0.05 level used for each individual comparison.

Table 21 Immunogenicity Comparisons for Previously Unvaccinated Groups

Objective	$\frac{[\mathbf{GMT}_{\mathbf{comparator}}]}{[\mathbf{GMT}_{\mathbf{reference}}]}$	$\Delta = [\mathbf{Seroresponse}_{\mathbf{comparator}}] - [\mathbf{Seroresponse}_{\mathbf{reference}}]$
To evaluate the immune responses elicited by a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week interval in previously unvaccinated participants	$\frac{[\text{P4: 2816: V: 2}]}{[\text{P4: 1222: W: 2}]}$	$[\text{P4: 2816: V: 2}] - [\text{P4: 1222: W: 2}]$
	$\frac{[\text{P4: 2816: V: 1}]}{[\text{P4: 1222: W: 1}]}$	$[\text{P4: 2816: V: 1}] - [\text{P4: 1222: W: 1}]$
	$\frac{[\text{P4: 2816: W: 2}]}{[\text{P4: 1222: W: 2}]}$	$[\text{P4: 2816: W: 2}] - [\text{P4: 1222: W: 2}]$
	$\frac{[\text{P4: 2816: W: 1}]}{[P4\text{: 1222: W: 1}]}$	$[\text{P4: 2816: W: 1}] - [\text{P4: 1222: W: 1}]$
	$\frac{[\text{P4: 2816: V: 2}]}{[\text{P4: 1222: V: 2}]}$	$[\text{P4: 2816: V: 2}] - [\text{P4: 1222: V: 2}]$
	$\frac{[P4\text{: 2816: V: 1}]}{[P4\text{: 1222: V: 1}]}$	$[\text{P4: 2816: V: 1}] - [\text{P4: 1222: V: 1}]$
To evaluate the immune responses elicited by a 2-dose primary heterologous vaccination with AZD1222/AZD2816 with a 4-week dosing interval relative to the response elicited by a 2-dose primary homologous vaccination with AZD1222 with a 4-week interval in previously unvaccinated participants	$\frac{[\text{P4: 1222/2816: V: 2}]}{[\text{P4: 1222: W: 2}]}$	$[\text{P4: 1222/2816: V: 2}] - [\text{P4: 1222: W: 2}]$
	$\frac{[\text{P4: 1222/2816: W: 2}]}{[\text{P4: 1222: W: 2}]}$	$[\text{P4: 1222/2816: W: 2}] - [\text{P4: 1222: W: 2}]$
	$\frac{[\text{P4: 1222/2816: V: 2}]}{[\text{P4: 1222: V: 2}]}$	$[\text{P4: 1222/2816: V: 2}] - [\text{P4: 1222: V: 2}]$
To evaluate the immune responses elicited by a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval relative to the response elicited by a 2-dose primary vaccination with AZD2816 with a 4-week interval in previously unvaccinated participants	$\frac{[\text{P12: 2816: W: 2}]}{[\text{P4: 2816: W: 2}]}$	$[\text{P12: 2816: W: 2}] - [\text{P4: 2816: W: 2}]$
	$\frac{[\text{P12: 2816: V: 2}]}{[\text{P4: 2816: V: 2}]}$	$[\text{P12: 2816: V: 2}] - [\text{P4: 2816: V: 2}]$

Table 22 Immunogenicity Comparisons for Previously Vaccinated Groups

Objective	$\frac{[\mathbf{GMT_{comparator}}]}{[\mathbf{GMT_{reference}}]}$	$\Delta = [\mathbf{Seroresponse_{comparator}}] - [\mathbf{Seroresponse_{reference}}]$
To evaluate the immune responses elicited by 1 dose of AZD2816 in participants previously vaccinated with AZD1222 relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated participants	$\frac{[\text{P1222: B2816: V}]}{[\text{P4: 1222: W: 2}]}$	$[\text{P1222: B2816: V}] - [\text{P4: 1222: W: 2}]$
	$\frac{[\text{P1222: B2816: W}]}{[\text{P4: 1222: W: 2}]}$	$[\text{P1222: B2816: W}] - [\text{P4: 1222: W: 2}]$
To evaluate the immune responses elicited by 1 dose of AZD2816 in participants previously vaccinated with a mRNA vaccine relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated participants	$\frac{[\text{PmRNA: B2816: V}]}{[\text{P4: 1222: W: 2}]}$	$[\text{PmRNA: B2816: V}] - [\text{P4: 1222: W: 2}]$
	$\frac{[\text{PmRNA: B2816: W}]}{[\text{P4: 1222: W: 2}]}$	$[\text{PmRNA: B2816: W}] - [\text{P4: 1222: W: 2}]$
To evaluate the immune responses elicited by 1 dose of AZD2816 in participants previously vaccinated with an mRNA vaccine relative to the response with 1 dose of AZD1222 in participants previously vaccinated with AZD1222	$\frac{[\text{PmRNA: B2816: V}]}{[\text{P1222: B1222: W}]}$	$[\text{PmRNA: B2816: V}] - [\text{P1222: B1222: W}]$
	$\frac{[\text{PmRNA: B2816: W}]}{[\text{P1222: B1222: W}]}$	$[\text{PmRNA: B2816: W}] - [\text{P1222: B1222: W}]$
	$\frac{[\text{PmRNA: B2816: V}]}{[\text{P1222: B1222: V}]}$	$[\text{PmRNA: B2816: V}] - [\text{P1222: B1222: V}]$
To evaluate the immune responses elicited by 1 dose of AZD2816 relative to the response with 1 dose of AZD1222 in participants previously vaccinated with AZD1222	$\frac{[\text{P1222: B2816: V}]}{[\text{P1222: B1222: W}]}$	$[\text{P1222: B2816: V}] - [\text{P1222: B1222: W}]$
	$\frac{[\text{P1222: B2816: W}]}{[\text{P1222: B1222: W}]}$	$[\text{P1222: B2816: W}] - [\text{P1222: B1222: W}]$
	$\frac{[\text{P1222: B2816: V}]}{[\text{P1222: B1222: V}]}$	$[\text{P1222: B2816: V}] - [\text{P1222: B1222: V}]$
To evaluate the immune responses elicited by 1 dose of AZD1222 in participants previously vaccinated with AZD1222 relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated participants	$\frac{[\text{P1222: B1222: V}]}{[\text{P4: 1222: W: 2}]}$	$[\text{P1222: B1222: V}] - [\text{P4: 1222: W: 2}]$
	$\frac{[\text{P1222: B1222: W}]}{[\text{P4: 1222: W: 2}]}$	$[\text{P1222: B1222: W}] - [\text{P4: 1222: W: 2}]$
To evaluate the immune responses elicited by 1 dose of AZD1222 in	$\frac{[\text{PmRNA: B1222: V}]}{[\text{P4: 1222: W: 2}]}$	$[\text{PmRNA: B1222: V}] - [\text{P4: 1222: W: 2}]$

Table 22 Immunogenicity Comparisons for Previously Vaccinated Groups

Objective	$\frac{[\mathbf{GMT}_{\mathbf{comparator}}]}{[\mathbf{GMT}_{\mathbf{reference}}]}$	$\Delta = [\mathbf{Seroresponse}_{\mathbf{comparator}}] - [\mathbf{Seroresponse}_{\mathbf{reference}}]$
participants previously vaccinated with an mRNA vaccine relative to the response elicited by a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in unvaccinated participants	$\frac{[\mathrm{PmRNA:B1222:W}]}{[\mathrm{P4:1222:W:2}]}$	$[\mathrm{PmRNA:B1222:W}] - [\mathrm{P4:1222:W:2}]$
To evaluate the immune responses elicited by 1 dose of AZD2816 versus 1 dose of AZD1222 in participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	$\frac{[\mathrm{PmRNA:B2816:V}]}{[\mathrm{PmRNA:B1222:W}]}$	$[\mathrm{PmRNA:B2816:V}] - [\mathrm{PmRNA:B1222:W}]$
	$\frac{[\mathrm{PmRNA:B2816:W}]}{[\mathrm{PmRNA:B1222:W}]}$	$[\mathrm{PmRNA:B2816:W}] - [\mathrm{PmRNA:B1222:W}]$
	$\frac{[\mathrm{PmRNA:B2816:V}]}{[\mathrm{PmRNA:B1222:V}]}$	$[\mathrm{PmRNA:B2816:V}] - [\mathrm{PmRNA:B1222:V}]$

9.4.4 Data Safety Monitoring Board

An independent COVID-19 Vaccine Data Safety Monitoring Board will provide oversight, to ensure safe and ethical conduct of the study. During the study, the benefit/risk assessment will be continuously monitored by the Board to ensure that the balance remains favourable. Further details, composition, and operation of the COVID-19 Vaccine Data Safety Monitoring Board will be described in a separate charter. For further details, see Appendix A 5.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Not applicable.

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

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

Regulatory Reporting Requirements for SAEs

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

A 2 Financial Disclosure

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

A 3 Informed Consent Process

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

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

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

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

A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

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

A 5 Committee Structure

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

A COVID-19 Vaccine Data Safety Monitoring Board comprised of independent experts will be convened to provide oversight and to ensure safe and ethical conduct of the study. The COVID 19 Vaccine Data Safety Monitoring Board will have the responsibility of evaluating cumulative safety and other clinical study data at regular intervals and making appropriate recommendations based on the available data. During the study, the benefit/risk assessment will be continuously monitored by the COVID-19 Vaccine Data Safety Monitoring Board to ensure that the balance remains favourable. Full details of the COVID-19 Vaccine Data Safety Monitoring Board composition and operations can be found in the COVID-19 Vaccine Data Safety Monitoring Board Charter.

An independent Neurological AESI Expert Committee will be available to review and provide on request about the diagnosis and causality assessment of selected neurological AEs of special interest occurring in the study. Details on the composition and operation of this committee are described in the Neurological AESI Expert Committee Charter.

A 6 Dissemination of Clinical Study Data

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

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

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

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A 9 Study and Site Start and Closure

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

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or ICH/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 IRB/IECs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of 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 SAEs and non-SAEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

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

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

AEs for **malignant tumours** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-SAE**. 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 hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life Threatening

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

Hospitalization

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

Important Medical Event or Medical Treatment

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

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used. Examples of important medical events include such events as listed below:

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

Intensity Rating Scale

A revised toxicity grading scale found in the US FDA guidance for healthy volunteers enrolled in a preventive vaccine clinical study (FDA 2007) will be utilized for all events with an assigned severity grading including Grade 5.

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

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

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 investigational product.

- 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 investigational product?
- Consistency with known investigational product profile. Was the AE consistent with the previous knowledge of the suspect investigational product (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 investigational product?
- 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 investigational product was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

- Is this a recognized feature of overdose of the investigational medicinal product?
- 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 3 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 investigational product, but rather a human or process related failure while the investigational product 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 investigational product
- 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:

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

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

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

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

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

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

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

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

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

C 2 Withdrawal of Informed Consent for Donated Biological Samples

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

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

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

The investigator:

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

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

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

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

Appendix D 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 23: Clinical Abnormalities, Local Reactions to Injectable Product
- Table 24: Clinical Abnormalities, Vital Signs
- Table 25: Clinical Abnormalities, Systemic (General or Illness)

Table 23 Tables for Clinical Abnormalities: Local Reactions to Injectable Product

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

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

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

ER: emergency room.

Table 24 Tables for Clinical Abnormalities: Vital Signs

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

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

Table 25 Tables for Clinical Abnormalities: Systemic (General or Illness)

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

Appendix E Adverse Events of Special Interest

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

Table 26 Adverse Events of Special Interest

Category	Medical Concept
Neurologic	Generalized convulsion: episodes of neuronal hyperactivity most commonly resulting in sudden, involuntary muscular contractions. They may also manifest as sensory disturbances, autonomic dysfunction and behavioural abnormalities, and impairment or loss of consciousness.
	Guillain-Barré syndrome: a peripheral nerve demyelinating disease, which can present as temporary ascending paralysis.
	Acute disseminated encephalomyelitis: defined as a uniphasic syndrome of brain inflammation and demyelination occurring in temporal association with an antecedent immunologic challenge, such as infection or an immunization. ADEM most commonly occurs in the paediatric population.
	Other neurologic events: include new onset event (acute or subacute) motor and sensory disturbances (eg, weakness, numbness, paraesthesia, hypoesthesia, hyperesthesia, dysesthesias), bowel/bladder dysfunction, gait impairment, or visual disturbance, or any event of myelitis, encephalomyelitis, myelitis transverse, or other sudden neurological deficit.
Vascular	Thrombotic, thromboembolic, and neurovascular events: events that can manifest as transient or permanent vision problems, dizziness, trouble understanding, facial droop, slurred speech, unilateral weakness, deep vein thrombosis with swollen, warm or painful leg, pulmonary embolism with shortness of breath, chest pain or irregular heart rate.
Hematologic	Thrombocytopenia: a disorder in which there is an abnormally low platelet count; a normal platelet count ranges from 150 000 to 450 000 platelets per µL.
Immunologic	Vasculitides: a group of related disorders characterized by inflammation of blood vessels (vasculitis) leading to tissue or end-organ injury.
	Anaphylaxis: an acute hypersensitivity reaction with multi-organ-system involvement that can present as, or rapidly progress to, a severe life-threatening reaction requiring immediate medical attention.
	Vaccine-associated enhanced respiratory disease: pathogenicity has been linked to a vaccine immune response characterized by induction of non-neutralizing antibodies, and a T-cell response of the Th2 type with hypereosinophilia (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: 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 27.

Table 27 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

Table 27 List of Potential Immune-mediated Medical Conditions

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, Bechet's syndrome, leukocytoclastic vasculitis

Table 27 List of Potential Immune-mediated Medical Conditions

Category	Condition
Other	Antiphospholipid syndrome
	Autoimmune haemolytic anaemia
	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 anaemia
	Raynaud's phenomenon
	Sarcoidosis
	Sjögren's syndrome
	Stevens-Johnson syndrome
	Uveitis

Appendix F Actions Required in Cases of Thrombotic Events With Thrombocytopenia and/or Bleeding

F 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of thrombotic events with thrombocytopenia and/or bleeding. It is not intended to be a comprehensive guide to the management of all venous thromboembolic events.

During the course of the study, the investigator will remain vigilant for occurrence of thrombotic events with thrombocytopenia and/or bleeding. Appropriate investigations (eg, imaging) to diagnose these events should be made on a case-by-case basis. The investigator is responsible for determining whether a participant meets criteria for thrombotic events with thrombocytopenia and/or bleeding at any point during the study.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting criteria for thrombotic events with thrombocytopenia and/or bleeding. The Study Physician contacts the investigator to provide guidance, discuss, and agree an approach for the participant's follow-up and the continuous review of data. Guidance from the International Society of Thrombosis and Haemostasis for management of thrombocytopenic thromboembolism occurring after vaccination can be found at www.isth.org. Notably, participants should only be treated with heparin if a test for heparin-induced thrombocytopenia antibodies is negative. An alternative explanation for thrombocytopenia should be considered (eg, alcohol use, liver cirrhosis, concomitant medications, exposure to toxic chemicals, viral infections).

The investigator is responsible for recording data pertaining to thrombotic events with thrombocytopenia and/or bleeding and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

F 2 Tests that Should Be Considered if Thrombotic Events With Thrombocytopenia and/or Bleeding Are Suspected

The following tests should be considered, but not limited to:

1. Measurement of platelet levels, prothrombin time, activated partial thromboplastin time, D-dimer levels, and fibrinogen levels

2. Complete blood count, reticulocyte count, blood film, haptoglobins

3. Anti-platelet factor 4 antibodies

4. Anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies, rheumatoid factor, human leucocyte antigen B27, ADAMTS13 activity, anti-cardiolipin antibodies IgG + IgM, and anti-B2GPI antibodies IgG + IgM

5. Complement (eg, C3, C4, complement complex C5b-9, C5a), autoantibodies (eg, antinuclear IgG, anti-double stranded DNA IgG, anti-Smith IgG, anti-SSA IgG, anti-SSB IgG, anti-Jo1 IgG, anti-MPO IgG, anti-PR3 IgG, anti-glomerular basement membrane IgG)

6. Factor V Leiden, Factor II (prothrombin) variant

7. Platelet activation markers and functional assays (eg: sCD40L, soluble glycoproteins, degranulation markers [PF4, vWF, P-selectin, annexin V]), anti-PF4-plasma-serotonin release assay (if anti-PF4 ELISA positive)

8. Inflammatory markers: TNFa, IL-1, IL-4, IL-6, IL-10, IL-13

9. Cell adhesion molecules: VCAM, ICAM, E-selectin

10. Adenovirus serology

11. Additional viral serology: Cytomegalovirus (IgG and IgM), Ebstein-Barr virus (IgG and IgM), HIV, Parvo virus B19

12. COVID-19 testing, including PCR and serology

13. Calculation of an International Society of Thrombosis and Haemostatis score for Disseminated Intravascular Coagulation (derived from platelet levels, fibrinogen, and D-Dimer)

Appendix G Abbreviations

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ChAdOx1 MERS	Chimpanzee adenovirus Ox1 with MERS Spike antigen
ChAdOx1 nCoV-19	AZD1222 when initially developed by the University of Oxford
COVID-19	Coronavirus disease 2019
eCRF	Electronic case report form
e-Diary	Electronic diary
GMT	Geometric mean titre
ICF	Informed consent form
ICH/GCP	International Council for Harmonisation/Good Clinical Practice
IRB/IEC	Institutional Review Board/ Independent Ethics Committee
IRT	Interactive Response Technology
MAAEs	Medically attended adverse events
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
S	Spike
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome-coronavirus-2

Appendix H Protocol Amendment History

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	2 June 2021
Version 1	14 May 2021

Amendment 1 (Protocol Version 2): 1 June 2021

Version 1 of the protocol was amended prior to the commencement of the study (ie, prior to approval of the protocol by an ethics committee) based on feedback from internal and regulatory authority reviews. The most substantial changes were as follows:

- addition of 2 treatment arms: 1) AZD1222 as a single booster vaccination in participants previously vaccinated with an mRNA COVID-19 vaccine and 2) heterologous vaccination with AZD1222 plus AZD2816 in previously unvaccinated participants
- further definition of analysis sets
- addition of thrombotic events with thrombocytopenia as a discontinuation criteria

In addition, corrections and revisions to text to improve readability were made.

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SIGNATURE PAGE

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Clinical Study Protocol	
Study Intervention	AZD2816
Study Code	D7220C00001
Version	Amendment GBR-2
Date	30 July 2021

TITLE PAGE

A Phase II/III Partially Double-Blinded, Randomised, Multinational, Active-Controlled Study in Both Previously Vaccinated and Unvaccinated Adults Ages 30 and Above to Determine the Safety and Immunogenicity of AZD2816, a Vaccine for the Prevention of COVID-19 Caused by Variant Strains of SARS-CoV-2

Sponsor Name:	**AstraZeneca AB**
Legal Registered Address:	151 85 Södertälje, Sweden
Regulatory Agency Identifier Numbers:	EudraCT: 2021-002530-17

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: D7220C00001

Amendment Number: GBR-2

Study Intervention: AZD2816

Study Phase: II/III

Short Title: Phase II/III Study of AZD2816, a Vaccine for the Prevention of COVID-19 in Adults

Study Physician Name and Contact Information will be provided separately.

International Coordinating Investigator: Andrew J Pollard, FRCPCH PhD FMedSci
University of Oxford
Oxford, United Kingdom

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment GBR-2	30 July 2021
Amendment GBR-1	3 June 2021
Amendment 1	1 June 2021
Version 1	14 May 2021

Amendment GBR-2: 30 July 2021

The principal reason for this amendment was to

1) add an additional interim analysis to evaluate immunogenicity in a subset of AZD1222 previously vaccinated subjects boosted with AZD1222 or AZD2816

2) revise Objectives/Endpoints from descriptive to comparative, with ranking of primary, key secondary, other secondary, and exploratory objectives

3) add non-inferiority margins to primary analysis and add additional participants to maintain power.

This amendment has also been implemented in the global version of the study D7220C00001 Clinical Study Protocol.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.1 Synopsis (Objectives and Endpoints)	Revised this section from primarily descriptive to primarily comparative. Comparative immunogenicity objectives created and ranked as primary, key secondary, other secondary.	Objectives of study changed from descriptive to comparative, testing for non-inferiority across treatment comparisons	Substantial
1.1 Synopsis (Number of Participants; Statistical Methods)	Overall size increased to 2590 participants	Adjustments made to maintain power with the added non-inferiority margins	Substantial
1.1 Synopsis (Statistical Methods)	An additional interim analysis added. Second interim analysis changed to include only the previously vaccinated with AZD1222 cohort.	Interim analysis plan was reviewed and revised.	Substantial
1.2 Schema	Figures updated with increased participant numbers	Adjustments made to maintain power with the added non-inferiority margins	Substantial
1.3 Schedule of Activities	Table 2: footnote clarification added Table 3: minor corrections	Clarification/Correction	Non-substantial
2.1 Study Rationale (and elsewhere in protocol)	Clarification on previous vaccination criteria	Clarification	Non-substantial
3 Objectives	Section completely rewritten. Divided into 2 sections: Previously unvaccinated and previously vaccinated. Immunogenicity objectives created for comparisons. Objectives ranked as primary, key secondary, other secondary, or exploratory.	Objectives of study changed to show non-inferiority across treatments.	Substantial
4.1 Overall design	Participant numbers increased	Adjustments made to maintain power with the added non-inferiority margins	Substantial
4.1 Overall design	Cap on age added	To ensure good representation across age groups	Substantial
8.3.2	Removal of severity grade 5	Correction	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
8.5.2.3 CCI [redacted]	Addition of information on number of patients sampled for CCI [redacted]	Clarification	Non-substantial
9.1 Statistical Hypotheses	Addition of statistical hypotheses	Include hypothesis being tested.	Substantial
9.2 Sample size determination	Confidence intervals for populations of 350 and 380 added to Table 14 and Table 15	Updated to include current populations of 350 and 380 participants	Non-substantial
9.2 Sample size determination	Power estimates for populations of 350 and 380 added to Table 17 and Table 18	Updated to include current populations of 350 and 380 participants	Non-substantial
9.4.1 General considerations	Details on the initial interim, second interim, and third interim analysis added	Include revised information on the analysis plan, including interim analyses	Substantial
9.4.3.1.1 Estimand framework for immunogenicity descriptions and comparisons	Objectives removed from descriptive analysis Table 23 and Table 24	Objectives of study changed from descriptive to comparative, showing non-inferiority across treatments	Substantial
9.4.3.1.1 Estimand framework for immunogenicity descriptions and comparisons	Section of Immunogenicity Comparisons added.	Objectives of study changed from descriptive to comparative, showing non-inferiority across treatments	Substantial
9.4.3.1.1 Estimand framework for immunogenicity descriptions and comparisons	Table 25 and Table 26 on immunogenicity comparisons revised, aligned with the revised objectives/endpoints.	Objectives of study changed from descriptive to comparative, showing non-inferiority across treatments	Substantial
9.4.4 Multiple Comparisons	Section added.	Objectives of study changed from descriptive to comparative, showing non-inferiority across treatments	Substantial

In addition, the protocol has been revised with minor corrections and clarifications.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A phase II/III partially double-blinded, randomised, multinational, active-controlled study in both previously vaccinated and unvaccinated adults to determine the safety and immunogenicity of AZD2816, a vaccine for the prevention of COVID-19 caused by variant strains of SARS-CoV-2.

Short Title: Phase II/III study of AZD2816, a vaccine for the prevention of COVID-19 in adults.

Rationale: Recently, several variants of the SARS-CoV-2 virus with increased transmissibility have emerged, including B.1.1.7, first identified in the UK, P.1, first identified in Brazil, and B.1.351, first identified in South Africa. In an ongoing clinical trial of AZD1222 in South Africa, interim results failed to show protection against mild to moderate disease caused by the B.1.351 variant; protection against severe disease could not be determined as no severe cases were identified (Madhi et al 2021).

Based on available evidence about vaccine effectiveness and molecular epidemiology of emerging variants, B.1.351 is estimated to have a potential to escape vaccine-induced immunity. B.1.351 carries sequence mutations in common with other variants of concerns; immunity to B.1.351 therefore has the potential to provide some cross-immunity against other emerging strains. Development of candidate vaccines that include the B.1.351 S-protein variant is underway. AstraZeneca is developing AZD2816, a vaccine against the B.1.351 SARS-CoV-2 variant using the same ChAdOx1 platform and manufacturing processes used for AstraZeneca's currently available COVD-19 vaccine, AZD1222.

Objectives and Endpoints:

The purpose of this study is to characterize the safety and immunogenicity of AZD2816, AstraZeneca's candidate ChAdOx1 vector vaccine against SARS-CoV-2 variant strain B.1.351, when administered:

- As a single booster dose to SARS-CoV-2 seronegative participants who previously received a 2-dose primary vaccination against SARS-CoV-2 with AZD1222 or an mRNA COVID-19 vaccine
- As a 2-dose primary homologous vaccination to SARS-CoV-2 seronegative participants who are previously unvaccinated
- As the second dose of 2-dose primary heterologous vaccination (with AZD1222 as first dose) to SARS-CoV-2 seronegative participants who are unvaccinated.

It is anticipated that the majority of the patients recruited in the United Kingdom will belong to the previously-vaccinated cohort that will receive a single booster dose of AZD2816 or AZD1222.

The following table lists the primary and secondary endpoints:

Objectives	Endpoints
Safety Objectives: Previously unvaccinated participants	
- Primary	
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose
- Secondary	
To characterize the safety and tolerability of a 2-dose primary heterologous vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in previously unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of a 2-dose primary heterologous vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in previously unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
Immunogenicity objectives: Previously unvaccinated participants	
To determine if the pseudoneutralizing antibody GMT response elicited by a 2-dose AZD2816 primary vaccination is non-inferior to the response elicited by a 2-dose AZD1222 primary vaccination Estimand:	

Treatment	AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination

Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Primary	B.1.351	Wuhan-hu-1
Key Secondary 2.2	B.1.351	B.1.351
Key Secondary 2.4	Wuhan-hu-1	Wuhan-hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD2816 vaccination/AZD1222 vaccination	
To determine if the seroresponse rate elicited by a 2-dose AZD2816 primary vaccination is non-inferior to the seroresponse rate elicited by a 2-dose AZD1222 primary vaccination Estimand:		
Treatment	AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Key Secondary 2.1	B.1.351	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 vaccination - AZD1222 vaccination	
To determine if the neutralizing antibody GMT response elicited by a 2-dose AZD1222+AZD2816 heterologous primary vaccination is non-inferior to the response elicited by a 2-dose AZD1222 primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Key Secondary 2.3	B.1.351	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD1222+AZD2816 vaccination/AZD1222 vaccination	
To determine if the seroresponse rate elicited by a 2-dose AZD1222+AZD2816 heterologous primary vaccination is non-inferior to the seroresponse rate elicited by a 2-dose AZD1222 primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD1222+AZD2816 vaccination - AZD1222 vaccination	
To determine if the neutralizing antibody GMT response against the B.1.351 variant is non-inferior to the response against the original Wuhan-hu-1 strain following a 2-dose AZD2816 primary vaccination Estimand:		
Treatment	AZD2816 vaccination	AZD2816 vaccination

Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 2-dose AZD2816 primary vaccination Estimand:		
Treatment	AZD2816 vaccination	AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) against B.1.351 versusWuhan-hu-1	
To determine if the neutralizing antibody GMT response against the B.1.351 variant is non-inferior to the response against the original Wuhan-hu-1 strain following a 2-dose AZD1222+AZD2816 heterologous primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222+AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 2-dose AZD1222+AZD2816 heterologous primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222+AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) against B.1.351 versusWuhan-hu-1	
To also determine non-inferiority of the s-protein binding antibody response for the above comparisons as other secondary objectives		
To also determine the neutralizing antibody GMT responses 28 days after first vaccination dose in the above primary and key secondary objectives		

Objectives	**Endpoints**
Safety Objectives: Previously vaccinated participants	
- Primary	

To characterize the safety and tolerability of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose
- Secondary	
To characterize the safety and tolerability of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
Immunogenicity objectives: previously vaccinated participants	
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:	

Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Primary	B.1.351	Wuhan-hu-1
Key Secondary 2.1	B.1.351	B.1.351
Key Secondary 2.3	Wuhan-hu-1	Wuhan-hu-1

Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 vaccination	
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose is non-inferior to response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Key Secondary 2.2	B.1.351	B.1.351
Key Secondary 2.5	Wuhan-hu-1	Wuhan-hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 booster	
To determine if the neutralizing antibody GMT response elicited by an AZD1222 booster dose in patients previously vaccinated with AZD1222 is non-inferior to the response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD1222 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective Level:	Serotype comparison:	
Key Secondary 2.4	Wuhan-hu-1	Wuhan-hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD1222 booster/AZD1222 vaccination	
To determine if the seroresponse elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other secondary	B.1.351	Wuhan-hu-1
Other secondary	B.1.351	B.1.351
Other secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 primary vaccination	
To determine if the seroresponse elicited by an AZD2816 booster dose is non-inferior to response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 booster	
To determine if the seroresponse elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD1222 booster	AZD1222 primary vaccination

Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 primary vaccination	
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose in participants previously vaccinated with an mRNA-based vaccine is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand		
Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	mRNA vaccine vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 vaccination	
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with an mRNA-based vaccine Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	mRNA vaccine vaccinated seronegative participants	mRNA vaccine vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 booster	
To determine if the seroresponse elicited by an AZD2816 booster dose in participants previously vaccinated with an mRNA-based vaccine is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	mRNA vaccine vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 primary vaccination	
To determine if the seroresponse elicited by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with an mRNA-based vaccine Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	mRNA vaccine vaccinated seronegative participants	mRNA vaccine vaccinated seronegative participants

Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 booster	
To determine if the neutralizing antibody GMT response rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 2816 booster dose. Estimand:		
Treatment	AZD2816 booster	AZD2816 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-hu-1	
To determine if the neutralizing antibody GMT response against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 1222 booster dose. Estimand:		
Treatment	AZD1222 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 2816 booster dose. Estimand:		
Treatment	AZD2816 booster	AZD2816 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for B.1.351/Wuhan-hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 1222 booster dose. Estimand:		
Treatment	AZD1222 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for B.1.351/Wuhan-hu-1	
To also determine non-inferiority of the s-protein binding antibody response for the above comparisons as other secondary objectives.		

SAEs: serious adverse events; MAAEs: medically attended adverse events; AESIs: adverse events of special interest.

[a] At least a 4-fold increase in geometric mean titre from baseline

Overall Design: This is a phase II/III, multinational, randomised, partially double-blind, controlled study in two distinct cohorts: previously vaccinated and previously unvaccinated participants.

Disclosure Statement: This is a parallel-group preventive study with 8 treatment arms.

Number of Participants: Approximately 2590 SARS-CoV-2 nucleocapsid seronegative participants will be assigned to study intervention to support the primary and secondary objectives of this study. In addition, participants that are SARS-Cov-2 nucleocapsid seropositive at screening will be enrolled and assigned to study intervention for an exploratory analysis, with a cap of 10% of the seronegative population (ie, approximately 259 total participants).

Intervention Groups and Duration: Previously vaccinated participants will receive 1 dose of AZD1222 or AZD2816 on Day 1. Previously unvaccinated participants will receive one of the following 2-dose vaccinations:

- 1 dose of AZD2816 on Day 1 and on Day 29
- 1 dose of AZD1222 on Day1 and on Day 29
- 1 dose of AZD1222 on Day 1 and 1 dose of AZD2816 on Day 29
- 1 dose of AZD2816 on Day 1 and on Day 85.

Participants will be followed up for safety for 180 days after last study vaccine administration.

Data Monitoring Committee: A Data Safety Monitoring Board will provide oversight to ensure safe and ethical conduct of the study.

Statistical Methods:

Sample sizes of 300-380 seronegative participants per group are deemed appropriate based upon available immunogenicity data from previous clinical studies with AZD1222 for the primary and secondary objectives of this study.

The safety analysis set for adverse events consists of all participants who have received at least one dose of study intervention. The immunogenicity analysis set includes all participants in the safety analysis set who have no protocol deviations or intercurrent events judged to have the potential to interfere with the generation or interpretation of an immune response.

An initial interim analysis will be performed on a subset of previously AZD1222 vaccinated participants that have received a booster dose to consider unblinded sample size adjustment. A second interim analysis will be performed when all previously AZD1222 vaccinated participants have completed their Day 29 visit to support registration of a booster dose. A third interim analysis will be performed on a subset of naïve previously unvaccinated

participants that have received their second dose to consider blinded sample size adjustment in this population. The primary analysis will be performed when there are data from all naïve participatns28 days after the second dose of the 4-week dosing intervals to support assessment of these 2-dose primary vaccinations. A secondary analysis will be performed on data from 28 days after the second dose of the 12-week dosing interval to support assessment of this 2-dose primary vaccination. The final analysis will be performed on data from 6 months follow-up after participant's vaccination.

1.2 Schema

Figure 1 Study Design for Unvaccinated Seronegative/Seropositive Participants Receiving a 2-Dose Primary Vaccination

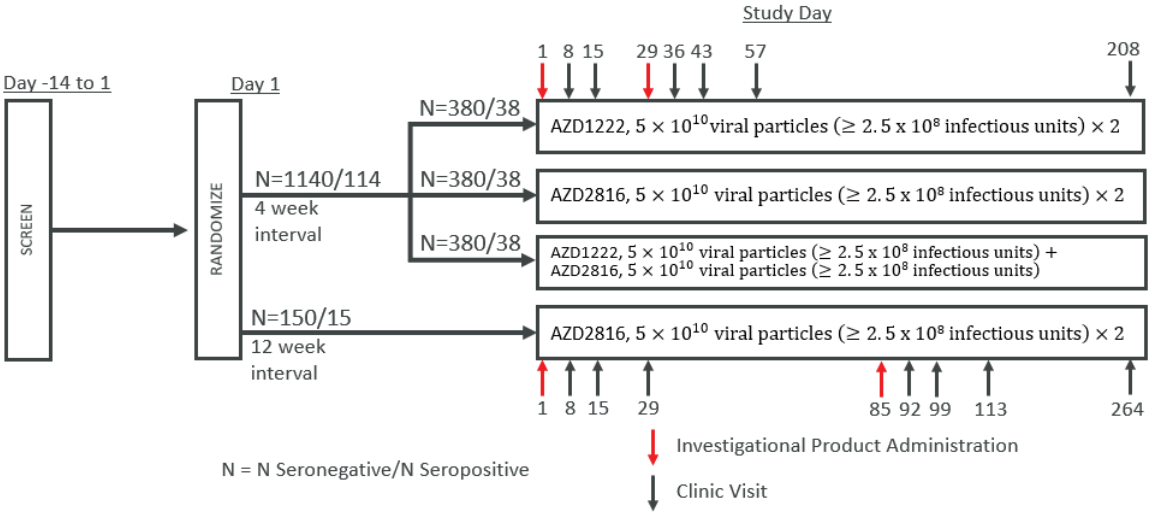
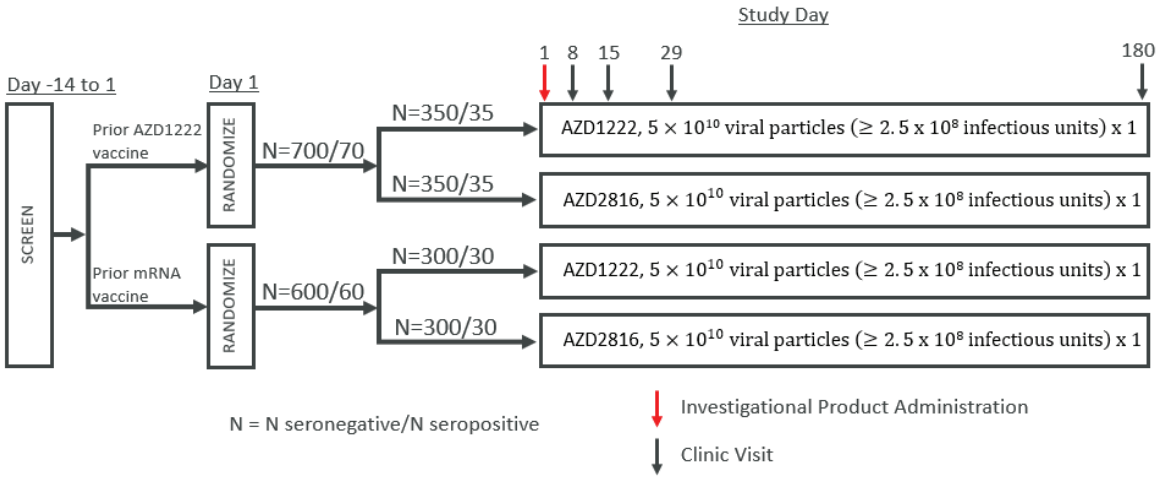


Figure 2 Study Design for Previously Vaccinated Seronegative/Seropositive Participants Receiving a 1-Dose Booster



Note: In addition to the approximately 2590 seronegative participants enrolled to support the primary/secondary objectives, seropositive participants will also be enrolled in the study to support exploratory objectives in this population, with a cap of 10% of the planned seronegative participants (ie, a maximum of 259 seropositive participants, bringing total enrollment to 2849).

1.3 Schedule of Activities

Table 1 Schedule of Activities: Screening

Procedure	Day -14 to Day 1	See Section
Informed consent	X	5.1, Appendix A 3
Demography	X	-
Medical and surgical history	X	-
Prior and concomitant medications	X	6.5
Complete physical examination, including height and weight	X	8.2.1
Vital signs	X	8.2.2
Urine pregnancy test (for women of childbearing potential only)	X	8.2.3
Clinical safety laboratory assessments	X	8.2.3
Assessment of serious adverse events	X	8.3, Appendix B
Blood sample for SARS-CoV-2 antibody testing (lateral flow test)	X	8.5.2
Verify eligibility criteria	X	5.1, 5.2

Note: Screening activities can occur at same visit as initial vaccination with investigational product (ie, Visit 1 in Table 2, Table 3, and Table 4).

Table 2 Schedule of Activities: Treatment/Follow-up Period for Participants Previously Vaccinated with 2 Doses of AZD1222 or an mRNA Vaccine

Procedure	Treatment and Follow-up Period					Section
Day	**1**	**8**	**15**	**29**	**180**	
Window (days)	**-**	**±2**	**±2**	**±3**	**±14**	
Medical and surgical history	X	-	-	-	-	-
Urine pregnancy test (women of childbearing potential)	X	-	-	-	-	8.2.3
Concomitant medications/vaccinations	X	X	X	X	X	6.5
Verify eligibility criteria	X	-	-	-	-	5.1, 5.2
Monitoring of COVID-19	X	X	X	X	X	8.3.8
Vaccine administration (after screening activities, the activities listed above, and the pre-dose sampling activities listed below)	X	-	-	-	-	6.1.1
Immunological assessments						
Serum sample to assess SARS-CoV-2 serology/neutralising antibodies	X (pre-dose)	-	X	X	X	8.5.2
Serum sample to assess additional immunogenicity	X (pre-dose)	-	X	X	X	8.5.2
Blood sample to assess B-cell and T-cell responses in a sub-group of participants	X (pre-dose)	-	X	X	X	8.5.2.3
Blood sample for B-cell and T-cell response sequencing in a sub-group of participants	X (pre-dose)	-	X	X	X	8.5.2.3
Safety assessments						
Targeted physical examination	X	-	-	-	-	8.2.1
Vital signs	X	X	X	X	X	8.2.2
e-Diary provided with training	X	-	-	-	-	8.3.7
e-Diary collected	-	X	-	-	-	8.3.7
Unsolicited AEs	X (post-dose)	X	X	X	-	8.3
MAAEs, SAEs, and AESIs	X[a]	X	X	X	X	8.3.8, 8.3.8
Clinical safety laboratory assessments	X (pre-dose)[b]	X	-	X	X	8.2.3

[a] Only SAEs pre-dose
[b] Not required to be repeated if performed on screening day prior to Day 1.

AE: adverse event; AESI: adverse event of special interest; MAAE: medically-attended adverse event; SAE: serious adverse event

Table 3 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 4-Week Dosing Interval

Procedure	Treatment and Follow-up Period								Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	
Day	**1**	**8**	**15**	**29**	**V4+7**	**V4+14**	**V4+28**	**V4+180**	
Window (days)	**-**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
Medical and surgical history	X	-	-	-	-	-	-	-	-
Urine pregnancy test (women of childbearing potential)	X	-	-	X	-	-	-	-	8.2.3
Concomitant medications/vaccinations	X	X	X	X	X	X	X	X	6.5
Verify eligibility criteria	X	-	-	-	-	-	-	-	5.1, 5.2
Monitoring of COVID-19	X	X	X	X	X	X	X	X	8.3.8
Vaccine administration (after screening activities, the activities listed above, and the pre-dose sampling activities listed below)	X	-	-	X	-	-	-	-	6.1.1
Immunogenicity assessments									
Serum sample for SARS-CoV-2 serology/neutralising antibodies	X (pre-dose)	-	X	X (pre-dose)	-	X	X	X	8.5.2
Serum sample for additional immunogenicity	X (pre-dose)	-	X	X (pre-dose)	-	X	X	X	8.5.2
Blood sample to assess B-cell and T-cell responses in a sub-group of participants	X (pre-dose)	-	X	X (pre-dose)	-	-	X	X	8.5.2.3
Blood sample for B-cell and T-cell response sequencing in a sub-group of participants	X (pre-dose)	-	X	X (pre-dose)	-	-	X	X	8.5.2.3
Safety assessments									
Targeted physical examination	X	-	-	X	-	-	-	-	8.2.1
Vital signs	X	X	X	X	X	X	X	X	8.2.2
e-Diary provided with training	X	-	-	X	-	-	-		8.3.7

Table 3 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 4-Week Dosing Interval

Procedure	**Treatment and Follow-up Period**								**Section**
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	
Day	**1**	**8**	**15**	**29**	**V4+7**	**V4+14**	**V4+28**	**V4+180**	
Window (days)	**-**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
e-Diary collected	-	X	-	-	X	-	-		8.3.7
Unsolicited AEs	X (post-dose)	X	X	X	X	X	X	-	8.3
MAAEs, SAEs, and AESIs	X[a]	X	X	X	X	X	X	X	8.3.8
Clinical safety laboratory assessments	X (pre-dose)	X	-	X (pre-dose)	X	-	X	X	8.2.3

[a] Only SAEs pre-dose

AE: adverse event; AESI: adverse event of special interest; MAAE: medically-attended adverse event; SAE: serious adverse event

Table 4 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 12-Week Dosing Interval

Procedure	Treatment and Follow-up Period									Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	
Day	**1**	**8**	**15**	**29**	**85**	**V5+7**	**V5+14**	**V5+28**	**V5+180**	
Window (days)	**-**	**±2**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
Medical and surgical history	X	-	-	-	-	-	-	-	-	-
Urine pregnancy test (women of childbearing potential)	X	-	-	-	X	-	-	-	-	8.2.3
Concomitant medications/vaccinations	X	X	X	X	X	X	X	X	X	6.5
Verify eligibility criteria	X	-	-	-	-	-	-	-	-	5.1, 5.2
Monitoring of COVID-19	X	X	X	X	X	X	X	X	X	8.3.8
Vaccine administration (after screening activities, the activities listed above, and the pre-dose sampling activities listed below)	X	-	-	-	X	-	-	-	-	6.1.1
Immunogenicity assessments										
Serum sample to assess SARS-CoV-2 serology/neutralising antibodies	X (pre-dose)	-	X	X	X (pre-dose)	-	X	X	X	8.5.2
Serum sample to assess additional immunogenicity	X (pre-dose)	-	X	X	X (pre-dose)	-	X	X	X	8.5.2
Blood sample to assess B-cell and T-cell responses in a sub-group of participants	X (pre-dose)	-	X	X	X (pre-dose)	-	-	X	X	8.5.2.3
Blood sample for B-cell and T-cell response sequencing in a sub-group of participants	X (pre-dose)	-	X	X	X (pre-dose)	-	-	X	X	8.5.2.3
Safety assessments										
Targeted physical examination	X	-	-	-	X	-	-	-	-	8.2.1
Vital signs	X	X	X	X	X	X	X	X	X	8.2.2
e-Diary provided with training	X	-	-	-	X	-	-	-		8.3.7

Table 4 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 12-Week Dosing Interval

Procedure	Treatment and Follow-up Period									Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	
Day	**1**	**8**	**15**	**29**	**85**	**V5+7**	**V5+14**	**V5+28**	**V5+180**	
Window (days)	**-**	**±2**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
e-Diary collected	-	X	-	-	-	X	-	-	-	8.3.7
Unsolicited AEs	X (post-dose)	X	X	X	X	X	X	X	-	8.3
MAAEs, SAEs, and AESIs	X[a]	X	X	X	X	X	X	X	X	8.3.8, 8.3.8
Clinical safety laboratory assessments	X (pre-dose)	X	-	X	X (pre-dose)	X	-	X	X	8.2.3

[a] Only SAEs pre-dose

AE: adverse event; AESI: adverse event of special interest; MAAE: medically-attended adverse event; SAE: serious adverse event

2 INTRODUCTION

AZD2816 is being developed for the prevention of COVID-19. It is a modified version of the current AstraZeneca SARS-CoV-2 vaccine (referred to as AZD1222 in clinical documentation) that has been modified to also provide immunity against the newly emerging SARS-CoV-2 variant strain B.1.351. Like AZD1222, AZD2816 is a recombinant replication-defective chimpanzee adenovirus vector (ChAdOx1) expressing the SARS-CoV-2 S surface glycoprotein driven by the human cytomegalovirus major immediate early promoter that includes intron A with a human tissue plasminogen activator leader sequence at the N terminus. AZD2816 differs from AZD1222 in that the S glycoprotein gene sequence used is from the B.1.351 variant strain instead of the original Wuhan-Hu-1 variant.

2.1 Study Rationale

The aim of the study is to assess the safety and immunogenicity of AZD2816 for prevention of COVID-19 as both a 2-dose primary vaccination in previously unvaccinated participants and a 1-dose booster vaccination in participants previously vaccinated against the original Wuhan-Hu-1 strain of SARS-CoV-2 by either AZD1222 or an mRNA-based vaccine. A safe and effective vaccine for COVID-19 prevention, including against the B.1.351 variant, would have significant global public health impact.

The study will also investigate the safety and immunogenicity of 1) a heterologous 2-dose vaccination with AZD1222 as first dose and AZD2816 as the second dose and 2) a single dose of AZD1222 as a booster vaccination in participants that have been previously vaccinated with an mRNA COVID-19 vaccine targeting the original Wuhan-Hu-1 strain.

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, which was named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (

Zhou et al 2020). The disease these patients contracted was subsequently named Coronavirus Disease 2019 (COVID-19). The World Health Organization declared the novel coronavirus a pandemic on 11 March 2020. The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has resulted in significant global morbidity and mortality as well as major disruption to healthcare systems. Measures to change the course of the pandemic have included the accelerated development vaccines against the original Wuhan-Hu-1 strain.

Coronaviruses are spherical, enveloped viruses with positive-sense single-stranded RNA genomes. SARS-CoV-2 belongs to the phylogenetic lineage B of the genus *Betacoronavirus*, and it is the seventh corona virus known to cause human infections and the third known to

cause severe disease after SARS-CoV and MERS-CoV. One fourth of the viral genome is responsible for coding structural proteins, such as the S glycoprotein, envelope, membrane, and nucleocapsid proteins. Envelope, membrane, and nucleocapsid proteins are mainly responsible for virion assembly while the S protein is involved in cellular receptor binding, mediating fusion of virus and cell membranes and virus entry into host cells during infection. The SARS-CoV-2 spike (S) glycoprotein is a type I trimeric, transmembrane protein that is located at the surface of the viral envelope forming spike-shaped protrusions. The S protein's subunits are responsible for cellular receptor angiotensin-converting enzyme 2 binding via the receptor binding domain and subsequent fusion of virus and cell membranes, thereby mediating the entry of SARS-CoV-2 into the target cells. The S protein has an essential role in virus entry and determines tissue and cell tropism, as well as host range. The roles of the S-protein in receptor binding and membrane fusion have made it a desirable target for vaccine and antiviral development. The AstraZeneca vaccine AZD1222 expresses a codon-optimized coding sequence for S protein from the SARS-CoV-2 genome sequence accession MN908947 (ie, the Wuhan-Hu-1 isolate).

To date, 5 vaccines that rely upon the expression of the SARS CoV-2 S glycoprotein to stimulate/prime a protective immune response against the virus have demonstrated safety and efficacy in phase III clinical trials. Four of these, AZD1222 (also referred to as ChAdOx1 nCoV-19, a recombinant replication-defective chimpanzee adenoviral vectored), BNT162b2 (Pfizer-BioNTech, mRNA), mRNA-1273 (Moderna, mRNA), and Ad26.COV2-S (Janssen, adenovirus serotype 26 vectored) have received Emergency Use Authorization or Conditional Marketing Approval in the United States and/or the European Union, and elsewhere, and NVX-CoV2373 (Novavax; recombinant 86 protein) has also shown efficacy and is likely to be in use in the near future. These vaccines have been designed based upon the initial reported genetic sequence of the S protein from Wuhan in January 2020 (Lu et al 2020).

The immunogenicity and efficacy of AZD1222 has been shown in clinical trials (Ramasamy et al 2020, Voysey et al 2021a, Voysey et al 2021b). Immunogenicity data indicate that a single dose of AZD1222 elicits both humoral and cellular immunogenicity responses and that antibody responses are boosted after a second dose. In a pooled analysis of the 4 studies conducted in the United Kingdom, Brazil, and South Africa (database lock 07 December 2020), the vaccine was highly immunogenic; seroresponse of S binding antibody was > 98% after a single dose of AZD1222. Seroresponse of live neutralising antibody was 82.4% after 1 dose, which rose to 99.4% after a second dose. Efficacy analyses of the pooled DCO2 data demonstrated effective protection of AZD1222 against COVID-19 with a vaccine efficacy of 66.73% (95.84% CI: 57.41%, 74.01%) ($p < 0.001$) from 15 days after the second dose in seronegative participants receiving 2 doses. The DCO2 data also demonstrated that the standard dose of AZD1222 (5×10^{10} viral particles) provides complete protection against COVID-19 hospital admission ≥ 22 days after the first dose in the seronegative analysis set (0 versus 14 cases in the control group, 2 of which were severe, including one with a fatal

outcome). Vaccine efficacy was similar in participants with pre-existing comorbidities, being those at greatest risk of severe outcomes of COVID-19, compared to that in the general population. Recently available primary analysis data from a Phase III study performed in the United States and Latin America showed primary endpoint vaccine efficacy of 76% (95% CI: 67.60%, 82.22%; p-value < 0.001).

A sharp rise in COVID-19 cases was reported in late 2020, which was attributed to the emergence of new SARS-CoV-2 variant strains: B.1.1.7 in the United Kingdom, B.1.351 in South Africa, and P.1 in Brazil. These variant strains carry a number mutations in the S protein sequence: 9 amino acids in B.1.1.7, 10 amino acids in B.1.351, and 12 amino acids in P.1 compared with the Wuhan-Hu-1 sequence. These mutations may result in an increase of transmissibility and/or reduced vaccine effectiveness. Variant B.1.351 was first identified in South Africa in October 2020. Its attributes include approximately 50% increased transmission and moderate impact of neutralization by monoclonal antibody therapeutics, convalescent plasma and vaccine sera. In vitro neutralization assays suggest that the B.1.351 lineage viruses may be the most antigenically distinct from the original Wuhan-like strains (Zhou et al 2021). In addition, evidence suggests that AZD1222 may afford diminished protection against mild-moderate COVID-19 disease arising from the B.1.351 variant which is also antigenically the most different from the Wuhan-Hu-1 virus (Madhi et al 2021).

The development of candidate vaccines that would be effective against the B.1.351 variant strain is underway. AZD2816 is being developed as an updated ChADOx-nCOv19 vaccine designed to provide protective immunity against the newly arising B.1.351 variant strain, using the same ChAdOx1 platform and manufacturing processes used for AstraZeneca's currently approved COVID-19 vaccine, AZD1222. The purpose of this Phase II/III, multinational, randomised, partially double-blind, active-controlled study is to demonstrate the safety and characterize the immunogenicity of AZD2816, AstraZeneca's candidate ChAdOx1 vector vaccine against B.1.351, when administered:

- As a single booster dose to SARS-CoV-2 seronegative participants who have previously received a 2-dose primary vaccination series against the original SARS-CoV-2 Wuhan-hu-1 strain (AZD1222 or an mRNA vaccine)
- As a 2-dose homologous primary vaccination to SARS-CoV-2 seronegative participants who have not been vaccinated previously.

It is anticipated that the majority of the patients recruited in the United Kingdom will belong to the previously-vaccinated cohort that will receive a single booster dose.

The immunogenicity of a 2-dose primary heterologous vaccination (with AZD1222 as first dose and AZD2816 as second dose) to SARS-CoV-2 seronegative participants who are unvaccinated and a single booster dose of AZD1222 to SARS-CoV-2 seronegative

participants who have previously received a 2-dose primary mRNA vaccination series against the original SARS-CoV-2 Wuhan-hu-1 strain will also be investigated.

SARS-CoV-2 seropositive participants will be enrolled in separate cohorts to support a parallel exploratory analysis in these participants.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD1222 and AZD2816 is provided in the respective Investigator's Brochures.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of AZD2816 and AZD1222 can be found in the respective Investigator's Brochures.

2.3.1 Risk Assessment

AZD2816 has been developed using the same vaccine vector, ChAdOx1, as AZD1222 and only differs in the sequence for SARS-CoV-2 S glycoprotein that is inserted in the vector. The anticipated safety profile of AZD2816 is the same as the observed safety profile of AZD1222. Risks associated with AZD2816 are thus the same as the risks associated with AZD1222, and no additional risks are anticipated due to the change in the targeted sequence.

A number of essentially mild and moderate adverse reactions to AZD1222 have been identified and resemble reactions frequently observed after many vaccines. Based on pooled clinical data from studies with AZD1222, the most commonly expected local solicited AEs for participants in this study are vaccination site pain and tenderness. The most commonly expected systemic solicited AEs are fatigue, headache, and malaise. The majority of reported events have been 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.

Post-authorisation hypersensitivity reactions, including anaphylaxis and angioedema, have occurred following administration of AZD1222 and are considered an identified risk.

A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with COVID-19 Vaccine (ie, AZD1222) during post-authorisation use. No events have been observed in the AZD1222 clinical development programme. Thrombosis in combination with thrombocytopenia is thus considered to be an important identified risk. This includes cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. Considering the frequency of this rare event and the size of this study, the risk for participants in this trial is considered to be low. The protocol includes exclusion criteria and instructions for

heightened vigilance and thorough investigations for suspected cases to mitigate against further the risk for these rare event.

Important potential risks are 1) neurologic events and potential immune-mediated neurologic conditions and 2) vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease.

2.3.2 Benefit Assessment

All participants will receive active treatment: either AZD1222, which has been shown to be effective in providing protection against SARS-CoV-2, or AZD2816, which as a modified form of AZD1222 designed to be effective against the emergent B.1.351 variant strain and may also provide participants with protection. The information gained from this study will inform development decisions with regard to the efficacy of AZD2816 as both a primary 2-dose vaccination in participants that have not been previously vaccinated and a 1-dose booster vaccination in participants previously vaccinated against SARS-CoV-2.

2.3.3 Benefit: Risk Assessment for Inclusion of Adults from 30 to 39 Years of Age

There have been reports of very rare adverse events of concurrent thrombosis and thrombocytopenia following vaccination with the first dose of AstraZeneca CoV-19 vaccine (AZD1222). There have been no safety concerns identified for thrombosis/thrombocytopenia associated with the second dose of the AstraZeneca (AZD1222) vaccine. Up to 19 May 2021, the MHRA has received reports of 332 cases of major thromboembolic events with concurrent thrombocytopenia in the United Kingdom following vaccination with COVID-19 Vaccine AstraZeneca. The estimated number of first doses of COVID-19 Vaccine AstraZeneca administered was 24.2 million, and the estimated number of second doses was 10.7 million.

Any risk for serious thromboembolic events with thrombocytopenia is expected to be similar for AZD1222 and AZD2816 due to the similarity of the investigational products.

In the context of this extremely rare adverse event, current advice from the United Kingdom's Joint Committee on Vaccination and Immunization (JCVI) recommends that unvaccinated adults aged 30 to 39 years who are not in a clinical priority group at higher risk of severe COVID-19 disease should be preferentially offered an alternative to AZD1222 where possible and only where no substantial delay or barrier in access to vaccination would arise (JCVI 2021). The recommendations are not a contra-indication in this age group but a public vaccination policy recommendation in the context of a current low incidence of disease, the availability of alternative vaccines, and current speed and uptake of the vaccination programme overall in the UK. The recommendations further advise that AZD1222 can be

used in the age group 30-39 if these factors deteriorate, stating that if other vaccines are not available “the benefits of receiving the AstraZeneca (AZD1222) vaccine outweigh the risks”.

The participants of the proposed study differ from the general public in that they are carefully selected, with exclusion of individuals with a wide range of risk factors for thrombosis/thrombocytopenia, to minimize this risk. The study also includes careful monitoring both pre-treatment and post-treatment to detect risk for thrombotic events with thrombocytopenia and promptly identify safety concerns at the individual participant level. The protocol and training for the investigators urges increased vigilance for these events of thrombosis with thrombocytopenia. Furthermore, Appendix F provides guidance on identifying, treating, and assessing these very rare events. The risk of these events occurring is disclosed in the Participant Information Sheet and Informed Consent Form. Furthermore, participants are advised to be alert for the following side effects in the 28 days after vaccination: severe/unusual headache, new or unexplained bruising/bleeding, shortness of breath, chest pain, leg swelling, persistent abdominal pain. The exclusion of individuals with a wide range of risk factors for thrombosis with thrombocytopenia and measures included in the study to ensure early detection of these events mitigates the risk for these rare events.

With regard to benefit, all patients enrolled in the study will receive active treatment, either with the approved AZD1222, which has a good safety profile and high efficacy in adults ages 18 and over, including protection against severe disease, or the experimental but closely related AZD2816, which is expected to have a similar safety profile with the potential to have broader efficacy than AZD1222, including against the emergent B.1.351 variant. Furthermore, the inclusion of these patients in the trial is important to investigate safety and immunogenicity of AZD2816, as both a primary vaccination and a booster vaccination, across the age groups for which it may be administered in clinical practice.

To summarise, the risk of serious harm due to vaccine-induced thrombotic thrombocytopenia is known to be small. As of 19 May 2021, the MHRA’s estimate of the overall incidence after first or unknown doses is 1.3 per 100,000 doses. Thus, the risk of one of these events occurring in the sub-group of participants 30 to 39 year of age from a study population of around 2000 patients is extremely low. This risk is appropriately mitigated in the study protocol to the extent that the risk-benefit of patients 30 to 39 years of age participating in this study is considered to be small, acceptable, and justified by the potential public health benefits of the study.

2.3.4 Overall Benefit: Risk Conclusion

For the safety of participants, the protocol has incorporated various risk mitigation measures including appropriate inclusion and exclusion criteria and close monitoring of participants to minimize known and potential risks.

An independent Data Safety Monitoring Board will provide study oversight, evaluating cumulative safety and other clinical data at regular intervals.

Taking these measures into account, the potential risks identified in association with the administration of AZD2816 and AZD1222 are justified by the anticipated benefit that may be afforded to participants for the prevention of COVID-19.

3 OBJECTIVES AND ENDPOINTS

3.1 Naïve unvaccinated cohort receiving a 2-dose primary vaccination

The primary safety objective for the cohort of previously unvaccinated participants receiving a 2-dose dose primary vaccination is to characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in previously unvaccinated seronegative participants.

The primary and key secondary immunogenicity objectives for this cohort are as follows:

Primary:

1: To determine if the neutralizing antibody GMT response against the B.1.351 variant elicited by a 2-dose AZD2816 vaccination is non-inferior to the response against the original Wuhan-hu-1 strain elicited by a 2-dose AZD1222 vaccination.

Key secondary:

2.1: To determine if seroresponse against the B.1.351 variant elicited by a 2-dose AZD2816 vaccination is non-inferior to seroresponse against the original Wuhan-hu-1 strain elicited by a 2-dose AZD1222 vaccination**.**

2.2: To determine if the neutralizing antibody GMT response against the B.1.351 variant elicited by a 2-dose AZD2816 vaccination is non-inferior to the response elicited by a 2-dose AZD1222 vaccination.

2.3: To determine if the neutralizing antibody GMT response against the B.1.351 variant elicited by a 2-dose heterologous AZD1222 + AZD2816 vaccination is non-inferior to the response against the original Wuhan-hu-1 strain elicited by a 2-dose AZD1222 vaccination

2.4: To determine if the neutralizing antibody GMT response against the original Wuhan-hu-1 elicited by a 2-dose AZD2816 vaccination is non-inferior to the response elicited by a 2-dose AZD1222 vaccination

The above primary and the key secondary immunogenicity objectives will be supported by other secondary immunogenicity objectives (see below) for which there will be no formal hypothesis testing.

Table 5 further describes the objectives and endpoints for this cohort of participants, including estimands for the immunogenicity objectives.

Table 5 Study Objectives and Endpoints for Previously Unvaccinated Participants Receiving a 2-Dose Primary Vaccination

Safety Objectives	
Objectives	**Endpoints**
- Primary	
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose
- Secondary	
To characterize the safety and tolerability of a heterologous primary vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in previously unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety and tolerability of a heterologous primary vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
Immunogenicity Objectives	
To determine if the pseudoneutralizing antibody GMT response elicited by a 2-dose AZD2816 primary vaccination is non-inferior to the response elicited by a 2-dose AZD1222 primary vaccination Estimand:	

Treatment	AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Primary	B.1.351	Wuhan-hu-1
Key Secondary 2.2	B.1.351	B.1.351
Key Secondary 2.4	Wuhan-hu-1	Wuhan-hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD2816 vaccination/AZD1222 vaccination	
To determine if the seroresponse rate elicited by a 2-dose AZD2816 primary vaccination is non-inferior to the seroresponse rate elicited by a 2-dose AZD1222 primary vaccination Estimand:		
Treatment	AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Key Secondary 2.1	B.1.351	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 vaccination - AZD1222 vaccination	
To determine if the neutralizing antibody GMT response elicited by a 2-dose AZD1222+AZD2816 heterologous primary vaccination is non-inferior to the response elicited by a 2-dose AZD1222 primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Key Secondary 2.3	B.1.351	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD1222+AZD2816 vaccination/AZD1222 vaccination	
To determine if the seroresponse rate elicited by a 2-dose AZD1222+AZD2816 heterologous primary vaccination is non-inferior to the seroresponse rate elicited by a 2-dose AZD1222 primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD1222+AZD2816 vaccination - AZD1222 vaccination	

To determine if the neutralizing antibody GMT response against the B.1.351 variant is non-inferior to the response against the original Wuhan-hu-1 strain following a 2-dose AZD2816 primary vaccination Estimand:		
Treatment	AZD2816 vaccination	AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 2-dose AZD2816 primary vaccination Estimand:		
Treatment	AZD2816 vaccination	AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) against B.1.351 versusWuhan-hu-1	
To determine if the neutralizing antibody GMT response against the B.1.351 variant is non-inferior to the response against the original Wuhan-hu-1 strain following a 2-dose AZD1222+AZD2816 heterologous primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222+AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 2-dose AZD1222+AZD2816 heterologous primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222+AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) against B.1.351 versusWuhan-hu-1	
To also determine non-inferiority of the s-protein binding antibody response for the above comparisons as other secondary objectives		
To also determine the neutralizing antibody GMT responses 28 days after first vaccination dose in the above primary and key secondary objectives		
To explore anti-vector responses to the ChAdOx-1 adenovirus vector following a 2-dose homologous or	• GMT of ChAdOx1 neutralizing antibody titres	

heterologous primary vaccination with AZD2816 and/or AZD1222 in sub-groups of seronegative and seropositive participants	• Seroresponse rate of ChAdOx1 neutralizing antibody titres Pairwise correlations between anti-S, pseudo-neutralization, and ChAdOx1 neutralizing antibody titres, 1 month after both Dose 1 and Dose 2
Exploratory Objectives	
Objective	Endpoints
To explore the immune response elicited by a 2-dose AZD2816 primary vaccination with a 12-week dosing interval compared to the response elicited by a 2-dose AZD2814 primary vaccination with a 4-week dosing interval	• GMT ratio of pseudoneutralizing antibodies • Seroresponse
To explore antibody response to selected SARS-CoV-2 variants of interest/variants of concern following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in a sub-group of seronegative participants	• GMT of SARS-CoV-2 anti-S binding antibodies for selected variants of concern/variants of interest • Seroresponse rate of SARS-CoV-2 specific binding antibody titres for selected variants of concern/variants of interest • GMT of SARS-CoV-2 pseudoneutralizing antibody responses against the B.1.617.2 (delta) variant • Seroresponse rate of SARS-CoV-2 pseudoneutralizing antibody responses against the B.1.617.2 (delta) variant
To explore B-cell and T-cell responses following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in a sub-group of seronegative participants	• Intracellular cytokine staining and flow cytometry for T-cell responses over time • Quantification of (IFN-γ) ELISpot responses to SARS-CoV-2 B.1.351 or Wuhan-Hu-1 S protein from day of dosing baseline over time • Breadth and depth of peripheral blood B-cell and T-cell repertoire over time through immunosequencing
To monitor the incidence of SARS-CoV-2 infection following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in previously unvaccinated seronegative participants	• The incidence of SARS-CoV-2 infection defined by the seroresponse to nucleocapsid antibodies occurring post-second dose of study intervention
To monitor the incidence of COVID-19 following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in previously unvaccinated seronegative participants	• Incidence of COVID-19, defined as SARS-CoV-2 RT-PCR-positive symptomatic illness.
To explore the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in sub-groups of seronegative and seropositive participants	• Magnitude of SARS-CoV-2 neutralization titres (geometric mean titre) as determined by a live virus neutralization assay • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres as determined by a live virus neutralization assay

To explore additional immune responses following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in sub-groups of seronegative and seropositive participants	• Other exploratory assays for humoral and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data
To explore the immunogenicity objectives in seropositive participants	• GMT of pseudoneutralizing antibodies • Seroresponse rates

MAAEs: medically attended adverse events; SAEs: serious adverse events; AESIs: adverse events of special interest

[a] Seroresponse: An at least 4-fold increase in geometric mean titre from baseline.

3.2 Previously vaccinated cohort receiving a 1-dose booster vaccination

The primary safety objective for the cohort of seronegative previously vaccinated participants receiving a booster dose is to characterize the safety and tolerability of 1 booster dose of AZD2816 in participants previously vaccinated with AZD1222.

The primary and key secondary immunogenicity objectives for this cohort are as follows:

Primary:

1: To determine if the humoral immune response against the B.1.351 variant elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to the response against the original Wuhan-hu-1 strain elicited by 2-dose AZD1222 vaccination administered to vaccination naïve participants.

Key secondary:

2.1: To determine if the humoral immune response against the B.1.351 variant elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to the response elicited by 2-dose AZD1222 vaccination administered to vaccination naïve participants.

2.2: To determine if the humoral immune response elicited against the B.1.351 variant by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222.

2.3: To determine if the humoral immune response against the original Wuhan-hu-1 strain elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to the response elicited by 2-dose AZD1222 vaccination administered to vaccination naïve participants.

2.4: To determine if the humoral immune response against the original Wuhan-hu-1 strain elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 is non-inferior to the response elicited by a 2-dose AZD1222 vaccination

2.5: To determine if the humoral immune response against the original Wuhan-hu-1 strain elicited by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222.

The primary and key secondary immunogenicity objectives will be supported by other secondary objectives for which there will be no formal hypothesis testing.

Table 6 further describes the objectives and endpoints for this cohort of participants, including estimands for the primary and secondary immunogenicity objectives.

Table 6 Study Objectives and Endpoints for Previously Vaccinated Participants Receiving a 1-Dose Booster

Safety Objectives	Endpoints
- Primary	
To characterize the safety and tolerability of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Incidence of local and systemic solicited AEs for 7 days post dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose
- Secondary	
To characterize the safety and tolerability of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination

To characterize the extended safety of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination

Immunogenicity objectives

To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination
Estimand:

Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Primary	B.1.351	Wuhan-hu-1
Key Secondary 2.1	B.1.351	B.1.351
Key Secondary 2.3	Wuhan-hu-1	Wuhan-hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 vaccination	

To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose is non-inferior to response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222
Estimand:

Treatment	AZD2816 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Key Secondary 2.2	B.1.351	B.1.351
Key Secondary 2.5	Wuhan-hu-1	Wuhan-hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 booster	

To determine if the neutralizing antibody GMT response elicited by an AZD1222 booster dose in patients previously vaccinated with AZD1222 is non-inferior to the response elicited by a 2-dose AZD1222 vaccination
Estimand:

Treatment	AZD1222 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective Level:	Serotype comparison:	
Key Secondary (2.4)	Wuhan-hu-1	Wuhan-hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD1222 booster/AZD1222 vaccination	

To determine if the seroresponse elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination
Estimand:

Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other secondary	B.1.351	Wuhan-hu-1
Other secondary	B.1.351	B.1.351
Other secondary	Wuhan-hu-1	Wuhan-hu-1

Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 primary vaccination	
To determine if the seroresponse elicited by an AZD2816 booster dose is non-inferior to response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 booster	
To determine if the seroresponse elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD1222 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 primary vaccination	
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose in participants previously vaccinated with an mRNA-based vaccine is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	mRNA vaccine vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 vaccination	
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with an mRNA-based vaccine Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	mRNA vaccine vaccinated seronegative participants	mRNA vaccine vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	Wuhan-hu-1	Wuhan-hu-1

Other Secondary	B.1.351	B.1.351
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 booster	
To determine if the seroresponse elicited by an AZD2816 booster dose in participants previously vaccinated with an mRNA-based vaccine is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	mRNA vaccine vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 primary vaccination	
To determine if the seroresponse elicited by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with an mRNA-based vaccine Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	mRNA vaccine vaccinated seronegative participants	mRNA vaccine vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	Wuhan-hu-1	Wuhan-hu-1
Other Secondary	B.1.351	B.1.351
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 booster	
To determine if the neutralizing antibody GMT response rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 2816 booster dose. Estimand:		
Treatment	AZD2816 booster	AZD2816 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-hu-1	
To determine if the neutralizing antibody GMT response against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 1222 booster dose. Estimand:		
Treatment	AZD1222 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-hu-1
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-hu-1	

<table>
<tr><td colspan="3">To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 2816 booster dose.
Estimand:</td></tr>
<tr><td>Treatment</td><td>AZD2816 booster</td><td>AZD2816 booster</td></tr>
<tr><td>Population</td><td>AZD1222 vaccinated seronegative participants</td><td>AZD1222 vaccinated seronegative participants</td></tr>
<tr><td>Timepoint</td><td>28 days after booster administration</td><td>28 days after booster administration</td></tr>
<tr><td>Objective level:</td><td colspan="2">Serotype comparison:</td></tr>
<tr><td>Other Secondary</td><td>B.1.351</td><td>Wuhan-hu-1</td></tr>
<tr><td>Endpoint</td><td colspan="2">Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for B.1.351/Wuhan-hu-1</td></tr>
<tr><td colspan="3">To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 1222 booster dose.
Estimand:</td></tr>
<tr><td>Treatment</td><td>AZD1222 booster</td><td>AZD1222 booster</td></tr>
<tr><td>Population</td><td>AZD1222 vaccinated seronegative participants</td><td>AZD1222 vaccinated seronegative participants</td></tr>
<tr><td>Timepoint</td><td>28 days after booster administration</td><td>28 days after booster administration</td></tr>
<tr><td>Objective level:</td><td colspan="2">Serotype comparison:</td></tr>
<tr><td>Other Secondary</td><td>B.1.351</td><td>Wuhan-hu-1</td></tr>
<tr><td>Endpoint</td><td colspan="2">Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for B.1.351/Wuhan-hu-1</td></tr>
<tr><td colspan="3">To also determine non-inferiority of the s-protein binding antibody response for the above comparisons as other secondary objectives.</td></tr>
<tr><td>To explore anti-vector responses to the ChAdOx-1 adenovirus vector following a booster dose of AZD2816 in sub-groups of seronegative and seropositive participants</td><td colspan="2">• Magnitude of ChAdOx1 nAb titres (geometric mean titre)
• Seroresponse rate of ChAdOx1 neutralizing antibody titres
Pairwise correlations between anti-S, pseudo-neutralization, and ChAdOx1 neutralizing antibody titres, 1 month after both Dose 1 and Dose 2</td></tr>
<tr><td>Exploratory Objectives</td><td colspan="2">Endpoints</td></tr>
<tr><td>To explore antibody response to selected SARS-CoV-2 variants of interest/variants of concern following a booster dose of AZD2816 and in a sub-group of seronegative participants</td><td colspan="2">• Magnitude of SARS-CoV-2 specific antibody binding titres (geometric mean titre) for selected variants of concern/variants of interest
• Seroresponse rate of SARS-CoV-2 specific antibody binding titres for selected variants of concern/variants of interest
• GMT of SARS-CoV-2 pseudoneutralizing antibody responses against the B.1.617.2 (delta) variant
• Seroresponse rate of SARS-CoV-2 pseudoneutralizing antibody responses against the B.1.617.2 (delta) variant</td></tr>
<tr><td>To explore B-cell and T-cell responses following a booster dose of AZD2816 in a sub-group of seronegative participants</td><td colspan="2">• Intracellular cytokine staining and flow cytometry for T-cell responses over time</td></tr>
</table>

	• Quantification of (IFN-γ) ELISpot responses to SARS-CoV-2 B.1.351 or Wuhan-Hu-1 S protein from day of dosing baseline over time • Breadth and depth of peripheral blood B-cell and T-cell repertoire over time through immunosequencing
To monitor the incidence of SARS-CoV-2 infection following a booster dose of AZD2816 in previously vaccinated seronegative participants	• The incidence of SARS-CoV-2 infection defined by the presence of nucleocapsid antibodies occurring post-dose of study intervention
To monitor the incidence of COVID-19 following a booster dose of AZD2816 in previously vaccinated seronegative participants	• Incidence of COVID-19, defined as SARS-CoV-2 RT-PCR-positive symptomatic illness.
To explore the immunogenicity objectives in seropositive participants	• GMT of pseudoneutralizing antibodies • Seroresponse rates

MAAEs: medically attended adverse events; SAEs: serious adverse events; AESIs: adverse events of special interest.

[a] Seroresponse: An at least 4-fold increase in geometric mean titre from baseline.

4 DESIGN

4.1 Overall Design

This is a multi-country Phase II/III study to evaluate the safety and immunogenicity of AZD2816 as single-dose vaccination in previously vaccinated adult participants and as a 2-dose primary vaccination in previously unvaccinated adult participants.

A total of approximately 2590 SARS-CoV-2 nucleocapsid seronegative participants that have been screened and judged to be eligible for the study will be enrolled across these 2 populations with the goal of 1300 previously vaccinated participants receiving single-dose vaccination and 1050 unvaccinated participants receiving 2-dose primary vaccination. In addition, seropositive participants will be enrolled (with a cap of 10% of the seronegative population or 259 participants) to support exploratory analysis is these participants.

The enrollment and randomization strategy is intended to minimize group differences in terms of age, gender and the presence of comorbidities; to support this strategy, the study randomisation will include caps to ensure that at least 25% of enrolled participants within each treatment arm will be ≥ 65 years of age.

In both the single-dose booster treatment regimen and the 2-dose primary vaccination treatment regimen, participants will receive study intervention consisting of intramuscular administration of either AZD1222 (5×10^{10} viral particles) or AZD2816 (5×10^{10} viral particles).

Approximately 700 seronegative participants previously vaccinated with AZD1222 will be randomised 1:1 to receive a single intramuscular dose of either AZD1222 or AZD2816 in a double-blinded fashion.

Approximately 600 seronegative participants previously vaccinated with an approved mRNA based vaccination against the original Wuhan-hu-1 strain will be randomised 1:1 to receive a single intramuscular dose of AZD2816 or AZD1222 in a double-blinded fashion.

It is anticipated that the majority of the patients recruited in the United Kingdom will belong to 1 of the 2 above previously-vaccinated groups.

Approximately 1290 seronegative, previously unvaccinated participants will be randomised approximately 5:5:5:2 to receive a 2-dose primary vaccination of the following:

- 2 doses of AZD1222 with a 4-week dosing interval
- 2 doses of AZD2816 with a 4-week dosing interval
- 1 dose of AZD1222 followed by 1 dose of AZD2816 with a 4-week dosing interval
- 2 doses of AZD2816 with a 12-week dosing interval.

The 3 treatments with a 4-week dosing interval will be double-blinded while the treatment with the 12-week interval will be open-label due to the difference in dosing interval. In addition, a smaller population seropositive participants (approximately 10% of the seronegative population), will be randomised to treatment in a similar manner as above.

Immunogenicity (ie, anti-Wuhan-Hu-1 and anti-B.1.351 immune responses including S-binding antibody titres and neutralizing antibody levels [pseudo-neutralization]) will be assessed in serum samples collected pre-dose on the day of each vaccination (baseline levels before vaccination), 14 and 28 days after each vaccination, and 180 days after the last vaccination.

All participants will be given a thermometer, tape measure or ruler, and a proprietary e-diary application designed for use with a smart device with instructions for use. All participants will be asked to report on solicited signs and symptoms for 7 days following vaccination (Days 1-8 for all participants and Days 29-36 for the 4-week dosing interval and Days 85-92 for the 12-week dosing interval). An e-diary will be used to collect information on the timing and severity of the solicited signs and symptoms.

Follow-up visits will take place as per the schedule of assessment within respective windows. All participants will be assessed for local and systemic AE, physical examination, review of e-diaries at these time points as detailed in the schedule of assessment. Blood will also be taken for safety assessments and immunology purposes.

All study participants will be followed for safety for 180 days after administration of their last vaccination dose. In every participant, solicited local and systemic events will be reported for up to 7 days after each dose, all unsolicited AEs will be reported for up to 28 days after each dose, and SAEs and AEs of special interest will be evaluated through study completion (up to 180 days after the last study vaccination).

An independent COVID-19 Vaccine Data Safety Monitoring Board will provide oversight, to ensure safe and ethical conduct of the study.

4.1.1 COVID-19 Assessments

Occurrence of COVID-19 in the trial will be reported as safety events, including monitoring of the potential risk of vaccine-induced enhanced disease as an AE of special interest (see Appendix E). COVID-19 will be diagnosed and treated as per standard medical practice. In addition, experimental treatments are permitted. Detailed information will be collected in a standard way and reported on a specific case report form.

4.1.2 Screening

All potential participants will be screened, which may take place at a visit up to 14 days prior to Day 1 or on Day 1 itself.

Informed consent will be obtained before screening/enrollment. If written consent is obtained, the screening procedures specified in the Schedule of Activities (Section 1.3) will be undertaken including a medical history, physical examination, height and weight, a SARS-CoV-2 screening test and clinical safety laboratory assessments. Baseline information collected in the previously vaccinated participants will include which vaccine was received, immunization dose interval, and time since last vaccination.

For women of childbearing potential, it will be recorded that they verbally confirmed use of one highly effective form of birth control for at least 28 days prior to the planned vaccination and a urine pregnancy test will be performed that must be negative for the participant to be enrolled. (Note: Women with urine test results that are positive or undetermined will not be enrolled and should be advised to seek medical attendance outside the context of the trial if pregnancy is suspected.)

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 enrollment or to withdraw a participant from the study will be at the discretion of the Investigator.

4.1.3 Vaccination Visit

Participants will be considered enrolled at the point of vaccination. Before vaccination, the eligibility of the participant will be reviewed. Body temperature will be observed and a medical history and physical examination will be undertaken before the first vaccination to determine need to postpone vaccination or screen fail the participant. A negative pregnancy test (urine test) will need to be obtained from women of childbearing potential before vaccination. Baseline blood samples will be obtained before the first vaccination.

Participants will receive 1 dose of AZD2816 or AZD1222 at vaccination visits, administered by intramuscular injection. Previously immunized participants will have a single vaccination visit, Day 1. Participants that have not been previously vaccinated at baseline will have a second vaccination visit on Day 29 (4-week interval) or Day 85 (12-week interval).

All participants will be given a thermometer, tape measure or ruler, and a proprietary e-diary application designed for use with a smart device with instructions for use. All participants will be asked to report on solicited signs and symptoms for 7 days following vaccination (Days 1 to 8 and Days 29 to 36 or Days 85 to 92 when applicable).

4.1.4 Follow-up visits

Follow-up visits will take place as specified in the Schedule of Activities (Section 1.3). All participants will be assessed for local and systemic AE, physical examination, review of the e-diary and blood tests at these time points as detailed in the Schedule of Activities. Blood will also be taken for safety and immunogenicity assessments.

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 the last study visit in order to collect information on any SAEs/AE of special interest.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Study Design and Participant Population

The participant population includes adults ≥ 30 years of age. Persons who are healthy or have medically stable underlying conditions will be eligible. Adults with medically-stable chronic diseases may participate if, according to the judgement of the investigator, hospitalization within the study period is not anticipated and the participant appears likely to be able to remain on study through the end of protocol-specified follow-up.

For the primary and secondary objectives, those enrolled in the study must test negative for SARS-CoV-2 nucleocapsid protein antibody during screening. Some seropositive participants (capped at 10% of the seronegative participant population) will be enrolled to support an exploratory analysis.

Those enrolled in the single-dose vaccination part of the study must have received 2 doses of AZD1222 (with a dosing interval of 4-12 weeks) or 2 doses of an approved mRNA-based COVID-19 vaccine (with a dosing interval of 3-12 weeks for the BNT162b2 mRNA vaccine [Pfizer-BioNTech] and 4-12 weeks for the mRNA-1273 vaccine [Moderna]) with the second doses administered at least 3 months prior to first study intervention administration.

Pregnant/breastfeeding women, persons with severe immunodeficiency or severe underlying disease will be excluded from participation in the study. Persons previously vaccinated with AZD1222 in the context of an AZD1222 vaccine trial are eligible for enrollment as previously vaccinated participants in the trial. Persons who have previously received any other investigational product for the prevention of COVID-19 will be excluded from participation in this study.

Participants with known risk factors for thrombosis and thrombocytopenia (excluding contraceptive hormonal therapy or replacement hormonal therapy) are excluded.

4.2.2 Rationale for Study Endpoints

There is no statistical hypothesis testing planned for this study. Descriptive statistics will support evaluation of safety, reactogenicity, and immunogenicity.

An interim analysis will occur when all previously vaccinated participants have completed their Day 29 visit. A second interim analysis may be conducted when previously unvaccinated participants have completed their Day 29 visit.

The primary analysis will occur when all participants have completed their Day 29 visit AND all previously unvaccinated participants randomised to a 4-week dosing interval have completed their Day 57 visit (ie, 28 days after their second dose).

A secondary analysis will occur when all participants have completed their Day 29 visit AND all previously unvaccinated participants (including those randomised to either a 4-week or a 12-week dosing interval) have completed their Day 57/Day 113 visit (ie, 28 days after their second dose).

The final analysis will occur when data from all vaccinated participants are available through completion of the last study visit (180 days after the single dose for previously vaccinated participants/180 days after the second dose for unvaccinated participants).

The primary safety analysis includes:

- Incidence of local and systemic solicited AEs for 7 days following each vaccination will be summarized by day and overall.

- Incidence of unsolicited AEs for 28 days following each vaccination will be summarized by system organ class and preferred term, and by relationship to vaccination as assessed by the investigator.
- SAEs and AEs of special interest following the first vaccination and throughout the study duration will be summarized by system organ class and preferred term and by relationship to vaccination as assessed by the investigator.

Solicited AEs will be collected for 7 days after each dose of study intervention, a period that has proven adequate to describe reactogenicity events in previous vaccine studies. For all participants, AEs will be collected through 28 days after each dose of study intervention. SAEs, medically-attended AEs, and AEs of special interest and will be collected from Day 1 through end of the study. AEs of special interest include terms identified by the Brighton Collaboration involving events associated with vaccination in general .

The immunogenicity endpoints of interest in this study are:

- Geometric mean titre
- Seroresponse, defined as ≥ 4-fold increase in the geometric mean titre from baseline

Geometric mean titre ratios and differences in seroresponses with 95% confidence intervals will be presented to support selected comparisons of immunogenicity across groups of interest.

Immunogenicity against SARS-CoV-2 Wuhan-Hu-1 and B.1.351 strains will be characterized through the quantification of Spike-binding antibodies, pseudo-neutralization and, in a subset of participants, live neutralization. Exploratory analysis of immunogenicity against other strains and induction of other immune effectors including cell-mediated immunity will be conducted.

4.3 Justification for Dose

The AZD2816 nominal dose of 5×10^{10} viral particles is the same dose as the approved dose for AZD1222, which was based on the accumulated non-clinical data and clinical data from the AZD1222 clinical studies, as well as from other SARS-CoV-2 vaccines in development. Safety and immunogenicity data from an additional clinical study, MERS001(NCT03399578), using the same ChAdOx1 vector, also helped inform dose selection. MERS001 was the first clinical study of a ChAdOx1-vectored vaccine expressing the full-length S protein from a separate, but related, beta-coronavirus. ChAdOx1 MERS has been given to 31 participants to date at doses ranging from 5×10^{9} viral particles to 5×10^{10} viral particles. Despite higher reactogenicity observed at the 5×10^{10} viral particles, this dose was safe, with self-limiting AEs and no serious adverse reactions recorded. The 5×10^{10} viral particles was the most immunogenic, in terms of inducing neutralizing antibodies 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} viral particles dose was chosen for AZD1222.

Based on accumulating nonclinical and clinical data gathered for AZD1222, a 2-dose regimen was selected for vaccination of unvaccinated participants with AZD2816 (AZD1222 Investigators Brochure). A single dose vaccination has been selected for participants previously vaccinated in line with both FDA and EMA guidance (FDA 2021, EMA 2021).

4.4 End of Study Definition

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

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

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as a protocol waiver or exemption, is not permitted.

5.1 Inclusion Criteria

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

5.1.1 All Participants:

Age

1 Adult, ≥ 30 years of age at the time of consent

COVID-19

For inclusion in the SARS-CoV-2 seronegative population supporting the primary and secondary objectives:

2 No history of laboratory-confirmed SARS-CoV-2 infection (ie, no positive nucleic acid amplification test and no positive antibody test).

3 Seronegative for SARS-CoV-2 at screening (lateral flow test to detect reactivity to the nucleoprotein).

Note, patients failing to meet criteria 2 and/or 3 may be included in the separate seropositive population supporting the seropositive exploratory objectives.

Type of Participant

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

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

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

6 Signed informed consent obtained before conducting any study-related procedures

Reproduction

7 Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
Female participants:

(a) Women of childbearing potential must:

- Have a negative pregnancy test on the day of screening and on days of vaccination
- 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 30 days following administration of the 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 7). Periodic abstinence, the rhythm method, and withdrawal are NOT acceptable methods of contraception.

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

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

    Until follicle-stimulating hormone is documented to be within menopausal range, the participant is to be considered of childbearing potential
  - For women aged ≥50 years, post-menopausal is defined as having a history of ≥12 months amenorrhea prior to randomization, without an alternative cause, following cessation of exogenous sex-hormonal treatment.

Table 7 Highly Effective Methods of Contraception

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

[a] This is also considered a hormonal method
[b] Provided that partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success
[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse from 28 days prior to Day 1 through 30 days following administration of the second dose of study intervention, and if it is the preferred and usual lifestyle of the participant

5.1.2 Previously COVID-19 Vaccinated Participants

8 Prior completion of a 2-dose primary homologous vaccination regimen against the original SARS-CoV-2 Wuhan-hu-1 strain with either AZD1222 (2 standard doses as authorized vaccine or as investigational product in a clinical trial with a 4- to 12-week dosing interval) or with an mRNA vaccine approved for emergency or conditional use (eg, BNT162b2 vaccine [Pfizer-BioNTech] with a 3- to 12-week dosing interval or mRNA-1273 vaccine [Moderna] with a 4- to 12-week dosing interval). The second dose in all cases should have been administered at least 3 months prior to first administration of study intervention.

5.2 Exclusion Criteria

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

Medical Conditions

1 History of allergy to any component of AZD1222/AZD2816.

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

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

4 Any confirmed or suspected immunosuppressive or immunodeficient state, including asplenia or HIV/AIDS.

5 Recurrent severe infections and use of immunosuppressant medication within the past 6 months (≥ 20 mg per day of prednisone or its equivalent, given daily or on alternate days for ≥ 15 days within 30 days prior to administration of study intervention)
The following exceptions are permitted:
   - Topical/inhaled steroids or short-term oral steroids (course lasting ≤ 14 days)

6 History of primary malignancy except for:
   (a) Malignancy with low potential risk for recurrence after curative treatment (for example, history of childhood leukaemia) or for metastasis (for example, indolent prostate cancer) in the opinion of the site investigator.
   (b) Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
   (c) Adequately treated uterine cervical carcinoma in situ without evidence of disease
   (d) Localized prostate cancer

7 History of thrombocytopenia and/or thrombosis, including participants who have experienced major venous and/or arterial thrombosis in combination with thrombocytopenia following vaccination with any COVID-19 vaccine

8 History of heparin-induced thrombocytopenia, congenital thrombophilia (ie, factor V Leiden, prothrombin G20210A, antithrombin III deficiency, protein C deficiency and protein S deficiency, factor XIII mutation, familial dysfibrinogenemia), auto-immune thrombophilia (antiphospholipid syndrome, anti-cardiolipin antibodies, anti-β_2-glycoprotein 1 antibodies), or paroxysmal nocturnal haemoglobinuria.

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

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

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

12 Any autoimmune conditions, except mild psoriasis and vitiligo

Note: The AEs of special interest as outlined in Appendix E (including Table 28) should be considered when evaluating a participant for exclusion criteria as the presence of these AEs of special interest, especially if untreated or uncontrolled, may be a safety risk to the participant, affect the ability of the participant to participate in the study, and/or impair interpretation of the study data. Investigators should review and consider the list of conditions in Appendix E. If any of these conditions are present in a participant, the Investigator is asked to utilize his/her clinical judgment in determining the participant's eligibility for the study. Should the

participant have conditions as outlined in Appendix E and the participant is enrolled, the Investigator is asked to document notes on site regarding the final rationale for enrollment.

Prior/Concomitant Therapy

13 Receipt of or planned receipt of investigational products indicated for the treatment or prevention of SARS-CoV-2 or COVID-19 with the exception of prior vaccination with AZD1222 or an mRNA COVID-10 vaccine (2 doses of the same vaccine within an approved dosing interval, see Section 5.1.2), which is allowed for participants in the previously vaccinated cohort
Note: For participants who develop COVID-19, receipt of licensed treatment options and/or participation in investigational treatment studies is permitted

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

15 Receipt of any influenza vaccine (licensed or investigational) within 7 days prior to and after administration of AZD1222/AZD2816.

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

Other Exclusions

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

18 Women who are currently pregnant (confirmed with positive pregnancy test), breastfeeding, having given birth less than 3 months before or planning pregnancy during the study.

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

20 Participants with a history of chronic alcohol or drug abuse or any condition associated with poor compliance.

21 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements or if vaccination would interfere with the participant's ongoing treatment.

22 Previous enrollment in the present study.

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 assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

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

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention, marketed product, or placebo intended to be administered to or medical device utilized by a study participant according to the study protocol. Study intervention is defined as AZD2816 or AZD1222 (Table 8).

6.1 Study Interventions Administered

6.1.1 Investigational Products

Table 8 Investigational Products

Intervention Name	AZD2816	AZD1222
Type	Vaccine	Vaccine
Dose Formulation	CCI [redacted]	CCI [redacted]
Unit Dose Strength	1×10^{11} viral particles/mL	1×10^{11} viral particles/mL
	$\geq 5 \times 10^{8}$ infectious units/mL	$\geq 5 \times 10^{8}$ infectious units/mL
Dosage Level	5×10^{10} viral particles (nominal, $\pm 1.5 \times 10^{10}$ viral particles)	5×10^{10} viral particles (nominal, $\pm 1.5 \times 10^{10}$ viral particles)
	$\geq 2.5 \times 10^{8}$ infectious units	$\geq 2.5 \times 10^{8}$ infectious units
Route	Intramuscular	Intramuscular
Use	Experimental	Experimental
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor

Packaging and Labelling	Will be provided in vials within a carton. Each carton and vial will be labelled as required per country requirement	Will be provided in vials within a carton. Each carton and vial will be labelled as required per country requirement
Current/Former Name	-	Previous clinical documentation: ChAdOx1 nCoV-19 Current tradename: Vaxzevria

IMP: investigational medicinal product; NIMP: non-investigational medical product; w/v: weight/volume.

AZD2816
AZD2816 will be supplied by the Sponsor as a vial solution for injection. It is a sterile, clear to slightly opaque solution, practically free from visible particles. Each vial of AZD2816 has a label-claim volume of 5 mL and can provide up to ten 0.5 mL doses.

AZD1222

AZD1222 will be supplied by the Sponsor as a vial solution for injection. It is a sterile, clear to slightly opaque solution, practically free from visible particles. Each vial of AZD1222 has a label-claim volume of 4 mL and can provide up to eight 0.5 mL doses.

Unopened vials of AZD2816 and AZD1222 must be stored at 2-8 ºC (36-46 ºF) for the duration of the assigned shelf-life and must not be frozen. Both investigational products must be kept in original packaging until use to prevent prolonged light exposure.

6.1.2 Dosing Instructions

Previously unvaccinated participants will receive 2 doses of either AZD1222, AZD2816, or AZD1222 plus AZD2816, with the first dose administered on Day 1 and the second dose on Day 29 (for a 4-week dosing interval) (Table 3) or Day 85 (for a 12-week dosing interval) (Table 4).

Previously vaccinated participants will receive 1 dose of either AZD1222 or AZD2816 (Table 2).

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

All study participants will be observed in the clinic for at least 15 minutes after vaccination. Allergic reactions to vaccines are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

6.2 Preparation/Handling/Storage/Accountability

The procedures for preparation, handling, storage, and accountability are identical for AZD2816 and AZD1222.

1 The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2 Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
3 The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4 Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual or specified handling instructions.

6.2.1 Dose Preparation and Administration

Doses of AZD2816 and 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 AZD2816 or AZD1222 in a sterile syringe.

AZD2816 and AZD1222 do not contain preservatives. Each vial must be assigned a beyond-use-date of 6 hours at 2-30 °C (36-86 °F) from first needle puncture of the vial, after which any unused portion must be discarded.

Once an AZD2816 or AZD1222 dose is drawn into a syringe for administration, the dose must be administered within the beyond-use-date of the vial. If dose administration is not completed within the 6-hour vial beyond-use-date, a new dose must be prepared from a new vial.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization

The study contains 3 cohorts that are randomised to a total of 8 treatments:

- Participants that have previously been vaccinated with 2 doses of AZD1222 will be randomised 1:1 to 1 dose of AZD2816 or 1 dose of AZD1222.
- Participants that have been previously vaccinated with an mRNA COVID-19 vaccine will be randomised 1:1 to 1 dose of AZD2816 or AZD1222.
- Vaccination naïve participants that will be randomised 2:2:2:1 to 2 doses of AZD2816 with a 4-week dosing interval, 2 doses of AZD1222 with a 4-week dosing interval, 1 dose of AZD1222 followed by 1 dose of AZD216 with a 4-week dosing interval, or 2 doses of AZD2816 with a 12-week dosing interval.

Separate populations of SARS-CoV-2 seronegative participants (supporting the primary and secondary objectives) and SARS-CoV-2 seropositive participants (supporting exploratory objectives) will be randomised/included in the above cohorts.

Randomization will be stratified based on age (less than 65, 65 and above), gender, and presence of at least one of the following comorbidities that are known risk factors for severe illness from COVID-19 (based on the participant's past and current medical history):

- Obesity (BMI $\geq$ 30 kg/m^2 at baseline)
- Significant cardiovascular disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, or pulmonary hypertension)
- Chronic lung disease (eg, chronic obstructive pulmonary disease, idiopathic pulmonary disease, cystic fibrosis, or moderate to severe asthma)
- Diabetes .

The randomised participants will be centrally assigned to randomised study intervention using an Interactive Response Technology (IRT)/Randomisation and Trial Supply Management. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information & directions for the Randomisation and Trial Supply Management will be provided to each site.

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

6.3.2 Blinding

Treatment will be double-blinded for previously vaccinated participants randomised to a single dose of either AZD2816 or AZD1222. Treatment will also be double-blind for previously unvaccinated participants randomised to 2 dose vaccinations with a 4-week dosing interval (ie, homologous AZD2816 or AZD1222 vaccination or heterologous AZD1222/AZD2816 vaccination). Previously unvaccinated participants randomised to a homologous AZD2816 vaccination with a 12-week dosing interval will receive treatment in an open-label fashion due to the different dosing interval.

For the double-blinded treatments, neither the participant nor any of the investigators or Sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the study intervention received. Since AZD2816 and AZD1222 are visually distinct prior to dose preparation (due to differences in container closure), all investigational 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, AZD2816 and AZD1222 are not visually distinct from each other.

The IRT will provide the investigators with a dose tracking number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IRT user manual that will be provided to each study site.

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

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

6.3.3 Procedures for Unblinding

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

In the event that a study participant is contacted about receiving a licensed and/or authorized COVID-19 vaccine outside of this clinical study, unblinding instructions are being provided to the sites. If the participant is unblinded, the Sponsor needs to be notified within 24 hours, and this should be documented in the site source documents.

6.4 Study Intervention Compliance

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

6.5 Concomitant Therapy

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

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

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

6.5.1 Permitted Concomitant Medications

- Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance.
- Primary care providers, or where appropriate investigators, should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study.
- Participants who develop COVID-19 after receiving study intervention should be treated with licensed medications and interventions according to standard of care. All routine vaccinations other than influenza are permitted beginning > 30 days after last dose of study intervention. Licensed influenza vaccines are permitted 7 days before and 7 days after administration of study intervention.
- Topical/inhaled steroids or short-term oral steroids (course lasting ≤ 14 days) are permitted

6.5.2 Prohibited Concomitant Medications

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

- Primary or booster vaccinations, other than AZD2816 or AZD1222, for prevention of SARS-CoV-2 or COVID-19**.**

  Note: Participants choosing to receive a licenced and/or authorized COVID-19 vaccine should inform the Investigator so it can be properly documented. Participants, who receive a licenced and/or authorized COVID-19 vaccine outside the study, should be encouraged to continue study conduct to be followed for safety reporting and all assessments.

- Receipt of any vaccine (licensed or investigational) other than licensed influenza vaccines within 30 days prior to and after administration of study intervention. Thirty days after the second vaccination, other routine vaccinations are permitted as clinically indicated.
- Glucocorticoids at a dose ≥ 20 mg/day of prednisone or equivalent given daily or on alternate days for ≥ 14 consecutive days between randomization and the participant's scheduled final visit
- Other systemically administered drugs with significant immunosuppressive activity, such as azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy between randomization and the participant's scheduled final visit
- Immunoglobulins and/or any blood product.

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

6.6 Dose Modification

Study intervention will be administered as described in Section 6.1. Dose modification is not permitted.

6.7 Intervention After the End of the Study

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

An individual participant will not receive the first or second dose (if applicable) of study intervention if any of the following occur in the participant in question:

1 Withdrawal of consent after signing informed consent
2 Participant meets one or more of the exclusion criteria or fails to meet all inclusion criteria for study participation
3 Participant is pregnant or nursing
4 Any grade 3 or greater allergic reaction including anaphylaxis that is assessed as related to study intervention
5 Occurrence of any thrombosis with concurrent thrombocytopenia
6 Any SAE assessed as related to study intervention

7 Any AE that, in the judgment of the site investigator, is related to study intervention and may jeopardize the safety of the study participant

8 Receipt of a prohibited concomitant medication that may jeopardize the safety of the study participant or interpretation of the data

Each participant who has received at least 1 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.

In the event that a study participant receives a licensed and/or authorized COVID-19 vaccine during the study, AstraZeneca needs to be notified within 24 hours and this should be documented in the site source documents. Participants who have received study intervention, regardless of reason, will be followed for the full study period.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Sponsor Study Team. If the participant does not specifically request withdrawal of consent for use of samples, then the samples collected prior to the consent withdrawal will be destroyed once per protocol analysis is complete.

7.3 Lost to Follow-up

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

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

- The study site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Schedule of Activities (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 Schedule of Activities (Section 1.3) is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities.

8.1 Efficacy Assessments

Not applicable.

8.2 Safety Assessments

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

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

8.2.2 Vital Signs

Vital signs, including heart rate, pulse oximetry, blood pressure, and body temperature, will be performed as specified in the Schedule of Activities (Section 1.3). The participant should be resting prior to the collection of vital signs. On vaccination days, vital signs should be assessed prior to vaccine administration.

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

8.2.3 Clinical Laboratory Assessments

Blood samples for determination of clinical chemistry and haematology will be taken at the visits indicated in the Schedule of Activities (Section 1.3). Additional unscheduled safety samples may be collected if clinically indicated at the discretion of the investigator, with the date and time of collection recorded in the appropriate eCRF.

The standard clinical chemistry and haematology analysis will be performed at a local laboratory at or near to the investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The following laboratory variables will be measured:

Table 9 Laboratory Safety Variables

Blood	Serum/Plasma
Haemoglobin	Activated partial thromboplastin time
Leukocyte count	Prothrombin time
Leukocyte differential count (absolute count)	Fibrinogen

Platelet count	D-dimer
-	Creatinine
-	Bilirubin, total
-	Alkaline phosphatase
-	Aspartate aminotransferase
-	Alanine aminotransferase

In case a participant shows an aspartate aminotransferase **or** alanine aminotransferase ≥ 3 × upper limit of normal together with total bilirubin ≥ 2 × the upper limit of normal, please refer to Section 8.3.6

For women participants of childbearing potential, a urine sample for pregnancy testing will be collected according to the Schedule of Activities (Section 1.3). Urine pregnancy tests for β-human chorionic gonadotropin may be performed at the site using a licensed dipstick test.

8.3 Adverse Events and Serious Adverse Events

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

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

Solicited AEs are local or systemic predefined events for assessment of reactogenicity. Solicited AEs will be collected in a e-diary (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 the reporting of solicited AEs via e-diary unless otherwise noted..

All other AEs are considered to be unsolicited AEs (collected by ‘open question’ at study visits).

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

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

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

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

Solicited AEs will be recorded for 7 days after each dose of study intervention (ie, Day 1 through Day 8). If a solicited AE is not resolved within the e-diary reporting period, the event will be reported as a non-solicited adverse event in the eCRF, with a start date of when started and the actual stop date.

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

Medically-attended AEs and AEs of special interest will be recorded from Day 1 through the last participant contact.

See the Schedule of Activities for the scheduled timepoints (Section 1.3).

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 Adverse Events and Serious Adverse Events

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. The Sponsor retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

AE variables

The following variables will be collected for each AE:

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

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

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

A revised toxicity grading scale from US FDA guidance for healthy volunteers enrolled in a preventive vaccine clinical study (FDA 2007) will be utilized for all unsolicited events.

8.3.3 Causality Collection

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

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

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

8.3.4 Adverse Events Based on Signs and Symptoms

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

8.3.5 Adverse Events Based on Examinations and Tests

The results from the Clinical Study Protocol-mandated vital signs and laboratory safety assessments will be summarized in the Clinical Study Report.

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

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

8.3.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation. Any occurrences of aspartate aminotransferase or alanine aminotransferase ≥ 3 × the upper limit of normal together with total bilirubin ≥ 2 × upper limit of normal at any point during the study following the administration of study medication should be reported to the Sponsor as a potential Hy's Law SAE within 1 day with a serious criteria of 'Important medical event' and causality assessment 'yes/related'.

The study physician will contact the investigator to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.

8.3.7 Solicited Adverse Events

Local and systemic predefined solicited AEs for reactogenicity assessment (Table 10) will be collected in a Solicited AE e-Diary for 7 days following administration of each dose of study intervention via e-diary collection. If a solicited AE is not resolved within the e-diary reporting period, the event will be also reported as a non-solicited adverse event in the eCRF, with a start date of when started and the actual stop date.

Solicited AEs should not be reported as unsolicited AEs unless they fulfil the criteria for SAEs or medically-attended AEs(see Sections 8.3 and 8.3.8, respectively).

Table 10 Predefined Solicited Adverse Events for Reactogenicity Assessment

Local	Systemic
Pain at the site of the injection	Fever (> 100 °F/37.8 °C)
Redness/erythema at the site of the injection	Chills
Tenderness at the site of the injection	Muscle pains
Induration/swelling at the site of the injection	Fatigue (physical or mental tiredness/exhaustion)
-	Headache
-	Malaise (general feeling of discomfort or uneasiness)
-	Nausea
-	Vomiting

Solicited AE e-Diary

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

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

Severity Assessment of Solicited AEs

Severity will be assessed for solicited AEs by the participant (or, if applicable, their caregiver, surrogate, or legally authorized representative) according to toxicity grading scales modified and abridged from the US FDA guidance (FDA 2007) as defined in Appendix D. Because solicited AEs are expected to occur after vaccination, they will not be assessed for relationship to study intervention.

8.3.8 COVID-19 Assessment

This study will describe the incidence of COVID-19 adverse events reported from Day 1 to 180 days after the participant's last/only dose of vaccine.

COVID-19 is defined as SARS-CoV 2-RT-PCR positive symptomatic illness. At all clinic visits following the initial vaccination, participants will be asked if they have had a diagnosis of COVID-19 since their last clinic visit (see Schedule of Activities in Section 1.3). Medical records will be obtained for confirmation of a participant-reported diagnoses of COVID-19. Qualifying symptoms are fever, shortness of breath, difficulty breathing, chills, cough, fatigue, muscle/body aches, headache, new loss of taste or smell, sore throat, congestion, runny nose, nausea, vomiting, or diarrhoea. Events will be reported as AEs/SAEs.

If a participant presents at clinic visit with COVID symptoms, diagnosis will be confirmed using RT-PCR.

8.3.9 Medically-Attended Adverse Events

Medically-attended AEs will be collected according to the timepoints specified in the Schedule of Activities (Section 1.3).

Medically-attended AEs are defined as AEs leading to medically-attended visits that were not routine visits for physical examination or vaccination, such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. AEs, including abnormal vital signs, identified on a routine study visit or during the scheduled illness visits will not be considered medically-attended AEs.

8.3.10 Adverse Events of Special Interest

AEs of special interest will be collected according to the timepoints specified in the Schedule of Activities (Section 1.3).

AEs of special interest 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. AEs of special interest are based on Brighton Collaboration case definitions (SPEAC 2020), clinical experience, and scientific interest. A list of events is provided in Appendix E.

An AE of special interest can be serious or non-serious. All AEs of special interest will be recorded in the eCRF. If any AE of special interest occurs in the course of the study, investigators or other site personnel will inform the appropriate Sponsor representatives within 1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it. Serious AEs of special interest will be recorded and reported as per Section 8.3.11.

8.3.10.1 Vascular/Hematologic Adverse Events of Special Interest

Both thrombotic, thromboembolic, and neurovascular events and thrombocytopenia events are considered to be adverse events of special interest. The investigator should remain vigilant for the occurrence of thrombotic events with thrombocytopenia and/or bleeding. If a participant experiences new onset thromboembolic events with thrombocytopenia, there should be prompt evaluation with a thorough haematological investigation. COVID-19 testing, including PCR and serology (nucleoprotein antibodies), should also be performed. See Appendix F for further guidance on investigation and management of suspected events.

In the event of such a case of thrombosis and in accordance with local laws and ethical procedures, one blood sample may be taken from the participant and whole genome

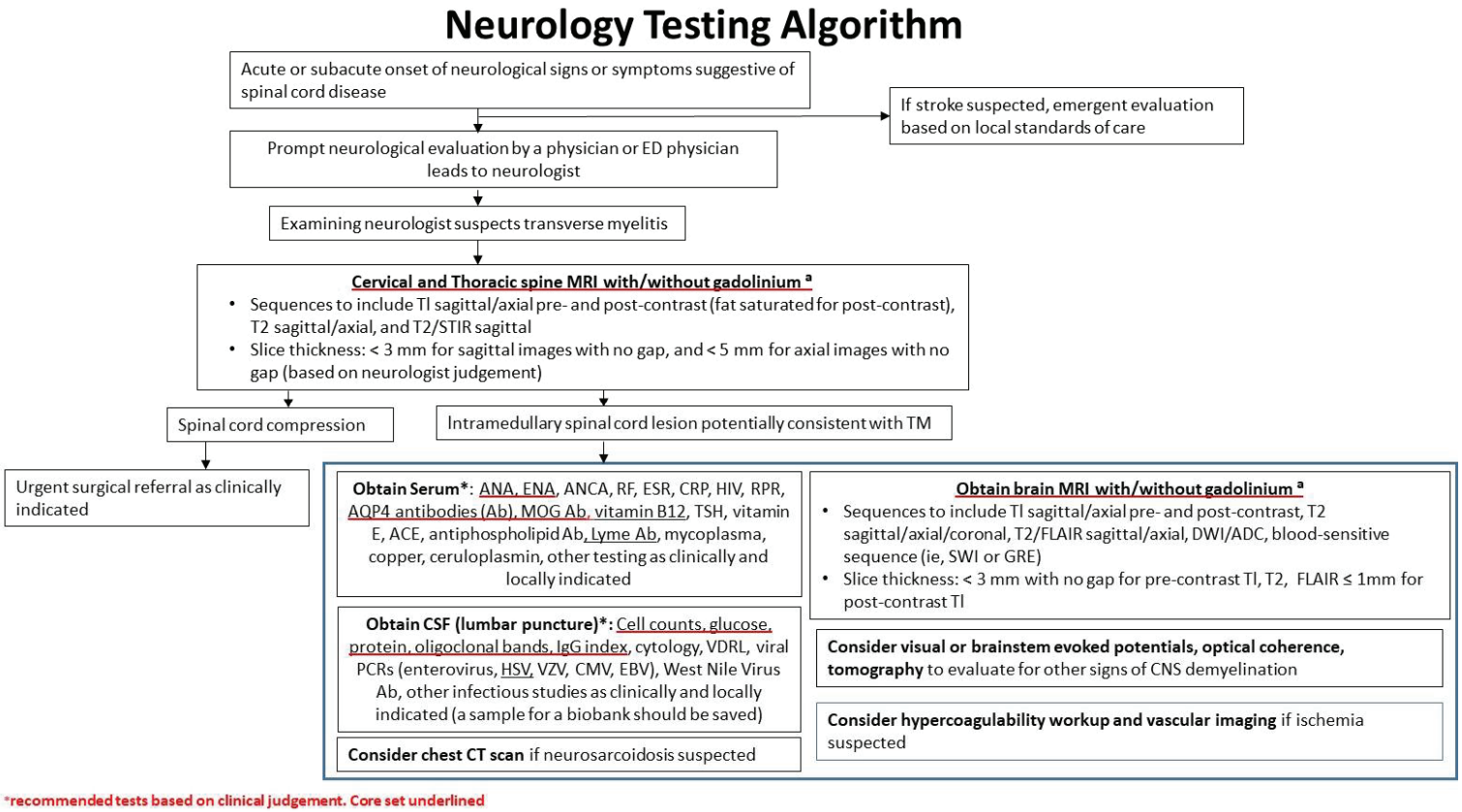
sequencing performed in order to enable investigations into the possible role of genetic polymorphisms as risk factors for these events.

8.3.10.2 Potential Neurological Adverse Events of Special Interest

If a participant experiences new onset (acute or subacute) motor and sensory disturbances (eg, weakness, numbness, paraesthesia, 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, including referral to a neurology specialist for further evaluation and testing, as clinically indicated. Testing can include evaluation for peripheral demyelinating conditions (eg, electromyography). In cases of concern for spinal cord disease, see Figure 3 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 AEs of special interest occurring in the AZD1222 clinical development program (see Appendix A 5).

Figure 3 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.

8.3.11 Reporting of Serious Adverse Events

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

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

The designated Sponsor representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform Sponsor representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but no later than 24 hours of when he or she becomes aware.

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 Sponsor representative.

If the Electronic Data Capture system is not available, then the investigator or other study site staff reports an SAE to the appropriate Sponsor representative by telephone or other method and the event is entered into the Electronic Data Capture system when available.

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

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

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

8.3.12 Pregnancy

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

8.3.12.1 Maternal Exposure

Female participants who are pregnant or have a confirmed positive pregnancy test at screening or Day 1 will be excluded from the study (see Section 5.2). Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and

spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the participant was discontinued from the study.

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

The designated Sponsor representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.11) and **within 30 days** for all other pregnancies that are not associated with an SAEs.

The same timelines apply when outcome information is available.

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

8.3.13 Medication Error

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

The designated Sponsor representative works with the investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) **or 5** (other serious initial and follow up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.11) and **within 30 days** for all other medication errors.

The definition of a Medication Error can be found in Appendix B 3.

8.4 Overdose

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

There is no specific treatment for an overdose with AZD2816 or AZD1222. If overdose occurs, the participant should be treated supportively with appropriate monitoring as necessary.

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

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

The designated Sponsor representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.11) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

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

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

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

8.5.1 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5.2 Immunogenicity Assessments

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

8.5.2.1 SARS-CoV-2 Serology Assessments

Serum samples will be collected to assess SARS-CoV-2 antigen-specific antibody levels from all participants according to the Schedule of Activities (Section 1.3). Authorized laboratories will assess serologic responses to AZD1222 and AZD2816 using validated (or qualified, where appropriate) assays. Serologic assessment to the S protein from different SARS-CoV-2 variants (which include Wuhan-Hu-1, B.1.351, B.1.1.7, and P.1) will be assessed quantitatively using a validated multiplexed ECL based immunoassay. Additionally, seroresponse will be assessed for each antigen over time. The rate of SARS-CoV-2 infection in participants receiving AZD2816 versus AZD1222 will be determined by seroresponse in a SARS-CoV-2 nucleocapsid antigen in a multiplexed electrochemiluminescence-based assay performed at an authorized laboratory. Additional exploratory assessments may be performed to measure binding antibodies to SARS-CoV-2 variants of interest (which may include B.1.429, B.1.525, B.1.526, P.2, P.3, B.1.617, and the Q677H mutation observed in multiple variants).

8.5.2.2 CCI

CCI

8.5.2.3 CCI

CCI

CCI

8.5.2.4 CCI

CCI

8.5.3 Pharmacodynamics

Pharmacodynamics are not evaluated in this study.

8.6 Human Biological Sample Biomarkers

Already collected samples may be analysed for biomarkers thought to play a role in COVID-19 severity or outcomes based upon emerging immunogenicity and pharmacodynamic analysis from this or other studies involving the study interventions. These analyses include but are not limited to serum or plasma cytokines, quantification of RNA, micro-RNA, and/or non-coding RNA using quantitative reverse transcriptase polymerase chain reaction (RT-PCR), microarray, sequencing, or other technologies in blood, or peripheral blood mononuclear cells to evaluate their association with AZD1222/2816 and observed clinical responses to these study interventions.

8.7 Optional Genomics Initiative Sample

Not applicable.

8.8 Medical Resource Utilization and Health Economics

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

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The overall hypothesis for this 8-armed study is that 28 days after vaccination (ie, following a single booster dose for the previously vaccinated participants or a second vaccination dose for previously unvaccinated participants), AZD2816 will be non-inferior to AZD1222 in terms of immunogenicity (ie, neutralising antibodies GMT ratio and difference in seroresponse). The specific null and alternative hypotheses for each objective are presented in Section 9.4.3

9.2 Sample Size Determination

Primary Objective: Characterise Immunogenicity (Precision)

Historical data were available for the immunogenicity responses (ie, pseudovirus neutralising antibodies, live virus neutralising antibodies, and spike protein binding antibodies) to AZD1222 from the pooled COV001/002/003/005 studies. Table 11 presents the log transformed immunogenicity responses (ie, geometric mean titres) by assay for participants that received 2 standard doses of AZD1222. These results indicate that the pseudo-neutralising antibodies exhibited the largest variation (standard deviation of 1.20 and 1.10 for the 4-week and 12-week dosing intervals respectively), while live-neutralising antibodies had the lowest (standard deviation of 0.72 for the 4-week dosing interval).

Table 11 Historic Immunogenicity Responses by Dosing Interval (Geometric Mean Antibody Titres, Standard Dose Immunogenicity Analysis Set)

	Post-1st Dose			Post-2nd dose with a 4-week dosing interval[a]			Post-2nd dose with a 12-week dosing interval[b]		
Assay	**N**	**Mean**	**Std Dev**	**N**	**Mean**	**Std Dev**	**N**	**Mean**	**Std Dev**
Pseudo	476	4.3	1.34	166	5.3	1.20	113	5.4	1.10
Live	51	4.9	1.15	42	6.2	0.72	0	-	-
Spike protein	1139	9.1	1.14	293	10.1	0.96	302	10.7	0.83

[a] Estimates from pooled COV001/002/003/005 study data from participants with 2- to 6-week dosing interval
[b] Estimates from pooled COV001/002/003/005 study data from participants with 10- to 14-week dosing interval

Table 12 presents the seroresponse (ie, > 4 fold increase from baseline) by assay. These results indicate that the pseudo-neutralising antibodies exhibited the lowest proportion of seroresponse (59.7% and 85.5% for the 4-week and 12-week dosing intervals respectively), while both live-neutralising and spike-binding seroresponse rates exceeded 95%.

Table 12 Historic Seroresponse Rates by Dosing Interval (>4-fold Increase from Baseline, Standard Dose Immunogenicity Analysis Set)

	Post-1st Dose		Post-2nd dose with a 4-week dosing interval[a]		Post-2nd dose with a 12-dose week interval[b]	
Assay	**N**	**Proportion**	**N**	**Proportion**	**N**	**Proportion**
Pseudo	499	32%	382	59.7%	117	85.5%
Live	96	75%	95	96.8%	-	-
Spike protein	940	96.6%	636	95.9%	304	99.3%

[a] Estimates from pooled COV001/002/003/005 study data from participants with 2- to 6-week dosing interval
[b] Estimates from pooled COV001/002/003/005 study data from participants with 10- to 14-week dosing interval

Under the assumption that the immunogenicity responses (ie, geometric mean antibody titres) associated with AZD2816 will be similar to the responses associated with AZD1222 in participants that received 2 standard doses in the pooled COV001/002/003/005 studies, in which standard deviations ranged from 0.72 to 1.2 (Table 11), 150 participants will provide a 95% confidence interval half-width between 0.115 and 0.192 (see Table 13). Similarly, 380 participants will provide a 95% confidence interval half-width between 0.072 and 0.120.

Under the assumption that the seroresponse rates associated with AZD2816 will be similar to the response rates in adults that received 2 standard doses of AZD1222 in the pooled COV001/002/003/005 studies (Table 12), 150 participants will provide a 95% confidence interval half-width between 1.33% and 7.85%, and 380 participants will provide a 95% confidence interval half-width between 0.84 % and 4.93 % (Table 14).

Table 13 Estimated Half-width of the 95% Confidence Intervals for Immunogenicity Responses (Geometric Mean Titres) Based on Historic Immunogenicity Assay Variances and the Proposed Sample Sizes

Standard Deviation	Number of participants	Estimated half-width of the 95% confidence interval (natural log scale)
0.72	150	0.115
	300	0.081
	350	0.075
	380	0.072
0.83	150	0.133
	300	0.094
	350	0.087
	380	0.084
0.96	150	0.154
	300	0.109
	350	0.101
	380	0.097
1.1	150	0.176
	300	0.124
	350	0.115
	380	0.111
1.2	150	0.192
	300	0.136
	350	0.126
	380	0.120

Table 14 Estimated Half-Width of the 95% Confidence Interval for the Seroresponse Rates based on Historic Serorepsonse Rates and Proposed Sample Sizes

Observed seroresponse rate	Number of participants	Estimated half-width of the 95% confidence interval
59.7%	150	7.85%
	300	5.55%
	350	5.14%
	380	4.93%
85.5%	150	5.63%
	300	3.98%
	350	3.69%
	380	3.54%
95.9%	150	3.17%
	300	2.24%
	350	2.08%
	380	1.99%
96.8%	150	2.82%
	300	1.99%
	350	1.84%
	380	1.77%
99.3%	150	1.33%
	300	0.94%
	350	0.87%
	380	0.84%

For a fixed sample size, the precision with which the 95% confidence interval of the binary seroresponse rate can be estimated is a function of the response rate. Table 14 provides the lower bounds of the 95% confidence interval for selected response proportions for alternate sample sizes. For a given response rate, we can be 95% confident that the true seroresponse rate is at least as large as the lower bound of the confidence interval.

Primary Objective: Safety

Table 15 indicates the probability of observing 1 or more safety events, such as solicited injection site or systemic reactogenicity events or an unsolicited non-serious AE of a particular type for participants in each treatment arm. With the sample size of 300 participants, at least 1 participant with an AE of incidence rate of 1% can be detected with probability of about 95%.

Table 15 Probability of detecting 1 or more safety events (N = 300)

Event Frequency	Probability (> 1 event)
≥ 10% (Very Common)	> 99%
≥ 1% (Common)	95%
≥ 0.1% (Uncommon)	26%
≥ 0.01% (Rare)	3%

Secondary Objective: Compare Immunogenicity

Under the assumption that there is no difference between treatment arms of interest (ie, a ratio of 1, difference on the log scale of 0), the power conferred by 150 and 380 participants respectively for the comparison of geometric mean titre ratio using a noninferiority margin of 1.5 (equivalent to a difference on the log scale of 0.405) is presented in Table 16 and for the comparison of seroresponse rate using the non-inferiority margin of -15% as the upper bound of the difference is presented in Table 17.

If there is no difference between treatment arms of interest (ie, a ratio of 1) in the proportion of seroresponders, 300 participants provides 98% power for to establish non-inferiority to within margin of -15% if the seroresponse rate is >50%. The observed pseudo-neutralising response rates (> 4 fold increase from baseline) from the COV001/002/003/005 studies for AZD1222 were 59.7% and 85.5% for the 4-week and 12-week dosing interval respectively (Table 12). A population of 300 participants provides >90% power to detect non-inferiority (using a non-inferiority margin of -15%) if the observed response rate is 59.7% (Table 17).

Table 16 Power for Non-inferiority Using 1.5 as the Upper Bound of the Geometric Mean Titre Ratio

Sides	Null difference	Assumed mean treatment difference	Assumed standard deviation	Number in comparator group	Number in reference group	Alpha	Power
Upper	ln1.5 = 0.405	0	0.72	150	300	0.025	>.999
				150	350		>.999
				150	380		>.999
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999
			0.83	150	300		0.998
				150	350		0.999
				150	380		>.999
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999
			0.96	150	300		0.988
				150	350		0.991
				150	380		0.992
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999
			1.10	150	300		0.957
				150	350		0.965
				150	380		0.968
				300	300		0.994
				300	350		0.997
				300	380		0.997
				350	380		0.999
				350	350		0.998
				380	380		>.999
			1.20	150	300		0.920
				150	350		0.932
				150	380		0.937
				300	300		0.985
				300	350		0.990
				300	380		0.992
				350	380		0.995
				350	350		0.994
				380	380		0.996

Table 17 Power for Non-inferiority Using -15% as the Upper Bound of the Difference in Seroresponse Rate

Sides	Null proportion difference	Assumed difference in proportion of seroresponders	Assumed proportion of seroresponders in both groups	Number in comparator group	Number in reference group	Alpha	Power
Lower	-0.15	0	0.597	150	300	0.025	0.878
				150	350		0.894
				150	380		0.902
				300	300		0.964
				300	350		0.975
				300	380		0.979
				350	380		0.986
				350	350		0.982
				380	380		0.989
			0.855	150	300		0.993
				150	350		0.995
				150	380		0.996
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999
			0.959	150	300		>.999
				150	350		>.999
				150	380		>.999
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999
			0.968	150	300		>.999
				150	350		>.999
				150	380		>.999
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999
			0.993	150	300		>.999
				150	350		>.999
				150	380		>.999
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999

9.3 Populations for Analyses

The following populations are defined:

Table 18 Populations for Analysis

Population	Description
All participants analysis set	All participants screened for the study, to be used for reporting disposition and screening failures.
Full analysis set	All randomised participants who received study treatment, irrespective of their protocol adherence and continued participation in the study. Participants will be analysed according to their randomised treatment, irrespective of whether or not they have prematurely discontinued, according to the intent-to-treat principle. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination.
Safety analysis set	The safety analysis set consists of all participants who have received study treatment. Erroneously-treated participants (eg, those randomised to AZD2816, but were actually given treatment AZD12222) are accounted for in this analysis set by assigning them to the treatment they actually received.
Immunogenicity analysis set	The vaccine immunogenicity analysis set will include all randomised participants, received at least 1 dose of planned study treatment (ie, 1 dose of either AZD2816 or 1 dose of AZD1222), had baseline and post-dose antibody measurements, have at least 1 post-dose quantifiable serum titre, and had no protocol deviations judged to have the potential to interfere with the generation or interpretation of an antibody response. The analyses conducted using this analysis set will be based on the actual treatment received.
Seronegative immunogenicity analysis set	The subset of the immunogenicity analysis set who were seronegative at baseline.
Seropositive immunogenicity analysis set	The subset of the immunogenicity analysis set who were seropositive at baseline.

Participants that are SARS-CoV-2 seropositive at screening will be included in seropositive analysis sets analogous to the above seronegative analysis sets. Further definition is provided in the Statistical Analysis Plan.

9.4 Statistical Analyses

This section provides a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints. A more technical and detailed description of the statistical analyses will be described in the Statistical Analysis Plan, and an approved version will be finalized prior to the interim analyses.

9.4.1 General Considerations

An initial interim analysis will occur when a subset of participants previously vaccinated with AZD1222 have completed their Day 29 visit (ie, 28 days after booster dose). This sample will include both participants randomised to receive both a booster dose of AZD2816 as well as those randomised to receive a booster dose of AZD1222. Analyses presenting treatment arm summaries of both the raw and model adjusted immunogenicity will be reviewed by an unblinded team within AstraZeneca to make a decision regarding the potential need for sample size re-estimation. Full details of this analyses are provided in the Interim Analysis Charter to be finalized prior to any interim analysis.

An second interim analysis will occur when all participants previously vaccinated with AZD1222 have completed their Day 29 visit (ie, 28 days after booster dose). It is estimated that this early analysis has the potential to provide clear signals about whether AZD2816 provides a strong neutralizing response against the B.1.351 strain while retaining immunogenicity against the Wuhan strain, and thereby influence programmatic decisions early. Analyses results will present treatment arm specific summaries of both the raw and model adjusted (baseline age and co-morbidities). The raw data outputs will be stratified by age group (<65, ≥ 65) while the model adjusted summaries will pool data across age groups. Full details of this analyses are provided in the Interim Analysis Statistical analysis Plan to be finalized prior to any interim analysis.

A third interim analysis may be performed when a subset of previously unvaccinated participants have completed their Day 57 visit (ie, 56 days after fist dose). The participant sample will include both participants randomised to AZD2816 as well as those randomised to AZD1222. This analysis is intended to assess immunogenicity variability. The number of previously unvaccinated participants per treatment arm may be increased based upon the results of this analysis. The details of this interim analysis, including the trigger and methods, will be specified in the Interim Analysis Charter Plan-The primary analysis will occur when all participants have completed their Day 29 visit and safety and immunogenicity data from all unvaccinated participants randomised to a 4-week dosing interval are available through completion of their visit 28 days after the second priming dose.

A secondary analysis will occur when all participants have completed their Day 29 visit and safety and immunogenicity data from all unvaccinated participants (including those randomised to a 12-week dosing interval) are available through completion of the visit 28 days after the second dose.

The final analysis will occur when data from all vaccinated participants is available through completion of the last study visit (180 days after the single dose for previously vaccinated participants / 180 days after the second dose for unvaccinated participants).

Further details of the primary analysis, secondary analysis and final analysis are contained within the Statistical Analysis Plan.

To maintain trial integrity sponsor roles with direct input into participant management and safety monitoring will not have access to unblinded participant level data or associated outputs from the interim analyses until end of study.

Further details on the tools and processes to maintain the blind will be presented in the Study Integrity Plan.

9.4.2 Safety

9.4.2.1 Primary Endpoints

Overview

Descriptive analyses will support evaluation of safety, reactogenicity and immunogenicity. The primary safety analysis includes:

- Incidence of local and systemic solicited AEs for 7 days following each vaccination will be summarised by day and overall.
- Incidence of unsolicited AEs for 28 days following each vaccination will be summarised by system organ class and preferred term, and by relationship to vaccination as assessed by the investigator.
- MAAEs, SAEs, and AESIs following the first vaccination and throughout the study duration will be summarised by system organ class and preferred term and by relationship to vaccination as assessed by the investigator.
- The change from baseline for safety laboratory measures at 7 and 28 days after vaccination.

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

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

A listing will cover details for each individual AE. Full details of all AE analyses will be provided in the Statistical Analysis Plan, including intercurrent events for safety due to potential unblinding of participants for administration of licensed and/or approved SARS-CoV-2 or COVID-19 vaccine.

At the time of the interim analyses, group assignment will not be presented when safety event data has the potential to unblind participant's study group attribution.

9.4.2.2 Other Safety Endpoints

Vital Signs

Vital sign measurements will be performed as specified in the Schedule of Activities (Section 1.3). The set of assessments will include pulse oximetry, blood pressure, and body temperature.

Details of all vital sign analyses will be provided in the Statistical Analysis Plan, which will include descriptive statistics presented for observed values for all vital sign parameters.

COVID-19

This study will describe the incidence of COVID-19 adverse events from the first dose of the vaccine to study end (180 days post-vaccination). Descriptive statistics will be produced based on the safety analysis set. Full details will be documented in the statistical analysis plan.

9.4.3 Immunogenicity

9.4.3.1 Immunogenicity Endpoints

The immunogenicity endpoints of interest in this study are:

- Geometric mean antibody titre.
- Seroresponse, defined as ≥ 4-fold increase in the geometric mean antibody titre from baseline

Both the geometric mean antibody titre and seroresponse of participants will be summarized descriptively by strain, treatment arm, and timepoint for the immunogenicity population.

9.4.3.1.1 Estimand framework for immunogenicity descriptions and comparisons

Target populations:

1) Previously unvaccinated participants

    a. Seronegative Analysis Set: and with no evidence of prior or current infection

2) Participants who previously received SARS-CoV-2 vaccination with either AZD1222 or a licensed mRNA vaccine according to the authorized dose and dosing regimen at least 3 months prior to first study intervention (see Section 5.1.2).

Outcome variable: neutralizing antibody and binding titres to SARS-CoV-2 at 28 days after each treatment administration (1 treatment administration for the previously vaccinated population and 2 planned treatment administrations for the unvaccinated population).

Treatment conditions:

Previously unvaccinated population

- 2 doses of AZD1222 given on Day 1 and on Day 29 (4-week dosing interval)
- 2 doses of AZD2816 given on Day 1 and on Day 29 (4-week dosing interval)
- 1 dose of AZD1222 given on Day 1 and 1 dose of AZD2816 on Day 29 (4-week dosing interval)
- 2 doses of AZD2816 given on Day 1 and on Day 85 (12-week dosing interval)

Previously vaccinated population

- 1 dose of AZD1222 given on Day 1.
- 1 dose of AZD2816 given on Day 1.

Intercurrent events: the following intercurrent events could impact the antibody levels achieved:

- missing the second vaccination (for the unvaccinated population)
- receiving of immune-modifying drugs or vaccines
- subsequent infection with SARS-CoV-2.

All immunogenicity descriptions and comparisons will use the principal stratum strategy, ie, all analyses will exclude participants who experience any of the above intercurrent events

Population-level summary:

Descriptive Analyses (see Table 20 and Table 21)

- geometric means of the antibody titres
- seroresponse proportions

Comparative Analyses (see Table 22 and Table 23)

- ratio of geometric means of the antibody titres.
- difference in seroresponse proportion

Planned Descriptive Analyses:

Table 20 and Table 21 present planned descriptive immunogenicity analyses for the unvaccinated and previously vaccinated populations respectively (each one exploring an individual treatment arm at a specific timepoint against a particular strain).

The tables show that without introduction of further variants, there are 24 planned descriptive analyses for the unvaccinated population and 16 planned descriptive analyses for the previously immunised population (index). Within each table there is an analysis key which describes the population (see Table 19). The descriptive analyses presented in Tables 19 and 20 will be repeated for the subset of participants who are seropositive at screening.

Table 19 Description of the Analysis Keys for Tables 19 and 20

Population	Analysis Key	Example
Previously unvaccinated	Primary series dosing interval: P4 (4-week dosing interval) or P12 (12-week dosing interval) Treatment received: 1222 (2 doses of AZD1222) or 2816 (2 doses of AZD2816) or 1222/2816 (1 dose of AZD1222 followed by 1 dose of AZD2816) Strain: W (Wuhan-Hu-1) or V (Variant B.1.351) Analysis Timepoint: 1 (28 days post-dose 1) 2 (28 days post-dose 2)	[P4:1222:W:1] = Immunogenicity following primary vaccination with a 4-week dosing interval of 2 doses of AZD1222 against Wuhan-Hu-1 28 days post-dose 1
Previously vaccinated	Pre-study primary vaccination: P1222 (2 doses of AZD1222) or PmRNA (2 doses of an mRNA vaccine) Treatment received: B1222 (1 booster dose of AZD1222) or B2816 (1 booster dose of AZD2816) Strain: W (Wuhan-Hu-1) or V (Variant B.1.351)	[P1222:B1222:V] = Immunogenicity in participants who were previously vaccinated with 2 doses of AZD1222 as primary vaccination series and received a single boost dose of AZD1222 against the B.1.351 variant

Table 20 Immunogenicity Descriptive Analysis for Previously Unvaccinated Treatment Groups (with Separate Seronegative and Seropositive Analyses)

Treatment	Dosing interval	Strain	Timepoint	Endpoint	Index	Analysis Key
AZD1222	4 weeks	Wuhan-Hu-1	28 days after 1st dose	GMT	1	[P4:1222:W:1]†
				Seroresponse	2	
			28 days after 2nd dose	GMT	3	[P4:1222:W:2]
				Seroresponse	4	
		B.1.351	28 days after 1st dose	GMT	5	[P4:1222:V:1] †
				Seroresponse	6	
			28 days after 2nd dose	GMT	7	[P4:1222:V:2]
				Seroresponse	8	
AZD2816	4 weeks	Wuhan-Hu-1	28 days after 1st dose	GMT	9	[P4:2816:W:1] ‡
				Seroresponse	10	
			28 days after 2nd dose	GMT	11	[P4:2816:W:2]
				Seroresponse	12	
		B.1.351	28 days after 1st dose	GMT	13	[P4:2816:V:1] ‡
				Seroresponse	14	
			28 days after 2nd dose	GMT	15	[P4:2816:V:2]
				Seroresponse	16	
AZD1222/ AZD2816	4 weeks	Wuhan-Hu-1	28 days after 2nd dose	GMT	17	[P4:1222/2816:W:2]
				Seroresponse	18	
		B.1.351	28 days after 2nd dose	GMT	19	[P4:1222/2816:V:2]
				Seroresponse	20	
AZD2816	12 weeks	Wuhan-Hu-1	28 days after 1st dose	GMT	21	[P12:2816:W:2]
				Seroresponse	22	
		B.1.351	28 days after 2nd dose	GMT	23	[P12:2816:V:2]
				Seroresponse	24	

† descriptive summaries for 28 days after 1st dose will pool all treatment groups who received AZD1222 as their first dose (ie, homologous and heterologous series).
‡ descriptive summaries for 28 days after 1st dose will pool all treatment groups who received AZD2816 as their first dose (4-week interval and 12-week interval treatment arms).

GMT: Geometric mean titre

Table 21 Immunogenicity Descriptive Analysis for Previously Vaccinated Treatment Groups (with Separate Seronegative and Seropositive Analyses)

Primary vaccination	Booster Treatment	Strain	Timepoint	Endpoint	Index	Analysis Key
AZD1222	AZD1222	Wuhan-Hu-1	28 days after booster dose	GMT	1	[P1222:B1222:W]
				Seroresponse	2	
		B.1.351	28 days after booster dose	GMT	3	[P1222:B1222:V]
				Seroresponse	4	
	AZD2816	Wuhan-Hu-1	28 days after booster dose	GMT	5	[P1222:B2816:W]
				Seroresponse	6	
		B.1.351	28 days after booster dose	GMT	7	[P1222:B2816:V]
				Seroresponse	8	
mRNA	AZD2816	Wuhan-Hu-1	28 days after booster dose	GMT	9	[PmRNA:B2816:W]
				Seroresponse	10	
		B.1.351	28 days after booster dose	GMT	11	[PmRNA:B2816:V]
				Seroresponse	12	
	AZD1222	Wuhan-Hu-1	28 days after booster dose	GMT	13	[PmRNA:B1222:W]
				Seroresponse	14	
		B.1.351	28 days after booster dose	GMT	15	[PmRNA:B1222:V]
				Seroresponse	16	

GMT: Geometric mean titre

Immunogenicity comparisons:

Immunogenicity analysis

A number of comparisons of geometric mean titres and seroresponse rates between vaccine regimens and vaccine types are intended to be made.

All non-inferiority comparisons of geometric mean titre ratios will be made utilizing the lower bound of two-sided score-based confidence intervals ($\alpha = 0.05$) with non-inferiority margin 0.67

All non-inferiority comparisons of seroresponse rates will be made utilizing the lower bound of two-sided score-based confidence intervals ($\alpha = 0.05$) with non-inferiority margin 15%, and superiority comparisons of seroresponse rates will be made using one-sided Fisher's exact test ($\alpha = 0.025$). Comparisons of Ab titres between treatment groups will be conducted using geometric mean titre (GMT) ratios and seroresponse rates, facilitated by an analysis of covariance (ANCOVA) model of the log2 titre, which adjusts for the baseline level, time since previous vaccination (for previously vaccinated individuals), baseline co-morbidities and

gender as fixed effects. All analyses of antibody titres (GMT ratios and differences in seroresponse) will be repeated using the unadjusted (raw observed) concentration values.

Geometric Mean Titres

The statistical methodology will be based on a 2-sided 95% CI of the ratio of the GMTs. Non-inferiority will be demonstrated if the lower limit of the 2-sided 95% CI of the GMT ratio of the reference group and comparator group is >0.67 (see table xx). The 2-sided 95% CI for the ratio of GMTs will be calculated using normal approximation of log-transformed concentrations.

The 95% CI for the GMT ratio between 2 groups will be constructed as follows:

Logarithm transformation of the individual concentrations will be calculated.

The 95% CI for the difference in log(GMT) between 2 groups: $Group_C$ and $Group_R$ will be in the form:

$$\bar{X}_C - \bar{X}_R \pm t\left(1 - {}^{\alpha}/_{2}, n_C + n_R - 2\right) \times S\sqrt{{}^{1}/_{n_C} + {}^{1}/_{n_R}}$$

Where $\bar{X}_C$ and $\bar{X}_R = \log(GMT)$ are the means of the log-transformed concentration for $Group_C$ and $Group_R$, respectively,

$S^2 = {}^{[(n_C - 1)S_C^2 + (n_R - 1)S_R^2]}/_{(n_C + n_R - 2)}$ is the pooled sample variance,

n_C and n_R are the sample sizes for $Group_C$ and $Group_R$, respectively,

S_C and S_R are the sample variances for $Group_C$ and $Group_R$, respectively,

$t\left(1 - {}^{\alpha}/_{2}, n_C + n_R - 2\right)$ is the $100\left(1 - \frac{\alpha}{2}\right)$ percentile of the t-distribution with degrees of freedom $df = n_C + n_R - 2$

To test this hypothesis, a 2- sided 95% CI will be constructed around the ratio $\frac{GMT_C}{GMT_R}$, where GMT_C and GMT_R are the geometric mean of the antibody titres in the comparator and reference groups respectively, at the timepoints post vaccination for which the groups are being compared.

The hypothesis will be supported by the data, if the lower bound of the calculated of the calculated 95% CI is > 0.67. This is equivalent to testing the null hypothesis using a 1-sided type-I error rate of 0.025.

$$H_0: {GMT_C}/{GMT_R} \leq 0.67$$

$$H_A: {GMT_C}/{GMT_R} > 0.67$$

Or equivalently

$$H_0: \log(GMT_C) - \log(GMT_R) \leq \log(0.67)$$

$$H_A: \log(GMT_C) - \log(GMT_R) > \log(0.67)$$

For the separately considered GMT hypotheses, if the null hypothesis is rejected, then the alternative hypothesis of non-inferiority will be supported.

Seroresponse

The statistical methodology will be based on a 2-sided 95% CI of the difference in seroresponse. Non-inferiority will be demonstrated if the upper bound of the 2-sided 95% CI rate difference in seroresponse between the reference group and comparator group is <15%. The 95% CI of the difference in proportions $P_C - P_R$ will be computed using the Wilson score without continuity correction.

To test this hypothesis, a 2- sided 95% CI will be constructed around the difference $P_C - P_R$, whereP_C and P_R are the proportions of participants in the comparator and reference groups respectively who are classified as seroresponders (> 4 fold increase from baseline) at the timepoints post vaccination for which the groups are being compared.

The hypothesis will be supported by the data, if the lower bound of the calculated of the calculated 95% CI is > 15%. This is equivalent to testing the null hypothesis using a 1-sided type-I error rate of 0.025.

$$H_0: P_C - P_R < -15\%$$

$$H_A: P_C - P_R \geq 15\%$$

If the null hypothesis is rejected, then the alternative hypothesis of non-inferiority will be supported.

Comparisons

The primary and secondary immunogenicity objectives and the GMT and seroresponse comparisons for the previously unvaccinated participants receiving a 2-dose primary vaccination are presented in Table 22.

The immunogenicity objectives and the GMT and seroresponse comparisons for the previously vaccinated participants receiving a 1-dose booster vaccination are presented in Table 23.

Table 22 Immunogenicity Comparisons for Previously Unvaccinated Groups

Objective	$\frac{[\mathbf{GMT}_{\mathbf{comparator}}]}{[\mathbf{GMT}_{\mathbf{reference}}]}$	$\Delta = [\mathbf{Seroresponse}_{\mathbf{comparator}}] - [\mathbf{Seroresponse}_{\mathbf{reference}}]$
To determine if the neutralizing antibody GMT response/seroresponse elicited by a 2-dose AZD2816 primary vaccination is non-inferior to the response elicited by a 2-dose AZD1222 primary vaccination	$\frac{[\mathrm{P4:2816:V:2}]}{[\mathrm{P4:1222:W:2}]}$ (Primary)	$[\mathrm{P4:2816:V:2}] - [\mathrm{P4:1222:W:2}]$ (Key Secondary 2.1)
	$\frac{[\mathrm{P4:2816:V:1}]}{[\mathrm{P4:1222:W:1}]}$	$[\mathrm{P4:2816:V:1}] - [\mathrm{P4:1222:W:1}]$
	$\frac{[\mathrm{P4:2816:W:2}]}{[\mathrm{P4:1222:W:2}]}$ (Key Secondary 2.4)	$[\mathrm{P4:2816:W:2}] - [\mathrm{P4:1222:W:2}]$ (Other Secondary)
	$\frac{[\mathrm{P4:2816:W:1}]}{[P4:1222:W:1]}$	$[\mathrm{P4:2816:W:1}] - [\mathrm{P4:1222:W:1}]$
	$\frac{[\mathrm{P4:2816:V:2}]}{[\mathrm{P4:1222:V:2}]}$ (Key Secondary 2.2)	$[\mathrm{P4:2816:V:2}] - [\mathrm{P4:1222:V:2}]$ (Other Secondary)
	$\frac{[P4:2816:V:1]}{[P4:1222:V:1]}$	$[\mathrm{P4:2816:V:1}] - [\mathrm{P4:1222:V:1}]$
To determine if the neutralizing antibody GMT response/seroresponse elicited by a 2-dose AZD1222 + AZD2816 heterologous primary vaccination is non-inferior to the response elicited by a 2-dose AZD1222 primary vaccination	$\frac{\left[\mathrm{P4:}\frac{1222}{2816}\mathrm{:V:2}\right]}{[\mathrm{P4:1222:W:2}]}$ (Key Secondary 2.3)	$\left[\mathrm{P4:}\frac{1222}{2816}\mathrm{:V:2}\right] - [\mathrm{P4:1222:W:2}]$ (Other Secondary)
	$\frac{\left[\mathrm{P4:}\frac{1222}{2816}\mathrm{:W:2}\right]}{[\mathrm{P4:1222:W:2}]}$ (Other Secondary)	$[\mathrm{P4:1222/2816:W:2}] - [\mathrm{P4:1222:W:2}]$ (Other Secondary)

Table 22 Immunogenicity Comparisons for Previously Unvaccinated Groups

Objective	$\frac{[\mathbf{GMT_{comparator}}]}{[\mathbf{GMT_{reference}}]}$	$\Delta = [\mathbf{Seroresponse_{comparator}}] - [\mathbf{Seroresponse_{reference}}]$
	$\frac{[\text{P4: 1222/2816: V: 2}]}{[\text{P4: 1222: V: 2}]}$ (Other Secondary)	$[\text{P4: 1222/2816: V: 2}] - [\text{P4: 1222: V: 2}]$ (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 2-dose AZD2816 primary vaccination	$[\text{P4: 2816: V: 2}]/[\text{P4: 2816: W: 2}]$ (Other Secondary)	$[\text{P4: 2816: V: 2}] - [\text{P4: 2816: W: 2}]$ (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 2-dose AZD1222/AZD2816 primary heterologous vaccination	$[\text{P4: 1222/2816: V: 2}]/[\text{P4: 1222/2816: W: 2}]$ (Other Secondary)	$[\text{P4: 1222/2816: V: 2}] - [\text{P4: 1222/2816: W: 2}]$ (Other Secondary)

Table 23 Immunogenicity Comparisons for Previously Vaccinated Group

Objective	$\frac{[\![\mathbf{[GMT]}]\!]_{\mathbf{comparator}}]}{[\![\mathbf{[GMT]}]\!]_{\mathbf{reference}}]}$	$[\![\mathbf{[Seroresponse]}]\!]_{\mathbf{comparator}}] - [\![\mathbf{[Seroresponse]}]\!]_{\mathbf{reference}}]$
To determine if the neutralizing antibody GMT response/seroresponse elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination	[P1222: B2816: V]/[P4: 1222: W: 2] (Primary)	[P1222: B2816: V] − [P4: 1222: W: 2] (Other Secondary)
	[P1222: B2816: V]/[P4: 1222: V: 2] (Key Secondary 2.1)	[P1222: B2816: V] − [P4: 1222: V: 2] (Other Secondary)
	[P1222: B2816: W]/[P4: 1222: W: 2] (Key Secondary 2.3)	[P1222: B2816: W] − [P4: 1222: W: 2] (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse elicited by an AZD2816 booster dose is non-inferior to response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222	[P1222: B2816: V]/[P1222: B1222: V] (Key Secondary 2.2)	[P1222: B2816: V] − [P1222: B1222: V] (Other Secondary)
	[P1222: B2816: W]/[P1222: B1222: W] (Key Secondary 2.5)	[P1222: B2816: W] − [P1222: B1222: W] (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse elicited by an AZD1222 booster dose in patients previously vaccinated with AZD1222 is non-inferior to the response elicited by a 2-dose AZD1222 vaccination	[P1222: B1222: W]/[P4: 1222: W: 2] (Key Secondary 2.4)	[P1222: B1222: W] − [P4: 1222: W: 2] (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse elicited by an AZD2816 booster dose in participants previously vaccinated with an mRNA-based vaccine is non-inferior to response elicited by a 2-dose AZD1222 vaccination	[PmRNA: B2816: V]/[P4: 1222: W: 2] (Other Secondary)	[PmRNA: B2816: V] − [P4: 1222: W: 2] (Other Secondary)
	[PmRNA: B2816: V]/[P4: 1222: V: 2] (Other Secondary)	[PmRNA: B2816: V] − [P4: 1222: V: 2] (Other Secondary)
	[PmRNA: B2816: W]/[P4: 1222: W: 2] (Other Secondary)	[PmRNA: B2816: W] − [P4: 1222: W: 2] (Other Secondary)

Table 23 Immunogenicity Comparisons for Previously Vaccinated Group

Objective	$\frac{[\![\mathbf{[GMT]}]\!]_{\mathbf{comparator}}]}{[\![\mathbf{[GMT]}]\!]_{\mathbf{reference}}]}$	$[\![\mathbf{[Seroresponse]}]\!]_{\mathbf{comparator}}] - [\![\mathbf{[Seroresponse]}]\!]_{\mathbf{reference}}]$
To determine if the neutralizing antibody GMT response/seroresponse elicited by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with an mRNA-based vaccine	[PmRNA: B2816: W])/[PmRNA: B1222: W] (Other Secondary)	[PmRNA: B2816: W] − [PmRNA: B1222: W] (Other Secondary)
	[PmRNA: B2816: V])/[PmRNA: B1222: V] (Other Secondary)	[PmRNA: B2816: V] − [PmRNA: B1222: V] (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 2816 booster dose	[P1222: B2816: V]/[P1222: B2816: W] (Other Secondary)	[P1222: B2816: V] − [P1222: B2816: W] (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-hu-1 strain following a 1222 booster dose	[P1222: B1222: V]/[P1222: B1222: W] (Other Secondary)	[P1222: B1222: V] − [P1222: B1222: W] (Other Secondary)

9.4.4 Multiple Comparisons

A hierarchical approach will be used to control for multiplicity of the primary and key secondary efficacy endpoints. That is, the null hypotheses for the efficacy endpoints will be tested in a hierarchical order, and the subsequent null hypothesis will be tested only if the prior null hypothesis is rejected. Consequently, no adjustment to alpha for multiplicity will be made in the analysis of immune response. The primary Statistical comparisons of safety data will not be adjusted for multiple comparisons. Further details are provided in the statistical analysis plan.

9.4.5 Data Safety Monitoring Board

An independent COVID-19 Vaccine Data Safety Monitoring Board will provide oversight, to ensure safe and ethical conduct of the study. During the study, the benefit/risk assessment will be continuously monitored by the Board to ensure that the balance remains favourable. Further details, composition, and operation of the COVID-19 Vaccine Data Safety Monitoring Board will be described in a separate charter. For further details, see Appendix A 5.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Not applicable.

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

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

Regulatory Reporting Requirements for SAEs

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

A 2 Financial Disclosure

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

A 3 Informed Consent Process

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

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

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

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

A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

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

A 5 Committee Structure

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

A COVID-19 Vaccine Data Safety Monitoring Board comprised of independent experts will be convened to provide oversight and to ensure safe and ethical conduct of the study. The COVID 19 Vaccine Data Safety Monitoring Board will have the responsibility of evaluating cumulative safety and other clinical study data at regular intervals and making appropriate recommendations based on the available data. During the study, the benefit/risk assessment will be continuously monitored by the COVID-19 Vaccine Data Safety Monitoring Board to ensure that the balance remains favourable. Full details of the COVID-19 Vaccine Data Safety Monitoring Board composition and operations can be found in the COVID-19 Vaccine Data Safety Monitoring Board Charter.

An independent Neurological AESI Expert Committee will be available to review and provide on request about the diagnosis and causality assessment of selected neurological AEs of special interest occurring in the study. Details on the composition and operation of this committee are described in the Neurological AESI Expert Committee Charter.

A 6 Dissemination of Clinical Study Data

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

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

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

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A 9 Study and Site Start and Closure

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

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or ICH/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 IRB/IECs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

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

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of 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 SAEs and non-SAEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

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

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

AEs for **malignant tumours** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-SAE**. 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 hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life Threatening

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

Hospitalization

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

Important Medical Event or Medical Treatment

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

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used. Examples of important medical events include such events as listed below:

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

Intensity Rating Scale

A revised toxicity grading scale found in the US FDA guidance for healthy volunteers enrolled in a preventive vaccine clinical study (FDA 2007) will be utilized for all events.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for

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

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 investigational product.

- 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 investigational product?
- Consistency with known investigational product profile. Was the AE consistent with the previous knowledge of the suspect investigational product (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 investigational product?
- 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 investigational product was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

- Is this a recognized feature of overdose of the investigational medicinal product?
- 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 3 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 investigational product, but rather a human or process related failure while the investigational product 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 investigational product
- 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:

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

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

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

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

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

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

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

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

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

C 2 Withdrawal of Informed Consent for Donated Biological Samples

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

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

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

The investigator:

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

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

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

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

Appendix D 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 24: Clinical Abnormalities, Local Reactions to Injectable Product
- Table 25: Clinical Abnormalities, Vital Signs
- Table 26: Clinical Abnormalities, Systemic (General or Illness)

Table 24 Tables for Clinical Abnormalities: Local Reactions to Injectable Product

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

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

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

ER: emergency room.

Table 25 Tables for Clinical Abnormalities: Vital Signs

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

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

Table 26 Tables for Clinical Abnormalities: Systemic (General or Illness)

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

Appendix E Adverse Events of Special Interest

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

Table 27 Adverse Events of Special Interest

Category	Medical Concept
Neurologic	Generalized convulsion: episodes of neuronal hyperactivity most commonly resulting in sudden, involuntary muscular contractions. They may also manifest as sensory disturbances, autonomic dysfunction and behavioural abnormalities, and impairment or loss of consciousness.
	Guillain-Barré syndrome: a peripheral nerve demyelinating disease, which can present as temporary ascending paralysis.
	Acute disseminated encephalomyelitis: defined as a uniphasic syndrome of brain inflammation and demyelination occurring in temporal association with an antecedent immunologic challenge, such as infection or an immunization. ADEM most commonly occurs in the paediatric population.
	Other neurologic events: include new onset event (acute or subacute) motor and sensory disturbances (eg, weakness, numbness, paraesthesia, hypoesthesia, hyperesthesia, dysesthesias), bowel/bladder dysfunction, gait impairment, or visual disturbance, or any event of myelitis, encephalomyelitis, myelitis transverse, or other sudden neurological deficit.
Vascular	Thrombotic, thromboembolic, and neurovascular events: events that can manifest as transient or permanent vision problems, dizziness, trouble understanding, facial droop, slurred speech, unilateral weakness, deep vein thrombosis with swollen, warm or painful leg, pulmonary embolism with shortness of breath, chest pain or irregular heart rate.
Hematologic	Thrombocytopenia: a disorder in which there is an abnormally low platelet count; a normal platelet count ranges from 150 000 to 450 000 platelets per µL.
Immunologic	Vasculitides: a group of related disorders characterized by inflammation of blood vessels (vasculitis) leading to tissue or end-organ injury.
	Anaphylaxis: an acute hypersensitivity reaction with multi-organ-system involvement that can present as, or rapidly progress to, a severe life-threatening reaction requiring immediate medical attention.
	Vaccine-associated enhanced respiratory disease: pathogenicity has been linked to a vaccine immune response characterized by induction of non-neutralizing antibodies, and a T-cell response of the Th2 type with hypereosinophilia (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: 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 28.

Table 28 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

Table 28 List of Potential Immune-mediated Medical Conditions

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, Bechet's syndrome, leukocytoclastic vasculitis

Table 28 List of Potential Immune-mediated Medical Conditions

Category	Condition
Other	Antiphospholipid syndrome
	Autoimmune haemolytic anaemia
	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 anaemia
	Raynaud's phenomenon
	Sarcoidosis
	Sjögren's syndrome
	Stevens-Johnson syndrome
	Uveitis

Appendix F Actions Required in Cases of Thrombotic Events With Thrombocytopenia and/or Bleeding

F 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of thrombotic events with thrombocytopenia and/or bleeding. It is not intended to be a comprehensive guide to the management of all venous thromboembolic events.

During the course of the study, the investigator will remain vigilant for occurrence of thrombotic events with thrombocytopenia and/or bleeding. Appropriate investigations (eg, imaging) to diagnose these events should be made on a case-by-case basis. The investigator is responsible for determining whether a participant meets criteria for thrombotic events with thrombocytopenia and/or bleeding at any point during the study.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting criteria for thrombotic events with thrombocytopenia and/or bleeding. The Study Physician contacts the investigator to provide guidance, discuss, and agree an approach for the participant's follow-up and the continuous review of data. Guidance from the International Society of Thrombosis and Haemostasis for management of thrombocytopenic thromboembolism occurring after vaccination can be found at www.isth.org. Notably, participants should only be treated with heparin if a test for heparin-induced thrombocytopenia antibodies is negative. An alternative explanation for thrombocytopenia should be considered (eg, alcohol use, liver cirrhosis, concomitant medications, exposure to toxic chemicals, viral infections).

The investigator is responsible for recording data pertaining to thrombotic events with thrombocytopenia and/or bleeding and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

F 2 Tests that Should Be Considered if Thrombotic Events With Thrombocytopenia and/or Bleeding Are Suspected

The following tests should be considered, but not limited to:

1. Measurement of platelet levels, prothrombin time, activated partial thromboplastin time, D-dimer levels, and fibrinogen levels

2. Complete blood count, reticulocyte count, blood film, haptoglobins

3. Anti-platelet factor 4 antibodies

4. Anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies, rheumatoid factor, human leucocyte antigen B27, ADAMTS13 activity, anti-cardiolipin antibodies IgG + IgM, and anti-B2GPI antibodies IgG + IgM

5. Complement (eg, C3, C4, complement complex C5b-9, C5a), autoantibodies (eg, antinuclear IgG, anti-double stranded DNA IgG, anti-Smith IgG, anti-SSA IgG, anti-SSB IgG, anti-Jo1 IgG, anti-MPO IgG, anti-PR3 IgG, anti-glomerular basement membrane IgG)

6. Factor V Leiden, Factor II (prothrombin) variant

7. Platelet activation markers and functional assays (eg: sCD40L, soluble glycoproteins, degranulation markers [PF4, vWF, P-selectin, annexin V]), anti-PF4-plasma-serotonin release assay (if anti-PF4 ELISA positive)

8. Inflammatory markers: TNFa, IL-1, IL-4, IL-6, IL-10, IL-13

9. Cell adhesion molecules: VCAM, ICAM, E-selectin

10. Adenovirus serology

11. Additional viral serology: Cytomegalovirus (IgG and IgM), Ebstein-Barr virus (IgG and IgM), HIV, Parvo virus B19

12. COVID-19 testing, including PCR and serology

13. Calculation of an International Society of Thrombosis and Haemostatis score for Disseminated Intravascular Coagulation (derived from platelet levels, fibrinogen, and D-Dimer)

Appendix G Abbreviations

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ChAdOx1 MERS	Chimpanzee adenovirus Ox1 with MERS Spike antigen
ChAdOx1 nCoV-19	AZD1222 when initially developed by the University of Oxford
COVID-19	Coronavirus disease 2019
eCRF	Electronic case report form
e-Diary	Electronic diary
GMT	Geometric mean titre
ICF	Informed consent form
ICH/GCP	International Council for Harmonisation/Good Clinical Practice
IRB/IEC	Institutional Review Board/ Independent Ethics Committee
IRT	Interactive Response Technology
MAAEs	Medically attended adverse events
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
S	Spike
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome-coronavirus-2

Appendix H Protocol Amendment History

DOCUMENT HISTORY	
Document	**Date**
Amendment GBR-2	30 July 2021
Amendment GBR-1	3 June 2021
Amendment 1	2 June 2021
Version 1	14 May 2021

Amendment GBR-2: 30 July 2021

The principal reason for this amendment was to

1) add an additional interim analysis to evaluate immunogenicity in a subset of AZD1222 previously vaccinated subjects boosted with AZD1222 or AZD2816

2) revise Objectives/Endpoints from descriptive to comparative, with ranking of primary, key secondary, other secondary, and exploratory objectives

3) add non-inferiority margins to primary analysis and add additional participants to maintain power

This amendment has also been implemented in the global version of the study D7220C00001 Clinical Study Protocol.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.1 Synopsis (Objectives and Endpoints)	Revised this section from primarily descriptive to primarily comparative. Comparative immunogenicity objectives created and ranked as primary, key secondary, other secondary.	Objectives of study changed from descriptive to comparative, testing for non-inferiority across treatment comparisons	Substantial
1.1 Synopsis (Number of Participants; Statistical Methods)	Overall size increased to 2590 participants	Adjustments made to maintain power with the added non-inferiority margins	Substantial
1.1 Synopsis (Statistical Methods)	An additional interim analysis added. Second interim analysis changed to include only the	Interim analysis plan was reviewed and revised.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	previously vaccinated with AZD1222 cohort.		

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.2 Schema	Figures updated with increased participant numbers	Adjustments made to maintain power with the added non-inferiority margins	Substantial
1.3 Schedule of Activities	Table 2: footnote clarification added Table 3: minor corrections	Clarification/Correction	Non-substantial
2.1 Study Rationale (and elsewhere in protocol)	Clarification on previous vaccination criteria	Clarification	Non-substantial
3 Objectives	Section completely rewritten. Divided into 2 sections: Previously unvaccinated and previously vaccinated. Immunogenicity objectives created for comparisons. Objectives ranked as primary, key secondary, other secondary, or exploratory.	Objectives of study changed to show non-inferiority across treatments.	Substantial
4.1 Overall design	Participant numbers increased	Adjustments made to maintain power with the added non-inferiority margins	Substantial
4.1 Overall design	Cap on age added	To ensure good representation across age groups	Substantial
8.3.2	Removal of severity grade 5	Correction	Non-substantial
8.5.2.3 CCI [redacted]	Addition of information on number of patients sampled for CCI [redacted]	Clarification	Non-substantial
9.1 Statistical Hypotheses	Addition of statistical hypotheses	Include hypothesis being tested.	Substantial
9.2 Sample size determination	Confidence intervals for populations of 350 and 380 added to Table 14 and Table 15	Updated to include current populations of 350 and 380 participants	Non-substantial
9.2 Sample size determination	Power estimates for populations of 350 and 380 added to Table 17 and Table 18	Updated to include current populations of 350 and 380 participants	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
9.4.1 General considerations	Details on the initial interim, second interim, and third interim analysis added	Include revised information on the analysis plan, including interim analyses	Substantial
9.4.3.1.1 Estimand framework for immunogenicity descriptions and comparisons	Objectives removed from descriptive analysis Table 23 and Table 24	Objectives of study changed from descriptive to comparative, showing non-inferiority across treatments	Substantial
9.4.3.1.1 Estimand framework for immunogenicity descriptions and comparisons	Section of Immunogenicity Comparisons added.	Objectives of study changed from descriptive to comparative, showing non-inferiority across treatments	Substantial
9.4.3.1.1 Estimand framework for immunogenicity descriptions and comparisons	Table 25 and Table 26 on immunogenicity comparisons revised, aligned with the revised objectives/endpoints.	Objectives of study changed from descriptive to comparative, showing non-inferiority across treatments	Substantial
9.4.4 Multiple Comparisons	Section added.	Objectives of study changed from descriptive to comparative, showing non-inferiority across treatments	Substantial

In addition, the protocol has been revised with minor corrections and clarifications.

Amendment GBR-1 (Protocol Version 2): 1 June 2021

Version 1 of the protocol was amended prior to the commencement of the study (ie, prior to approval of the protocol by an ethics committee) based on feedback from internal and regulatory authority reviews. The most substantial changes were as follows:

- addition of 2 treatment arms: 1) AZD1222 as a single booster vaccination in participants previously vaccinated with an mRNA COVID-19 vaccine and 2) heterologous vaccination with AZD1222 plus AZD2816 in previously unvaccinated participants
- further definition of analysis sets
- addition of thrombotic events with thrombocytopenia as a discontinuation criteria

In addition, corrections and revisions to text to improve readability were made.

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SIGNATURE PAGE

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Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.

Clinical Study Protocol	
Study Intervention	AZD2816
Study Code	D7220C00001
Version	Amendment GBR-3
Date	13 October 2021

TITLE PAGE

A Phase II/III Partially Double-Blinded, Randomised, Multinational, Active-Controlled Study in Both Previously Vaccinated and Unvaccinated Adults Ages 30 and Above to Determine the Safety and Immunogenicity of AZD2816, a Vaccine for the Prevention of COVID-19 Caused by Variant Strains of SARS-CoV-2

Sponsor Name:	**AstraZeneca AB**
Legal Registered Address:	151 85 Södertälje, Sweden
Regulatory Agency Identifier Numbers:	EudraCT: 2021-002530-17

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: D7220C00001

Amendment Number: GBR-3

Study Intervention: AZD2816

Study Phase: II/III

Short Title: Phase II/III Study of AZD2816, a Vaccine for the Prevention of COVID-19 in Adults

Study Physician Name and Contact Information will be provided separately.

International Coordinating Investigator: Andrew J Pollard, FRCPCH PhD FMedSci
University of Oxford
Oxford, United Kingdom

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	13 October 2021
Amendment GBR-2	30 July 2021
Amendment GBR-1	3 June 2021
Amendment 1	1 June 2021
Version 1	14 May 2021

Amendment GBR-3: 13 October 2021

The principal reason for this amendment was to remove the age cap and revise the primary and key secondary non-inferiority analyses to included historical controls due to difficulties in recruiting the previously unvaccinated cohort.

This amendment has also been implemented in the global version of the study D7220C00001 Clinical Study Protocol.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Synopsis Section 4.1 Section 9.4..3.1.1	Inserted information on use of historical controls	Required based on anticipated confounding between previously vaccinated and previously unvaccinated cohorts.	Substantial
Section 3.2, Table 6	Inserted exploratory objectives on exploration of humoral immune response with live virus neutralization assay and exploration of additional immune response based on emerging data	Omitted in error	Non-substantial
Section 4.1	Deleted age cap ensuring at least 25% enrolled participants were >65 years of age.	Due to enrollment difficulties in finding previously unvaccinated elderly	Substantial
Section 7.1	Inserted laboratory-confirmed SARS-CoV-2 infection as discontinuation of study intervention	To explicitly state this criterion (which is implicitly included in criteria 2) as a discontinuation of treatment criterion.	Non-substantial
Section 9.2	Section on immunogenicity comparisons and previous Table	Had been placed under Secondary Objective in error	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	16 and Table 17 were moved up under the Primary Objective sub-heading		
Section 9.4.3.1.1 Table 19 Table 20 Table 21 Table 22 Table 23	Analysis key (abbreviations) revised	Improvements in abbreviations for clarity	Non-substantial
Section 9.4..3.1.1	Description of statistical approach to be used with historical control comparisons added.	Inclusion of historical controls requires description of statistical methodology to be used.	Substantial

In addition, the protocol has been revised with minor rewordings, corrections, and clarifications which are all considered to be non-substantial.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A phase II/III partially double-blinded, randomised, multinational, active-controlled study in both previously vaccinated and unvaccinated adults to determine the safety and immunogenicity of AZD2816, a vaccine for the prevention of COVID-19 caused by variant strains of SARS-CoV-2.

Short Title: Phase II/III study of AZD2816, a vaccine for the prevention of COVID-19 in adults.

Rationale: Recently, several variants of the SARS-CoV-2 virus with increased transmissibility have emerged, including B.1.1.7, first identified in the UK, P.1, first identified in Brazil, and B.1.351, first identified in South Africa. In an ongoing clinical trial of AZD1222 in South Africa, interim results failed to show protection against mild to moderate disease caused by the B.1.351 variant; protection against severe disease could not be determined as no severe cases were identified (Madhi et al 2021).

Based on available evidence about vaccine effectiveness and molecular epidemiology of emerging variants, B.1.351 is estimated to have a potential to escape vaccine-induced immunity. B.1.351 carries sequence mutations in common with other variants of concerns; immunity to B.1.351 therefore has the potential to provide some cross-immunity against other emerging strains. Development of candidate vaccines that include the B.1.351 S-protein variant is underway. AstraZeneca is developing AZD2816, a vaccine against the B.1.351 SARS-CoV-2 variant using the same ChAdOx1 platform and manufacturing processes used for AstraZeneca's currently available COVD-19 vaccine, AZD1222.

Objectives and Endpoints:

The purpose of this study is to characterize the safety and immunogenicity of AZD2816, AstraZeneca's candidate ChAdOx1 vector vaccine against SARS-CoV-2 variant strain B.1.351, when administered:

- As a single booster dose to SARS-CoV-2 seronegative participants who previously received a 2-dose primary vaccination against SARS-CoV-2 with AZD1222 or an mRNA COVID-19 vaccine
- As a 2-dose primary homologous vaccination to SARS-CoV-2 seronegative participants who are previously unvaccinated
- As the second dose of 2-dose primary heterologous vaccination (with AZD1222 as first dose) to SARS-CoV-2 seronegative participants who are unvaccinated.

It is anticipated that the majority of the patients recruited in the United Kingdom will belong to the previously-vaccinated cohort that will receive a single booster dose of AZD2816 or AZD1222.

The following table lists the primary and secondary endpoints:

Objectives	Endpoints
Safety Objectives: Previously unvaccinated participants	
- Primary	
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose
- Secondary	
To characterize the safety and tolerability of a 2-dose primary heterologous vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in previously unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of a 2-dose primary heterologous vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in previously unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
Immunogenicity objectives: Previously unvaccinated participants	
To determine if the pseudoneutralizing antibody GMT response elicited by a 2-dose AZD2816 primary vaccination is non-inferior to the response elicited by a 2-dose AZD1222 primary vaccination Estimand:	

Treatment	AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination

Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Primary	B.1.351	Wuhan-Hu-1
Key Secondary 2.2	B.1.351	B.1.351
Key Secondary 2.4	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD2816 vaccination/AZD1222 vaccination	
To determine if the seroresponse rate elicited by a 2-dose AZD2816 primary vaccination is non-inferior to the seroresponse rate elicited by a 2-dose AZD1222 primary vaccination Estimand:		
Treatment	AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Key Secondary 2.1	B.1.351	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 vaccination - AZD1222 vaccination	
To determine if the neutralizing antibody GMT response elicited by a 2-dose AZD1222+AZD2816 heterologous primary vaccination is non-inferior to the response elicited by a 2-dose AZD1222 primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Key Secondary 2.3	B.1.351	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD1222+AZD2816 vaccination/AZD1222 vaccination	
To determine if the seroresponse rate elicited by a 2-dose AZD1222+AZD2816 heterologous primary vaccination is non-inferior to the seroresponse rate elicited by a 2-dose AZD1222 primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥4-fold increase from baseline in pseudoneutralizing antibodies) for AZD1222+AZD2816 vaccination - AZD1222 vaccination	
To determine if the neutralizing antibody GMT response against the B.1.351 variant is non-inferior to the response against the original Wuhan-Hu-1 strain following a 2-dose AZD2816 primary vaccination Estimand:		
Treatment	AZD2816 vaccination	AZD2816 vaccination

Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-Hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following a 2-dose AZD2816 primary vaccination Estimand:		
Treatment	AZD2816 vaccination	AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥4-fold increase from baseline in pseudoneutralizing antibodies) against B.1.351 versusWuhan-Hu-1	
To determine if the neutralizing antibody GMT response against the B.1.351 variant is non-inferior to the response against the original Wuhan-Hu-1 strain following a 2-dose AZD1222+AZD2816 heterologous primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222+AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-Hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following a 2-dose AZD1222+AZD2816 heterologous primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222+AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥4-fold increase from baseline in pseudoneutralizing antibodies) against B.1.351 versusWuhan-Hu-1	
To also determine non-inferiority of the s-protein binding antibody response for the above comparisons as other secondary objectives		
To also determine the neutralizing antibody GMT responses 28 days after first vaccination dose in the above primary and key secondary objectives		

Objectives	**Endpoints**
Safety Objectives: Previously vaccinated participants	
- Primary	

To characterize the safety and tolerability of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose
- Secondary	
To characterize the safety and tolerability of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
Immunogenicity objectives: previously vaccinated participants	
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:	

Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Primary	B.1.351	Wuhan-Hu-1
Key Secondary 2.1	B.1.351	B.1.351
Key Secondary 2.3	Wuhan-Hu-1	Wuhan-Hu-1

Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 vaccination	
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose is non-inferior to response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Key Secondary 2.2	B.1.351	B.1.351
Key Secondary 2.5	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 booster	
To determine if the neutralizing antibody GMT response elicited by an AZD1222 booster dose in patients previously vaccinated with AZD1222 is non-inferior to the response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD1222 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective Level:	Serotype comparison:	
Key Secondary 2.4	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD1222 booster/AZD1222 vaccination	
To determine if the seroresponse elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other secondary	B.1.351	Wuhan-Hu-1
Other secondary	B.1.351	B.1.351
Other secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Difference in seroresponse (>4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 primary vaccination	
To determine if the seroresponse elicited by an AZD2816 booster dose is non-inferior to response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Difference in seroresponse ($\geq$4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 booster	
To determine if the seroresponse elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD1222 booster	AZD1222 primary vaccination

Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 primary vaccination	
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose in participants previously vaccinated with an mRNA-based vaccine is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand		
Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	mRNA vaccine vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 vaccination	
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with an mRNA-based vaccine Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	mRNA vaccine vaccinated seronegative participants	mRNA vaccine vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 booster	
To determine if the seroresponse elicited by an AZD2816 booster dose in participants previously vaccinated with an mRNA-based vaccine is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	mRNA vaccine vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 primary vaccination	
To determine if the seroresponse elicited by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with an mRNA-based vaccine Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	mRNA vaccine vaccinated seronegative participants	mRNA vaccine vaccinated seronegative participants

Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Endpoint	Difference in seroresponse (≥4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 booster	
To determine if the neutralizing antibody GMT response rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following a 2816 booster dose. Estimand:		
Treatment	AZD2816 booster	AZD2816 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-Hu-1	
To determine if the neutralizing antibody GMT response against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following a 1222 booster dose. Estimand:		
Treatment	AZD1222 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-Hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following a 2816 booster dose. Estimand:		
Treatment	AZD2816 booster	AZD2816 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥4-fold increase from baseline in pseudoneutralizing antibodies) for B.1.351/Wuhan-Hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following a 1222 booster dose. Estimand:		
Treatment	AZD1222 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥4-fold increase from baseline in pseudoneutralizing antibodies) for B.1.351/Wuhan-Hu-1	
To also determine non-inferiority of the s-protein binding antibody response for the above comparisons as other secondary objectives.		

SAEs: serious adverse events; MAAEs: medically attended adverse events; AESIs: adverse events of special interest.

[a] At least a 4-fold increase in geometric mean titre from baseline

Overall Design: This is a phase II/III, multinational, randomised, partially double-blind, controlled study in two distinct cohorts: previously vaccinated and previously unvaccinated participants.

Disclosure Statement: This is a parallel-group preventive study with 8 treatment arms.

Number of Participants: Approximately 2590 SARS-CoV-2 nucleocapsid seronegative participants will be assigned to study intervention to support the primary and secondary objectives of this study. In addition, participants that are SARS-Cov-2 nucleocapsid seropositive at screening will be enrolled and assigned to study intervention for an exploratory analysis, with a cap of 10% of the seronegative population (ie, approximately 259 total participants).

Intervention Groups and Duration: Previously vaccinated participants will receive 1 dose of AZD1222 or AZD2816 on Day 1. Previously unvaccinated participants will receive one of the following 2-dose vaccinations:

- 1 dose of AZD2816 on Day 1 and on Day 29
- 1 dose of AZD1222 on Day1 and on Day 29
- 1 dose of AZD1222 on Day 1 and 1 dose of AZD2816 on Day 29
- 1 dose of AZD2816 on Day 1 and on Day 85.

Participants will be followed up for safety for 180 days after last study vaccine administration.

Data Monitoring Committee: A Data Safety Monitoring Board will provide oversight to ensure safe and ethical conduct of the study.

Statistical Methods:

Sample sizes of 300-380 seronegative participants per group are deemed appropriate based upon available immunogenicity data from previous clinical studies with AZD1222 for the primary and secondary objectives of this study.

Owing to national vaccine rollout in the recruitment countries, including the prioritization of elderly populations, it is anticipated that there will be critical differences between the previously vaccinated and previously unvaccinated cohorts that may confound the interpretation of the results. Consequently, the primary and key secondary non-inferiority analyses across these two cohorts will compare the previously vaccinated participants that received a booster dose in this study with a subset of matched participants from the previously unvaccinated participants that received the 2-dose AZD1222 primary vaccine series in the AZD1222 Phase 3 trial, Study D8110C00001.

The safety analysis set for adverse events consists of all participants who have received at least one dose of study intervention. The immunogenicity analysis set includes all participants in the safety analysis set who have no protocol deviations or intercurrent events judged to have the potential to interfere with the generation or interpretation of an immune response.

An initial interim analysis will be performed on a subset of previously AZD1222 vaccinated participants that have received a booster dose to consider unblinded sample size adjustment. A second interim analysis will be performed when all previously AZD1222 vaccinated participants have completed their Day 29 visit to support registration of a booster dose. A third interim analysis will be performed on a subset of previously unvaccinated participants that have received their second dose to consider blinded sample size adjustment in this population. The primary analysis will be performed when there are data from all previously unvaccinated participants 28 days after the second dose of the 4-week dosing intervals to support assessment of these 2-dose primary vaccinations. A secondary analysis will be performed on data from 28 days after the second dose of the 12-week dosing interval to support assessment of this 2-dose primary vaccination. The final analysis will be performed on data from 6 months follow-up after participant's vaccination.

1.2 Schema

Figure 1 Study Design for Unvaccinated Seronegative/Seropositive Participants Receiving a 2-Dose Primary Vaccination

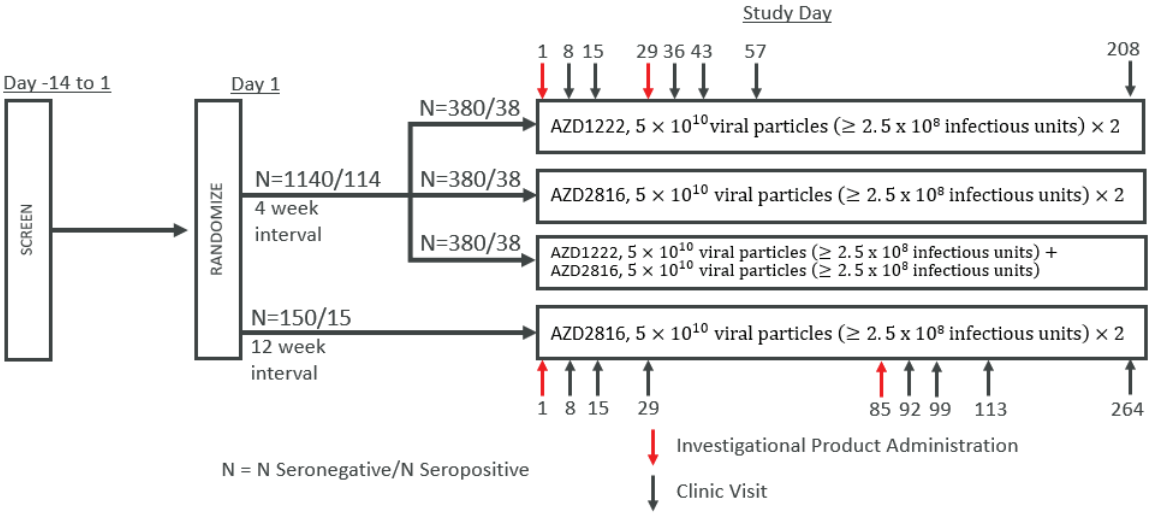
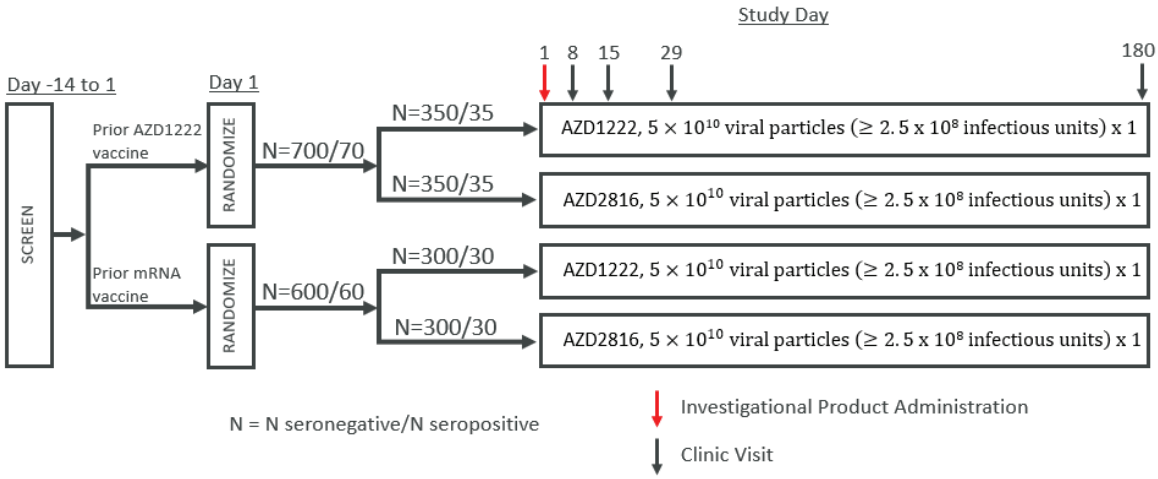


Figure 2 Study Design for Previously Vaccinated Seronegative/Seropositive Participants Receiving a 1-Dose Booster



Note: In addition to the approximately 2590 seronegative participants enrolled to support the primary/secondary objectives, seropositive participants will also be enrolled in the study to support exploratory objectives in this population, with a cap of 10% of the planned seronegative participants (ie, a maximum of 259 seropositive participants, bringing total enrollment to 2849).

1.3 Schedule of Activities

Table 1 Schedule of Activities: Screening

Procedure	Day -14 to Day 1	See Section
Informed consent	X	5.1, Appendix A 3
Demography	X	-
Medical and surgical history	X	-
Prior and concomitant medications	X	6.5
Complete physical examination, including height and weight	X	8.2.1
Vital signs	X	8.2.2
Urine pregnancy test (for women of childbearing potential only)	X	8.2.3
Clinical safety laboratory assessments	X	8.2.3
Assessment of serious adverse events	X	8.3, Appendix B
Blood sample for SARS-CoV-2 antibody testing (lateral flow test)	X	8.5.2
Verify eligibility criteria	X	5.1, 5.2

Note: Screening activities can occur at same visit as initial vaccination with investigational product (ie, Visit 1 in Table 2, Table 3, and Table 4).

Table 2 Schedule of Activities: Treatment/Follow-up Period for Participants Previously Vaccinated with 2 Doses of AZD1222 or an mRNA Vaccine

Procedure	Treatment and Follow-up Period					Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	
Day	**1**	**8**	**15**	**29**	**180**	
Window (days)	**-**	**±2**	**±2**	**±3**	**±14**	
Medical and surgical history	X	-	-	-	-	-
Urine pregnancy test (women of childbearing potential)	X	-	-	-	-	8.2.3
Concomitant medications/vaccinations	X	X	X	X	X	6.5
Verify eligibility criteria	X	-	-	-	-	5.1, 5.2
Monitoring of COVID-19	X	X	X	X	X	8.3.8
Vaccine administration (after screening activities, the activities listed above, and the pre-dose sampling activities listed below)	X	-	-	-	-	6.1.1
Immunological assessments						
Serum sample to assess SARS-CoV-2 serology/neutralising antibodies	X (pre-dose)	-	X	X	X	8.5.2
Serum sample to assess additional immunogenicity	X (pre-dose)	-	X	X	X	8.5.2
Blood sample to assess B-cell and T-cell responses in a sub-group of participants	X (pre-dose)	-	X	X	X	8.5.2.3
Blood sample for B-cell and T-cell response sequencing in a sub-group of participants	X (pre-dose)	-	X	X	X	8.5.2.3
Safety assessments						
Targeted physical examination	X	-	-	-	-	8.2.1
Vital signs	X	X	X	X	X	8.2.2
e-Diary provided with training	X	-	-	-	-	8.3.7
e-Diary collected	-	X	-	-	-	8.3.7
Unsolicited AEs	X (post-dose)	X	X	X	-	8.3
MAAEs, SAEs, and AESIs	X[a]	X	X	X	X	8.3.8, 8.3.8
Clinical safety laboratory assessments	X (pre-dose)[b]	X	-	X	X	8.2.3

[a] Only SAEs pre-dose
[b] Not required to be repeated if performed on screening day prior to Day 1.

AE: adverse event; AESI: adverse event of special interest; MAAE: medically-attended adverse event; SAE: serious adverse event

Table 3 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 4-Week Dosing Interval

Procedure	Treatment and Follow-up Period								Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	
Day	**1**	**8**	**15**	**29**	**V4+7**	**V4+14**	**V4+28**	**V4+180**	
Window (days)	**-**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
Medical and surgical history	X	-	-	-	-	-	-	-	-
Urine pregnancy test (women of childbearing potential)	X	-	-	X	-	-	-	-	8.2.3
Concomitant medications/vaccinations	X	X	X	X	X	X	X	X	6.5
Verify eligibility criteria	X	-	-	-	-	-	-	-	5.1, 5.2
Monitoring of COVID-19	X	X	X	X	X	X	X	X	8.3.8
Vaccine administration (after screening activities, the activities listed above, and the pre-dose sampling activities listed below)	X	-	-	X	-	-	-	-	6.1.1
Immunogenicity assessments									
Serum sample for SARS-CoV-2 serology/neutralising antibodies	X (pre-dose)	-	X	X (pre-dose)	-	X	X	X	8.5.2
Serum sample for additional immunogenicity	X (pre-dose)	-	X	X (pre-dose)	-	X	X	X	8.5.2
Blood sample to assess B-cell and T-cell responses in a sub-group of participants	X (pre-dose)	-	X	X (pre-dose)	-	-	X	X	8.5.2.3
Blood sample for B-cell and T-cell response sequencing in a sub-group of participants	X (pre-dose)	-	X	X (pre-dose)	-	-	X	X	8.5.2.3
Safety assessments									
Targeted physical examination	X	-	-	X	-	-	-	-	8.2.1
Vital signs	X	X	X	X	X	X	X	X	8.2.2
e-Diary provided with training	X	-	-	X	-	-	-		8.3.7

Table 3 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 4-Week Dosing Interval

Procedure	**Treatment and Follow-up Period**								**Section**
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	
Day	**1**	**8**	**15**	**29**	**V4+7**	**V4+14**	**V4+28**	**V4+180**	
Window (days)	**-**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
e-Diary collected	-	X	-	-	X	-	-		8.3.7
Unsolicited AEs	X (post-dose)	X	X	X	X	X	X	-	8.3
MAAEs, SAEs, and AESIs	X[a]	X	X	X	X	X	X	X	8.3.8
Clinical safety laboratory assessments	X (pre-dose)	X	-	X (pre-dose)	X	-	X	X	8.2.3

[a] Only SAEs pre-dose

AE: adverse event; AESI: adverse event of special interest; MAAE: medically-attended adverse event; SAE: serious adverse event

Table 4 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 12-Week Dosing Interval

Procedure	Treatment and Follow-up Period									Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	
Day	**1**	**8**	**15**	**29**	**85**	**V5+7**	**V5+14**	**V5+28**	**V5+180**	
Window (days)	**-**	**±2**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
Medical and surgical history	X	-	-	-	-	-	-	-	-	-
Urine pregnancy test (women of childbearing potential)	X	-	-	-	X	-	-	-	-	8.2.3
Concomitant medications/vaccinations	X	X	X	X	X	X	X	X	X	6.5
Verify eligibility criteria	X	-	-	-	-	-	-	-	-	5.1, 5.2
Monitoring of COVID-19	X	X	X	X	X	X	X	X	X	8.3.8
Vaccine administration (after screening activities, the activities listed above, and the pre-dose sampling activities listed below)	X	-	-	-	X	-	-	-	-	6.1.1
Immunogenicity assessments										
Serum sample to assess SARS-CoV-2 serology/neutralising antibodies	X (pre-dose)	-	X	X	X (pre-dose)	-	X	X	X	8.5.2
Serum sample to assess additional immunogenicity	X (pre-dose)	-	X	X	X (pre-dose)	-	X	X	X	8.5.2
Blood sample to assess B-cell and T-cell responses in a sub-group of participants	X (pre-dose)	-	X	X	X (pre-dose)	-	-	X	X	8.5.2.3
Blood sample for B-cell and T-cell response sequencing in a sub-group of participants	X (pre-dose)	-	X	X	X (pre-dose)	-	-	X	X	8.5.2.3
Safety assessments										
Targeted physical examination	X	-	-	-	X	-	-	-	-	8.2.1
Vital signs	X	X	X	X	X	X	X	X	X	8.2.2
e-Diary provided with training	X	-	-	-	X	-	-	-		8.3.7

Table 4 Schedule of Activities: Treatment/Follow-up Period for Previously Unvaccinated Participants Receiving Vaccination with a 12-Week Dosing Interval

Procedure	Treatment and Follow-up Period									Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	
Day	**1**	**8**	**15**	**29**	**85**	**V5+7**	**V5+14**	**V5+28**	**V5+180**	
Window (days)	**-**	**±2**	**±2**	**±2**	**±3**	**±2**	**±2**	**±3**	**±14**	
e-Diary collected	-	X	-	-	-	X	-	-	-	8.3.7
Unsolicited AEs	X (post-dose)	X	X	X	X	X	X	X	-	8.3
MAAEs, SAEs, and AESIs	X[a]	X	X	X	X	X	X	X	X	8.3.8, 8.3.8
Clinical safety laboratory assessments	X (pre-dose)	X	-	X	X (pre-dose)	X	-	X	X	8.2.3

[a] Only SAEs pre-dose

AE: adverse event; AESI: adverse event of special interest; MAAE: medically-attended adverse event; SAE: serious adverse event

2 INTRODUCTION

AZD2816 is being developed for the prevention of COVID-19. It is a modified version of the current AstraZeneca SARS-CoV-2 vaccine (referred to as AZD1222 in clinical documentation) that has been modified to also provide immunity against the newly emerging SARS-CoV-2 variant strain B.1.351. Like AZD1222, AZD2816 is a recombinant replication-defective chimpanzee adenovirus vector (ChAdOx1) expressing the SARS-CoV-2 S surface glycoprotein driven by the human cytomegalovirus major immediate early promoter that includes intron A with a human tissue plasminogen activator leader sequence at the N terminus. AZD2816 differs from AZD1222 in that the S glycoprotein gene sequence used is from the B.1.351 variant strain instead of the original Wuhan-Hu-1 variant.

2.1 Study Rationale

The aim of the study is to assess the safety and immunogenicity of AZD2816 for prevention of COVID-19 as both a 2-dose primary vaccination in previously unvaccinated participants and a 1-dose booster vaccination in participants previously vaccinated against the original Wuhan-Hu-1 strain of SARS-CoV-2 by either AZD1222 or an mRNA-based vaccine. A safe and effective vaccine for COVID-19 prevention, including against the B.1.351 variant, would have significant global public health impact.

The study will also investigate the safety and immunogenicity of 1) a heterologous 2-dose vaccination with AZD1222 as first dose and AZD2816 as the second dose and 2) a single dose of AZD1222 as a booster vaccination in participants that have been previously vaccinated with an mRNA COVID-19 vaccine targeting the original Wuhan-Hu-1 strain.

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, which was named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (

Zhou et al 2020). The disease these patients contracted was subsequently named Coronavirus Disease 2019 (COVID-19). The World Health Organization declared the novel coronavirus a pandemic on 11 March 2020. The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has resulted in significant global morbidity and mortality as well as major disruption to healthcare systems. Measures to change the course of the pandemic have included the accelerated development vaccines against the original Wuhan-Hu-1 strain.

Coronaviruses are spherical, enveloped viruses with positive-sense single-stranded RNA genomes. SARS-CoV-2 belongs to the phylogenetic lineage B of the genus *Betacoronavirus*, and it is the seventh corona virus known to cause human infections and the third known to

cause severe disease after SARS-CoV and MERS-CoV. One fourth of the viral genome is responsible for coding structural proteins, such as the S glycoprotein, envelope, membrane, and nucleocapsid proteins. Envelope, membrane, and nucleocapsid proteins are mainly responsible for virion assembly while the S protein is involved in cellular receptor binding, mediating fusion of virus and cell membranes and virus entry into host cells during infection. The SARS-CoV-2 spike (S) glycoprotein is a type I trimeric, transmembrane protein that is located at the surface of the viral envelope forming spike-shaped protrusions. The S protein's subunits are responsible for cellular receptor angiotensin-converting enzyme 2 binding via the receptor binding domain and subsequent fusion of virus and cell membranes, thereby mediating the entry of SARS-CoV-2 into the target cells. The S protein has an essential role in virus entry and determines tissue and cell tropism, as well as host range. The roles of the S-protein in receptor binding and membrane fusion have made it a desirable target for vaccine and antiviral development. The AstraZeneca vaccine AZD1222 expresses a codon-optimized coding sequence for S protein from the SARS-CoV-2 genome sequence accession MN908947 (ie, the Wuhan-Hu-1 isolate).

To date, 5 vaccines that rely upon the expression of the SARS CoV-2 S glycoprotein to stimulate/prime a protective immune response against the virus have demonstrated safety and efficacy in phase III clinical trials. Four of these, AZD1222 (also referred to as ChAdOx1 nCoV-19, a recombinant replication-defective chimpanzee adenoviral vectored), BNT162b2 (Pfizer-BioNTech, mRNA), mRNA-1273 (Moderna, mRNA), and Ad26.COV2-S (Janssen, adenovirus serotype 26 vectored) have received Emergency Use Authorization or Conditional Marketing Approval in the United States and/or the European Union, and elsewhere, and NVX-CoV2373 (Novavax; recombinant 86 protein) has also shown efficacy and is likely to be in use in the near future. These vaccines have been designed based upon the initial reported genetic sequence of the S protein from Wuhan in January 2020 (Lu et al 2020).

The immunogenicity and efficacy of AZD1222 has been shown in clinical trials (Ramasamy et al 2020, Voysey et al 2021a, Voysey et al 2021b). Immunogenicity data indicate that a single dose of AZD1222 elicits both humoral and cellular immunogenicity responses and that antibody responses are boosted after a second dose. In a pooled analysis of the 4 studies conducted in the United Kingdom, Brazil, and South Africa (database lock 07 December 2020), the vaccine was highly immunogenic; seroresponse of S binding antibody was > 98% after a single dose of AZD1222. Seroresponse of live neutralising antibody was 82.4% after 1 dose, which rose to 99.4% after a second dose. Efficacy analyses of the pooled DCO2 data demonstrated effective protection of AZD1222 against COVID-19 with a vaccine efficacy of 66.73% (95.84% CI: 57.41%, 74.01%) ($p < 0.001$) from 15 days after the second dose in seronegative participants receiving 2 doses. The DCO2 data also demonstrated that the standard dose of AZD1222 (5×10^{10} viral particles) provides complete protection against COVID-19 hospital admission ≥ 22 days after the first dose in the seronegative analysis set (0 versus 14 cases in the control group, 2 of which were severe, including one with a fatal

outcome). Vaccine efficacy was similar in participants with pre-existing comorbidities, being those at greatest risk of severe outcomes of COVID-19, compared to that in the general population. Recently available primary analysis data from a Phase III study performed in the United States and Latin America showed primary endpoint vaccine efficacy of 76% (95% CI: 67.60%, 82.22%; p-value < 0.001).

A sharp rise in COVID-19 cases was reported in late 2020, which was attributed to the emergence of new SARS-CoV-2 variant strains: B.1.1.7 in the United Kingdom, B.1.351 in South Africa, and P.1 in Brazil. These variant strains carry a number mutations in the S protein sequence: 9 amino acids in B.1.1.7, 10 amino acids in B.1.351, and 12 amino acids in P.1 compared with the Wuhan-Hu-1 sequence. These mutations may result in an increase of transmissibility and/or reduced vaccine effectiveness. Variant B.1.351 was first identified in South Africa in October 2020. Its attributes include approximately 50% increased transmission and moderate impact of neutralization by monoclonal antibody therapeutics, convalescent plasma and vaccine sera. In vitro neutralization assays suggest that the B.1.351 lineage viruses may be the most antigenically distinct from the original Wuhan-like strains (Zhou et al 2021). In addition, evidence suggests that AZD1222 may afford diminished protection against mild-moderate COVID-19 disease arising from the B.1.351 variant which is also antigenically the most different from the Wuhan-Hu-1 virus (Madhi et al 2021).

The development of candidate vaccines that would be effective against the B.1.351 variant strain is underway. AZD2816 is being developed as an updated ChADOx-nCOv19 vaccine designed to provide protective immunity against the newly arising B.1.351 variant strain, using the same ChAdOx1 platform and manufacturing processes used for AstraZeneca's currently approved COVID-19 vaccine, AZD1222. The purpose of this Phase II/III, multinational, randomised, partially double-blind, active-controlled study is to demonstrate the safety and characterize the immunogenicity of AZD2816, AstraZeneca's candidate ChAdOx1 vector vaccine against B.1.351, when administered:

- As a single booster dose to SARS-CoV-2 seronegative participants who have previously received a 2-dose primary vaccination series against the original SARS-CoV-2 Wuhan-Hu-1 strain (AZD1222 or an mRNA vaccine)
- As a 2-dose homologous primary vaccination to SARS-CoV-2 seronegative participants who have not been vaccinated previously.

It is anticipated that the majority of the patients recruited in the United Kingdom will belong to the previously-vaccinated cohort that will receive a single booster dose.

The immunogenicity of a 2-dose primary heterologous vaccination (with AZD1222 as first dose and AZD2816 as second dose) to SARS-CoV-2 seronegative participants who are unvaccinated and a single booster dose of AZD1222 to SARS-CoV-2 seronegative

participants who have previously received a 2-dose primary vaccination series against the original SARS-CoV-2 Wuhan-Hu-1 strain will also be investigated.

SARS-CoV-2 seropositive participants will be enrolled in separate cohorts to support a parallel exploratory analysis in these participants.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AZD1222 and AZD2816 is provided in the respective Investigator's Brochures.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of AZD2816 and AZD1222 can be found in the respective Investigator's Brochures.

2.3.1 Risk Assessment

AZD2816 has been developed using the same vaccine vector, ChAdOx1, as AZD1222 and only differs in the sequence for SARS-CoV-2 S glycoprotein that is inserted in the vector. The anticipated safety profile of AZD2816 is the same as the observed safety profile of AZD1222. Risks associated with AZD2816 are thus the same as the risks associated with AZD1222, and no additional risks are anticipated due to the change in the targeted sequence.

A number of essentially mild and moderate adverse reactions to AZD1222 have been identified and resemble reactions frequently observed after many vaccines. Based on pooled clinical data from studies with AZD1222, the most commonly expected local solicited AEs for participants in this study are vaccination site pain and tenderness. The most commonly expected systemic solicited AEs are fatigue, headache, and malaise. The majority of reported events have been 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.

Post-authorisation hypersensitivity reactions, including anaphylaxis and angioedema, have occurred following administration of AZD1222 and are considered an identified risk.

A combination of thrombosis and thrombocytopenia, in some cases accompanied by bleeding, has been observed very rarely following vaccination with COVID-19 Vaccine (ie, AZD1222) during post-authorisation use. No events have been observed in the AZD1222 clinical development programme. Thrombosis in combination with thrombocytopenia is thus considered to be an important identified risk. This includes cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. Considering the frequency of this rare event and the size of this study, the risk for participants in this trial is considered to be low. The protocol includes exclusion criteria and instructions for

heightened vigilance and thorough investigations for suspected cases to mitigate against further the risk for these rare event.

Important potential risks are 1) neurologic events and potential immune-mediated neurologic conditions and 2) vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease.

2.3.2 Benefit Assessment

All participants will receive active treatment: either AZD1222, which has been shown to be effective in providing protection against SARS-CoV-2, or AZD2816, which as a modified form of AZD1222 designed to be effective against the emergent B.1.351 variant strain and may also provide participants with protection. The information gained from this study will inform development decisions with regard to the efficacy of AZD2816 as both a primary 2-dose vaccination in participants that have not been previously vaccinated and a 1-dose booster vaccination in participants previously vaccinated against SARS-CoV-2.

2.3.3 Benefit: Risk Assessment for Inclusion of Adults from 30 to 39 Years of Age

There have been reports of very rare adverse events of concurrent thrombosis and thrombocytopenia following vaccination with the first dose of AstraZeneca CoV-19 vaccine (AZD1222). There have been no safety concerns identified for thrombosis/thrombocytopenia associated with the second dose of the AstraZeneca (AZD1222) vaccine. Up to 19 May 2021, the MHRA has received reports of 332 cases of major thromboembolic events with concurrent thrombocytopenia in the United Kingdom following vaccination with COVID-19 Vaccine AstraZeneca. The estimated number of first doses of COVID-19 Vaccine AstraZeneca administered was 24.2 million, and the estimated number of second doses was 10.7 million.

Any risk for serious thromboembolic events with thrombocytopenia is expected to be similar for AZD1222 and AZD2816 due to the similarity of the investigational products.

In the context of this extremely rare adverse event, current advice from the United Kingdom's Joint Committee on Vaccination and Immunization (JCVI) recommends that unvaccinated adults aged 30 to 39 years who are not in a clinical priority group at higher risk of severe COVID-19 disease should be preferentially offered an alternative to AZD1222 where possible and only where no substantial delay or barrier in access to vaccination would arise (JCVI 2021). The recommendations are not a contra-indication in this age group but a public vaccination policy recommendation in the context of a current low incidence of disease, the availability of alternative vaccines, and current speed and uptake of the vaccination programme overall in the UK. The recommendations further advise that AZD1222 can be

used in the age group 30-39 if these factors deteriorate, stating that if other vaccines are not available “the benefits of receiving the AstraZeneca (AZD1222) vaccine outweigh the risks”.

The participants of the proposed study differ from the general public in that they are carefully selected, with exclusion of individuals with a wide range of risk factors for thrombosis/thrombocytopenia, to minimize this risk. The study also includes careful monitoring both pre-treatment and post-treatment to detect risk for thrombotic events with thrombocytopenia and promptly identify safety concerns at the individual participant level. The protocol and training for the investigators urges increased vigilance for these events of thrombosis with thrombocytopenia. Furthermore, Appendix F provides guidance on identifying, treating, and assessing these very rare events. The risk of these events occurring is disclosed in the Participant Information Sheet and Informed Consent Form. Furthermore, participants are advised to be alert for the following side effects in the 28 days after vaccination: severe/unusual headache, new or unexplained bruising/bleeding, shortness of breath, chest pain, leg swelling, persistent abdominal pain. The exclusion of individuals with a wide range of risk factors for thrombosis with thrombocytopenia and measures included in the study to ensure early detection of these events mitigates the risk for these rare events.

With regard to benefit, all patients enrolled in the study will receive active treatment, either with the approved AZD1222, which has a good safety profile and high efficacy in adults ages 18 and over, including protection against severe disease, or the experimental but closely related AZD2816, which is expected to have a similar safety profile with the potential to have broader efficacy than AZD1222, including against the emergent B.1.351 variant. Furthermore, the inclusion of these patients in the trial is important to investigate safety and immunogenicity of AZD2816, as both a primary vaccination and a booster vaccination, across the age groups for which it may be administered in clinical practice.

To summarise, the risk of serious harm due to vaccine-induced thrombotic thrombocytopenia is known to be small. As of 19 May 2021, the MHRA’s estimate of the overall incidence after first or unknown doses is 1.3 per 100,000 doses. Thus, the risk of one of these events occurring in the sub-group of participants 30 to 39 year of age from a study population of around 2000 patients is extremely low. This risk is appropriately mitigated in the study protocol to the extent that the risk-benefit of patients 30 to 39 years of age participating in this study is considered to be small, acceptable, and justified by the potential public health benefits of the study.

2.3.4 Overall Benefit: Risk Conclusion

For the safety of participants, the protocol has incorporated various risk mitigation measures including appropriate inclusion and exclusion criteria and close monitoring of participants to minimize known and potential risks.

An independent Data Safety Monitoring Board will provide study oversight, evaluating cumulative safety and other clinical data at regular intervals.

Taking these measures into account, the potential risks identified in association with the administration of AZD2816 and AZD1222 are justified by the anticipated benefit that may be afforded to participants for the prevention of COVID-19.

3 OBJECTIVES AND ENDPOINTS

3.1 Previously unvaccinated cohort receiving a 2-dose primary vaccination

The primary safety objective for the cohort of previously unvaccinated participants receiving a 2-dose dose primary vaccination is to characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in previously unvaccinated seronegative participants.

The primary and key secondary immunogenicity objectives for this cohort are as follows:

Primary:

1: To determine if the neutralizing antibody GMT response against the B.1.351 variant elicited by a 2-dose AZD2816 vaccination is non-inferior to the response against the original Wuhan-Hu-1 strain elicited by a 2-dose AZD1222 vaccination.

Key secondary:

2.1: To determine if seroresponse against the B.1.351 variant elicited by a 2-dose AZD2816 vaccination is non-inferior to seroresponse against the original Wuhan-Hu-1 strain elicited by a 2-dose AZD1222 vaccination**.**

2.2: To determine if the neutralizing antibody GMT response against the B.1.351 variant elicited by a 2-dose AZD2816 vaccination is non-inferior to the response elicited by a 2-dose AZD1222 vaccination.

2.3: To determine if the neutralizing antibody GMT response against the B.1.351 variant elicited by a 2-dose heterologous AZD1222 + AZD2816 vaccination is non-inferior to the response against the original Wuhan-Hu-1 strain elicited by a 2-dose AZD1222 vaccination

2.4: To determine if the neutralizing antibody GMT response against the original Wuhan-Hu-1 elicited by a 2-dose AZD2816 vaccination is non-inferior to the response elicited by a 2-dose AZD1222 vaccination

The above primary and the key secondary immunogenicity objectives will be supported by other secondary immunogenicity objectives (see below) for which there will be no formal hypothesis testing.

Table 5 further describes the objectives and endpoints for this cohort of participants, including estimands for the immunogenicity objectives.

Table 5 Study Objectives and Endpoints for Previously Unvaccinated Participants Receiving a 2-Dose Primary Vaccination

Safety Objectives	
Objectives	**Endpoints**
- Primary	
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose
- Secondary	
To characterize the safety and tolerability of a heterologous primary vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in previously unvaccinated seronegative participants	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety and tolerability of a heterologous primary vaccination with 1 dose of AZD1222 followed by 1 dose of AZD2816 administered with a 4-week dosing interval in previously unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of a 2-dose primary vaccination with AZD2816 with a 12-week dosing interval in unvaccinated seronegative participants	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
Immunogenicity Objectives	
To determine if the pseudoneutralizing antibody GMT response elicited by a 2-dose AZD2816 primary vaccination is non-inferior to the response elicited by a 2-dose AZD1222 primary vaccination Estimand:	

Treatment	AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Primary	B.1.351	Wuhan-Hu-1
Key Secondary 2.2	B.1.351	B.1.351
Key Secondary 2.4	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD2816 vaccination/AZD1222 vaccination	
To determine if the seroresponse rate elicited by a 2-dose AZD2816 primary vaccination is non-inferior to the seroresponse rate elicited by a 2-dose AZD1222 primary vaccination Estimand:		
Treatment	AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Key Secondary 2.1	B.1.351	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 vaccination - AZD1222 vaccination	
To determine if the neutralizing antibody GMT response elicited by a 2-dose AZD1222+AZD2816 heterologous primary vaccination is non-inferior to the response elicited by a 2-dose AZD1222 primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Key Secondary 2.3	B.1.351	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD1222+AZD2816 vaccination/AZD1222 vaccination	
To determine if the seroresponse rate elicited by a 2-dose AZD1222+AZD2816 heterologous primary vaccination is non-inferior to the seroresponse rate elicited by a 2-dose AZD1222 primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective Level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥4-fold increase from baseline in pseudoneutralizing antibodies) for AZD1222+AZD2816 vaccination - AZD1222 vaccination	

To determine if the neutralizing antibody GMT response against the B.1.351 variant is non-inferior to the response against the original Wuhan-Hu-1 strain following a 2-dose AZD2816 primary vaccination Estimand:		
Treatment	AZD2816 vaccination	AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-Hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following a 2-dose AZD2816 primary vaccination Estimand:		
Treatment	AZD2816 vaccination	AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥4-fold increase from baseline in pseudoneutralizing antibodies) against B.1.351 versusWuhan-Hu-1	
To determine if the neutralizing antibody GMT response against the B.1.351 variant is non-inferior to the response against the original Wuhan-Hu-1 strain following a 2-dose AZD1222+AZD2816 heterologous primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222+AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-Hu-1	
To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following a 2-dose AZD1222+AZD2816 heterologous primary vaccination Estimand:		
Treatment	AZD1222+AZD2816 vaccination	AZD1222+AZD2816 vaccination
Population	Seronegative participants with no prior COVID-19 vaccination	Seronegative participants with no prior COVID-19 vaccination
Dosing interval	4 weeks	4 weeks
Timepoint	28 days after second vaccination dose	28 days after second vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥4-fold increase from baseline in pseudoneutralizing antibodies) against B.1.351 versusWuhan-Hu-1	
To also determine non-inferiority of the s-protein binding antibody response for the above comparisons as other secondary objectives		
To also determine the neutralizing antibody GMT responses 28 days after first vaccination dose in the above primary and key secondary objectives		
To explore anti-vector responses to the ChAdOx-1 adenovirus vector following a 2-dose homologous or	• GMT of ChAdOx1 neutralizing antibody titres	

heterologous primary vaccination with AZD2816 and/or AZD1222 in sub-groups of seronegative and seropositive participants	• Seroresponse rate of ChAdOx1 neutralizing antibody titres Pairwise correlations between anti-S, pseudo-neutralization, and ChAdOx1 neutralizing antibody titres, 28 days after both Dose 1 and Dose 2
Exploratory Objectives	
Objective	Endpoints
To explore the immune response elicited by a 2-dose AZD2816 primary vaccination with a 12-week dosing interval compared to the response elicited by a 2-dose AZD2814 primary vaccination with a 4-week dosing interval	• GMT ratio of pseudoneutralizing antibodies • Seroresponse
To explore antibody response to selected SARS-CoV-2 variants of interest/variants of concern following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in a sub-group of seronegative participants	• GMT of SARS-CoV-2 anti-S binding antibodies for selected variants of concern/variants of interest • Seroresponse rate of SARS-CoV-2 specific binding antibody titres for selected variants of concern/variants of interest • GMT of SARS-CoV-2 pseudoneutralizing antibody responses against the B.1.617.2 (delta) variant • Seroresponse rate of SARS-CoV-2 pseudoneutralizing antibody responses against the B.1.617.2 (delta) variant
To explore B-cell and T-cell responses following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in a sub-group of seronegative participants	• Intracellular cytokine staining and flow cytometry for T-cell responses over time • Quantification of (IFN-γ) ELISpot responses to SARS-CoV-2 B.1.351 or Wuhan-Hu-1 S protein from day of dosing baseline over time • Breadth and depth of peripheral blood B-cell and T-cell repertoire over time through immunosequencing
To monitor the incidence of SARS-CoV-2 infection following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in previously unvaccinated seronegative participants	• The incidence of SARS-CoV-2 infection defined by the seroresponse to nucleocapsid antibodies occurring post-second dose of study intervention
To monitor the incidence of COVID-19 following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in previously unvaccinated seronegative participants	• Incidence of COVID-19, defined as SARS-CoV-2 RT-PCR-positive symptomatic illness.
To explore the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in sub-groups of seronegative and seropositive participants	• Geometric mean titre of SARS-CoV-2 neutralization as determined by a live virus neutralization assay • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres as determined by a live virus neutralization assay

To explore additional immune responses following a 2-dose homologous or heterologous primary vaccination with AZD2816 and/or AZD1222 in sub-groups of seronegative and seropositive participants	• Other exploratory assays for humoral and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data
To explore the immunogenicity objectives in seropositive participants	• GMT of pseudoneutralizing antibodies • Seroresponse rates

MAAEs: medically attended adverse events; SAEs: serious adverse events; AESIs: adverse events of special interest

[a] Seroresponse: An at least 4-fold increase in geometric mean titre from baseline.

3.2 Previously vaccinated cohort receiving a 1-dose booster vaccination

The primary safety objective for the cohort of seronegative previously vaccinated participants receiving a booster dose is to characterize the safety and tolerability of 1 booster dose of AZD2816 in participants previously vaccinated with AZD1222.

The primary and key secondary immunogenicity objectives for this cohort are as follows:

Primary:

1: To determine if the humoral immune response against the B.1.351 variant elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to the response against the original Wuhan-Hu-1 strain elicited by 2-dose AZD1222 vaccination administered to previously unvaccinated participants.

Key secondary:

2.1: To determine if the humoral immune response against the B.1.351 variant elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to the response elicited by 2-dose AZD1222 vaccination administered to previously unvaccinated participants.

2.2: To determine if the humoral immune response elicited against the B.1.351 variant by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222.

2.3: To determine if the humoral immune response against the original Wuhan-Hu-1 strain elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to the response elicited by 2-dose AZD1222 vaccination administered to previously unvaccinated participants.

2.4: To determine if the humoral immune response against the original Wuhan-Hu-1 strain elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 is non-inferior to the response elicited by a 2-dose AZD1222 vaccination

2.5: To determine if the humoral immune response against the original Wuhan-Hu-1 strain elicited by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222.

The primary and key secondary immunogenicity objectives will be supported by other secondary objectives for which there will be no formal hypothesis testing.

Table 6 further describes the objectives and endpoints for this cohort of participants, including estimands for the primary and secondary immunogenicity objectives.

Table 6 Study Objectives and Endpoints for Previously Vaccinated Participants Receiving a 1-Dose Booster

Safety Objectives	Endpoints
- Primary	
To characterize the safety and tolerability of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Incidence of local and systemic solicited AEs for 7 days post dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs, for 28 days post-dose • The change from baseline for safety laboratory measures for 28 days post-dose
- Secondary	
To characterize the safety and tolerability of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the safety and tolerability of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of local and systemic solicited AEs for 7 days post-dose • Incidence of unsolicited AEs, including MAAEs, SAEs, and AESIs for 28 days post-dose
To characterize the extended safety of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with AZD1222	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination
To characterize the extended safety of 1 booster dose of AZD2816 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination

To characterize the extended safety of 1 booster dose of AZD1222 in seronegative participants previously vaccinated with a SARS-CoV-2 mRNA vaccine	• Incidence of MAAEs, SAEs, and AESIs from Day 1 through 6 months post-vaccination

Immunogenicity objectives

To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination
Estimand:

Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Primary	B.1.351	Wuhan-Hu-1
Key Secondary 2.1	B.1.351	B.1.351
Key Secondary 2.3	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 vaccination	

To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose is non-inferior to response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222
Estimand:

Treatment	AZD2816 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Key Secondary 2.2	B.1.351	B.1.351
Key Secondary 2.5	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 booster	

To determine if the neutralizing antibody GMT response elicited by an AZD1222 booster dose in patients previously vaccinated with AZD1222 is non-inferior to the response elicited by a 2-dose AZD1222 vaccination
Estimand:

Treatment	AZD1222 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective Level:	Serotype comparison:	
Key Secondary (2.4)	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	GMT ratio of pseudoneutralizing antibodies for AZD1222 booster/AZD1222 vaccination	

To determine if the seroresponse elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination
Estimand:

Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other secondary	B.1.351	Wuhan-Hu-1
Other secondary	B.1.351	B.1.351
Other secondary	Wuhan-Hu-1	Wuhan-Hu-1

Endpoint	Difference in seroresponse (≥4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 primary vaccination	
To determine if the seroresponse elicited by an AZD2816 booster dose is non-inferior to response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 booster	
To determine if the seroresponse elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD1222 booster	AZD1222 primary vaccination
Population	AZD1222 vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 primary vaccination	
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose in participants previously vaccinated with an mRNA-based vaccine is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	mRNA vaccine vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 vaccination	
To determine if the neutralizing antibody GMT response elicited by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with an mRNA-based vaccine Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	mRNA vaccine vaccinated seronegative participants	mRNA vaccine vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1

Other Secondary	B.1.351	B.1.351
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for AZD2816 booster/AZD1222 booster	
To determine if the seroresponse elicited by an AZD2816 booster dose in participants previously vaccinated with an mRNA-based vaccine is non-inferior to response elicited by a 2-dose AZD1222 vaccination Estimand:		
Treatment	AZD2816 booster	AZD1222 primary vaccination
Population	mRNA vaccine vaccinated seronegative participants	Seronegative participants with no prior COVID-19 vaccination
Timepoint	28 days after booster administration	28 days after 2nd vaccination dose
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Endpoint	Difference in seroresponse (≥4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 primary vaccination	
To determine if the seroresponse elicited by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with an mRNA-based vaccine Estimand:		
Treatment	AZD2816 booster	AZD1222 booster
Population	mRNA vaccine vaccinated seronegative participants	mRNA vaccine vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	Wuhan-Hu-1	Wuhan-Hu-1
Other Secondary	B.1.351	B.1.351
Endpoint	Difference in seroresponse (≥4-fold increase from baseline in pseudoneutralizing antibodies) for AZD2816 booster versus AZD1222 booster	
To determine if the neutralizing antibody GMT response rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following an AZD2816 booster dose. Estimand:		
Treatment	AZD2816 booster	AZD2816 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-Hu-1	
To determine if the neutralizing antibody GMT response against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following An AZD1222 booster dose. Estimand:		
Treatment	AZD1222 booster	AZD1222 booster
Population	AZD1222 vaccinated seronegative participants	AZD1222 vaccinated seronegative participants
Timepoint	28 days after booster administration	28 days after booster administration
Objective level:	Serotype comparison:	
Other Secondary	B.1.351	Wuhan-Hu-1
Endpoint	Geometric mean titre ratio of pseudoneutralizing antibodies for B.1.351/Wuhan-Hu-1	

<table>
<tr><td colspan="3">To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following an AZD2816 booster dose.
Estimand:</td></tr>
<tr><td>Treatment</td><td>AZD2816 booster</td><td>AZD2816 booster</td></tr>
<tr><td>Population</td><td>AZD1222 vaccinated seronegative participants</td><td>AZD1222 vaccinated seronegative participants</td></tr>
<tr><td>Timepoint</td><td>28 days after booster administration</td><td>28 days after booster administration</td></tr>
<tr><td>Objective level:</td><td colspan="2">Serotype comparison:</td></tr>
<tr><td>Other Secondary</td><td>B.1.351</td><td>Wuhan-Hu-1</td></tr>
<tr><td>Endpoint</td><td colspan="2">Difference in seroresponse (≥4-fold increase from baseline in pseudoneutralizing antibodies) for B.1.351/Wuhan-Hu-1</td></tr>
<tr><td colspan="3">To determine if the seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following an AZD1222 booster dose.
Estimand:</td></tr>
<tr><td>Treatment</td><td>AZD1222 booster</td><td>AZD1222 booster</td></tr>
<tr><td>Population</td><td>AZD1222 vaccinated seronegative participants</td><td>AZD1222 vaccinated seronegative participants</td></tr>
<tr><td>Timepoint</td><td>28 days after booster administration</td><td>28 days after booster administration</td></tr>
<tr><td>Objective level:</td><td colspan="2">Serotype comparison:</td></tr>
<tr><td>Other Secondary</td><td>B.1.351</td><td>Wuhan-Hu-1</td></tr>
<tr><td>Endpoint</td><td colspan="2">Difference in seroresponse (≥4-fold increase from baseline in pseudoneutralizing antibodies) for B.1.351/Wuhan-Hu-1</td></tr>
<tr><td colspan="3">To also determine non-inferiority of the s-protein binding antibody response for the above comparisons as other secondary objectives.</td></tr>
<tr><td>To explore anti-vector responses to the ChAdOx-1 adenovirus vector following a booster dose of AZD2816 in sub-groups of seronegative and seropositive participants</td><td colspan="2">• Magnitude of ChAdOx1 nAb titres (geometric mean titre)
• Seroresponse rate of ChAdOx1 neutralizing antibody titres
Pairwise correlations between anti-S, pseudo-neutralization, and ChAdOx1 neutralizing antibody titres, 1 month after both Dose 1 and Dose 2</td></tr>
<tr><td>Exploratory Objectives</td><td colspan="2">Endpoints</td></tr>
<tr><td>To explore antibody response to selected SARS-CoV-2 variants of interest/variants of concern following a booster dose of AZD2816 and in a sub-group of seronegative participants</td><td colspan="2">• Magnitude of SARS-CoV-2 specific antibody binding titres (geometric mean titre) for selected variants of concern/variants of interest
• Seroresponse rate of SARS-CoV-2 specific antibody binding titres for selected variants of concern/variants of interest
• GMT of SARS-CoV-2 pseudoneutralizing antibody responses against the B.1.617.2 (delta) variant
• Seroresponse rate of SARS-CoV-2 pseudoneutralizing antibody responses against the B.1.617.2 (delta) variant</td></tr>
<tr><td>To explore B-cell and T-cell responses following a booster dose of AZD2816 in a sub-group of seronegative participants</td><td colspan="2">• Intracellular cytokine staining and flow cytometry for T-cell responses over time</td></tr>
</table>

	• Quantification of (IFN-γ) ELISpot responses to SARS-CoV-2 B.1.351 or Wuhan-Hu-1 S protein from day of dosing baseline over time • Breadth and depth of peripheral blood B-cell and T-cell repertoire over time through immunosequencing
To monitor the incidence of SARS-CoV-2 infection following a booster dose of AZD2816 in previously vaccinated seronegative participants	• The incidence of SARS-CoV-2 infection defined by the presence of nucleocapsid antibodies occurring post-dose of study intervention
To monitor the incidence of COVID-19 following a booster dose of AZD2816 in previously vaccinated seronegative participants	• Incidence of COVID-19, defined as SARS-CoV-2 RT-PCR-positive symptomatic illness.
To explore the humoral immune responses against the B.1.351 and Wuhan-Hu-1 strains induced by a booster dose of AZD2816 or AZD1222 in sub-groups of seronegative and seropositive participants	• Geometric mean titre of SARS-CoV-2 neutralization as determined by a live virus neutralization assay • Seroresponse[a] rate of SARS-CoV-2 specific antibody binding and neutralization titres as determined by a live virus neutralization assay
To explore additional immune responses following a booster dose of AZD2816 or AZD1222 participants	• Other exploratory assays for humoral and cellular immune responses may be performed based upon emerging safety, efficacy, and immunogenicity data
To explore the immunogenicity objectives in seropositive participants	• GMT of pseudoneutralizing antibodies • Seroresponse rates

MAAEs: medically attended adverse events; SAEs: serious adverse events; AESIs: adverse events of special interest.
[a] Seroresponse: An at least 4-fold increase in geometric mean titre from baseline.

4 DESIGN

4.1 Overall Design

This is a multi-country Phase II/III study to evaluate the safety and immunogenicity of AZD2816 as single-dose vaccination in previously vaccinated adult participants and as a 2-dose primary vaccination in previously unvaccinated adult participants.

A total of approximately 2590 SARS-CoV-2 nucleocapsid seronegative participants that have been screened and judged to be eligible for the study will be enrolled across these 2 populations with the goal of 1300 previously vaccinated participants receiving single-dose vaccination and 1050 unvaccinated participants receiving 2-dose primary vaccination. In addition, seropositive participants will be enrolled (with a cap of 10% of the seronegative population or 259 participants) to support exploratory analysis is these participants.

The enrollment and randomization strategy is intended to minimize group differences in terms of age, gender and the presence of comorbidities.

In both the single-dose booster treatment regimen and the 2-dose primary vaccination treatment regimen, participants will receive study intervention consisting of intramuscular administration of either AZD1222 (5×10^{10} viral particles) or AZD2816 (5×10^{10} viral particles).

Approximately 700 seronegative participants previously vaccinated with AZD1222 will be randomised 1:1 to receive a single intramuscular dose of either AZD1222 or AZD2816 in a double-blinded fashion.

Approximately 600 seronegative participants previously vaccinated with an approved mRNA based vaccination against the original Wuhan-Hu-1 strain will be randomised 1:1 to receive a single intramuscular dose of AZD2816 or AZD1222 in a double-blinded fashion.

It is anticipated that the majority of the patients recruited in the United Kingdom will belong to 1 of the 2 above previously-vaccinated groups.

Approximately 1290 seronegative, previously unvaccinated participants will be randomised approximately 5:5:5:2 to receive a 2-dose primary vaccination of the following:

- 2 doses of AZD1222 with a 4-week dosing interval
- 2 doses of AZD2816 with a 4-week dosing interval
- 1 dose of AZD1222 followed by 1 dose of AZD2816 with a 4-week dosing interval
- 2 doses of AZD2816 with a 12-week dosing interval.

The 3 treatments with a 4-week dosing interval will be double-blinded while the treatment with the 12-week interval will be open-label due to the difference in dosing interval.

In addition, a smaller population seropositive participants (approximately 10% of the seronegative population), will be randomised to treatment in a similar manner as above.

Owing to national vaccine rollout in the recruitment countries, including the prioritization of elderly populations, it is anticipated that there will be critical differences between the previously vaccinated and previously unvaccinated cohorts that may confound the interpretation of the results. Consequently, the primary and key secondary non-inferiority analyses across these two cohorts will compare the previously vaccinated participants that received a booster dose in this study with a subset of matched participants from the previously unvaccinated participants that received the 2-dose AZD1222 primary vaccine series in the AZD1222 Phase 3 trial, Study D8110C00001.

Immunogenicity (ie, anti-Wuhan-Hu-1 and anti-B.1.351 immune responses including S-binding antibody titres and neutralizing antibody levels [pseudo-neutralization]) will be assessed in serum samples collected pre-dose on the day of each vaccination (baseline levels

before vaccination), 14 and 28 days after each vaccination, and 180 days after the last vaccination.

All participants will be given a thermometer, tape measure or ruler, and a proprietary e-diary application designed for use with a smart device with instructions for use. All participants will be asked to report on solicited signs and symptoms for 7 days following vaccination (Days 1-8 for all participants and Days 29-36 for the 4-week dosing interval and Days 85-92 for the 12-week dosing interval). An e-diary will be used to collect information on the timing and severity of the solicited signs and symptoms.

Follow-up visits will take place as per the schedule of assessment within respective windows. All participants will be assessed for local and systemic AE, physical examination, review of e-diaries at these time points as detailed in the schedule of assessment. Blood will also be taken for safety assessments and immunology purposes.

All study participants will be followed for safety for 180 days after administration of their last vaccination dose. In every participant, solicited local and systemic events will be reported for up to 7 days after each dose, all unsolicited AEs will be reported for up to 28 days after each dose, and SAEs and AEs of special interest will be evaluated through study completion (up to 180 days after the last study vaccination).

An independent COVID-19 Vaccine Data Safety Monitoring Board will provide oversight, to ensure safe and ethical conduct of the study.

4.1.1 COVID-19 Assessments

Occurrence of COVID-19 in the trial will be reported as safety events, including monitoring of the potential risk of vaccine-induced enhanced disease as an AE of special interest (see Appendix E). COVID-19 will be diagnosed and treated as per standard medical practice. In addition, experimental treatments are permitted. Detailed information will be collected in a standard way and reported on a specific case report form.

4.1.2 Screening

All potential participants will be screened, which may take place at a visit up to 14 days prior to Day 1 or on Day 1 itself.

Informed consent will be obtained before screening/enrollment. If written consent is obtained, the screening procedures specified in the Schedule of Activities (Section 1.3) will be undertaken including a medical history, physical examination, height and weight, a SARS-CoV-2 screening test and clinical safety laboratory assessments. Baseline information collected in the previously vaccinated participants will include which vaccine was received, immunization dose interval, and time since last vaccination.

For women of childbearing potential, it will be recorded that they verbally confirmed use of one highly effective form of birth control for at least 28 days prior to the planned vaccination and a urine pregnancy test will be performed that must be negative for the participant to be enrolled. (Note: Women with urine test results that are positive or undetermined will not be enrolled and should be advised to seek medical attendance outside the context of the trial if pregnancy is suspected.)

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 enrollment or to withdraw a participant from the study will be at the discretion of the Investigator.

4.1.3 Vaccination Visit

Participants will be considered enrolled at the point of vaccination. Before vaccination, the eligibility of the participant will be reviewed. Body temperature will be observed and a medical history and physical examination will be undertaken before the first vaccination to determine need to postpone vaccination or screen fail the participant. A negative pregnancy test (urine test) will need to be obtained from women of childbearing potential before vaccination. Baseline blood samples will be obtained before the first vaccination.

Participants will receive 1 dose of AZD2816 or AZD1222 at vaccination visits, administered by intramuscular injection. Previously immunized participants will have a single vaccination visit, Day 1. Participants that have not been previously vaccinated at baseline will have a second vaccination visit on Day 29 (4-week interval) or Day 85 (12-week interval).

All participants will be given a thermometer, tape measure or ruler, and a proprietary e-diary application designed for use with a smart device with instructions for use. All participants will be asked to report on solicited signs and symptoms for 7 days following vaccination (Days 1 to 8 and Days 29 to 36 or Days 85 to 92 when applicable).

4.1.4 Follow-up visits

Follow-up visits will take place as specified in the Schedule of Activities (Section 1.3). All participants will be assessed for local and systemic AE, physical examination, review of the e-diary and blood tests at these time points as detailed in the Schedule of Activities. Blood will also be taken for safety and immunogenicity assessments.

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 the last study visit in order to collect information on any SAEs/AE of special interest.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Study Design and Participant Population

The participant population includes adults ≥ 30 years of age. Persons who are healthy or have medically stable underlying conditions will be eligible. Adults with medically-stable chronic diseases may participate if, according to the judgement of the investigator, hospitalization within the study period is not anticipated and the participant appears likely to be able to remain on study through the end of protocol-specified follow-up.

For the primary and secondary objectives, those enrolled in the study must test negative for SARS-CoV-2 nucleocapsid protein antibody during screening. Some seropositive participants (capped at 10% of the seronegative participant population) will be enrolled to support an exploratory analysis.

Those enrolled in the single-dose vaccination part of the study must have received 2 doses of AZD1222 (with a dosing interval of 4-12 weeks) or 2 doses of an approved mRNA-based COVID-19 vaccine (with a dosing interval of 3-12 weeks for the BNT162b2 mRNA vaccine [Pfizer-BioNTech] and 4-12 weeks for the mRNA-1273 vaccine [Moderna]) with the second doses administered at least 90 days prior to first study intervention administration.

Pregnant/breastfeeding women, persons with severe immunodeficiency or severe underlying disease will be excluded from participation in the study. Persons previously vaccinated with AZD1222 in the context of an AZD1222 vaccine trial are eligible for enrollment as previously vaccinated participants in the trial. Persons who have previously received any other investigational product for the prevention of COVID-19 will be excluded from participation in this study.

Participants with known risk factors for thrombosis and thrombocytopenia (excluding contraceptive hormonal therapy or replacement hormonal therapy) are excluded.

4.2.2 Rationale for Study Endpoints

There is no statistical hypothesis testing planned for this study. Descriptive statistics will support evaluation of safety, reactogenicity, and immunogenicity.

An interim analysis will occur when all previously vaccinated participants have completed their Day 29 visit. A second interim analysis may be conducted when previously unvaccinated participants have completed their Day 29 visit.

The primary analysis will occur when all participants have completed their Day 29 visit AND all previously unvaccinated participants randomised to a 4-week dosing interval have completed their Day 57 visit (ie, 28 days after their second dose).

A secondary analysis will occur when all participants have completed their Day 29 visit AND all previously unvaccinated participants (including those randomised to either a 4-week or a 12-week dosing interval) have completed their Day 57/Day 113 visit (ie, 28 days after their second dose).

The final analysis will occur when data from all vaccinated participants are available through completion of the last study visit (180 days after the single dose for previously vaccinated participants/180 days after the second dose for unvaccinated participants).

The primary safety analysis includes:

- Incidence of local and systemic solicited AEs for 7 days following each vaccination will be summarized by day and overall.
- Incidence of unsolicited AEs for 28 days following each vaccination will be summarized by system organ class and preferred term, and by relationship to vaccination as assessed by the investigator.
- SAEs and AEs of special interest following the first vaccination and throughout the study duration will be summarized by system organ class and preferred term and by relationship to vaccination as assessed by the investigator.

Solicited AEs will be collected for 7 days after each dose of study intervention, a period that has proven adequate to describe reactogenicity events in previous vaccine studies. For all participants, AEs will be collected through 28 days after each dose of study intervention. SAEs, medically-attended AEs, and AEs of special interest and will be collected from Day 1 through end of the study. AEs of special interest include terms identified by the Brighton Collaboration involving events associated with vaccination in general .

The immunogenicity endpoints of interest in this study are:

- Geometric mean titre
- Seroresponse, defined as ≥ 4-fold increase in the geometric mean titre from baseline

Geometric mean titre ratios and differences in seroresponses with 95% confidence intervals will be presented to support selected comparisons of immunogenicity across groups of interest.

Immunogenicity against SARS-CoV-2 Wuhan-Hu-1 and B.1.351 strains will be characterized through the quantification of Spike-binding antibodies, pseudo-neutralization and, in a subset of participants, live neutralization. Exploratory analysis of immunogenicity against other strains and induction of other immune effectors including cell-mediated immunity will be conducted.

4.3 Justification for Dose

The AZD2816 nominal dose of 5×10^{10} viral particles is the same dose as the approved dose for AZD1222, which was based on the accumulated non-clinical data and clinical data from the AZD1222 clinical studies, as well as from other SARS-CoV-2 vaccines in development. Safety and immunogenicity data from an additional clinical study, MERS001(NCT03399578), using the same ChAdOx1 vector, also helped inform dose selection. MERS001 was the first clinical study of a ChAdOx1-vectored vaccine expressing the full-length S protein from a separate, but related, beta-coronavirus. ChAdOx1 MERS has been given to 31 participants to date at doses ranging from 5×10^9 viral particles to 5×10^{10} viral particles. Despite higher reactogenicity observed at the 5×10^{10} viral particles, this dose was safe, with self-limiting AEs and no serious adverse reactions recorded. The 5×10^{10} viral particles was the most immunogenic, in terms of inducing neutralizing antibodies 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} viral particles dose was chosen for AZD1222.

Based on accumulating nonclinical and clinical data gathered for AZD1222, a 2-dose regimen was selected for vaccination of unvaccinated participants with AZD2816 (AZD1222 Investigators Brochure). A single dose vaccination has been selected for participants previously vaccinated in line with both FDA and EMA guidance (FDA 2021, EMA 2021).

4.4 End of Study Definition

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

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

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as a protocol waiver or exemption, is not permitted.

5.1 Inclusion Criteria

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

5.1.1 All Participants:

Age

1 Adult, ≥ 30 years of age at the time of consent

COVID-19

For inclusion in the SARS-CoV-2 seronegative population supporting the primary and secondary objectives:

2 No history of laboratory-confirmed SARS-CoV-2 infection (ie, no positive nucleic acid amplification test and no positive antibody test).

3 Seronegative for SARS-CoV-2 at screening (lateral flow test to detect reactivity to the nucleoprotein).

Note, patients failing to meet criteria 2 and/or 3 may be included in the separate seropositive population supporting the seropositive exploratory objectives.

Type of Participant

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

- A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 90 days prior to enrollment

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

6 Signed informed consent obtained before conducting any study-related procedures

Reproduction

7 Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
Female participants:

(a) Women of childbearing potential must:

- Have a negative pregnancy test on the day of screening and on days of vaccination
- 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 30 days following administration of the 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 7). Periodic abstinence, the rhythm method, and withdrawal are NOT acceptable methods of contraception.

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

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

    Until follicle-stimulating hormone is documented to be within menopausal range, the participant is to be considered of childbearing potential
  - For women aged ≥50 years, post-menopausal is defined as having a history of ≥12 months amenorrhea prior to randomization, without an alternative cause, following cessation of exogenous sex-hormonal treatment.

Table 7 Highly Effective Methods of Contraception

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

[a] This is also considered a hormonal method

[b] Provided that partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success

[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse from 28 days prior to Day 1 through 30 days following administration of the second dose of study intervention, and if it is the preferred and usual lifestyle of the participant

5.1.2 Previously COVID-19 Vaccinated Participants

8 Prior completion of a 2-dose primary homologous vaccination regimen against the original SARS-CoV-2 Wuhan-Hu-1 strain with either AZD1222 (2 standard doses as authorized vaccine or as investigational product in a clinical trial with a 4- to 12-week dosing interval) or with an mRNA vaccine approved for emergency or conditional use (eg, BNT162b2 vaccine [Pfizer-BioNTech] with a 3- to 12-week dosing interval or mRNA-1273 vaccine [Moderna] with a 4- to 12-week dosing interval). The second dose in all cases should have been administered at least 90 days prior to first administration of study intervention.

5.2 Exclusion Criteria

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

Medical Conditions

1 History of allergy to any component of AZD1222/AZD2816.

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

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

4 Any confirmed or suspected immunosuppressive or immunodeficient state, including asplenia or HIV/AIDS.

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

- Topical/inhaled steroids or short-term oral steroids (course lasting ≤ 14 days)

6 History of primary malignancy except for:

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

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

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

(d) Localized prostate cancer

7 History of thrombocytopenia and/or thrombosis, including participants who have experienced major venous and/or arterial thrombosis in combination with thrombocytopenia following vaccination with any COVID-19 vaccine

8 History of heparin-induced thrombocytopenia, congenital thrombophilia (ie, factor V Leiden, prothrombin G20210A, antithrombin III deficiency, protein C deficiency and protein S deficiency, factor XIII mutation, familial dysfibrinogenemia), auto-immune thrombophilia (antiphospholipid syndrome, anti-cardiolipin antibodies, anti-β_2-glycoprotein 1 antibodies), or paroxysmal nocturnal haemoglobinuria.

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

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

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

12 Any autoimmune conditions, except mild psoriasis and vitiligo

Note: The AEs of special interest as outlined in Appendix E (including Table 28) should be considered when evaluating a participant for exclusion criteria as the presence of these AEs of special interest, especially if untreated or uncontrolled, may be a safety risk to the participant, affect the ability of the participant to participate in the study, and/or impair interpretation of the study data. Investigators should review and consider the list of conditions in Appendix E. If any of these conditions are present in a participant, the Investigator is asked to utilize his/her clinical judgment in determining the participant's eligibility for the study. Should the participant have conditions as outlined in Appendix E and the participant is enrolled, the Investigator is asked to document notes on site regarding the final rationale for enrollment.

Prior/Concomitant Therapy

13 Receipt of or planned receipt of investigational products indicated for the treatment or prevention of SARS-CoV-2 or COVID-19 with the exception of prior vaccination with AZD1222 or an mRNA COVID-10 vaccine (2 doses of the same vaccine within an approved dosing interval, see Section 5.1.2), which is allowed for participants in the previously vaccinated cohort
Note: For participants who develop COVID-19, receipt of licensed treatment options and/or participation in investigational treatment studies is permitted

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

15 Receipt of any influenza vaccine (licensed or investigational) within 7 days prior to and after administration of AZD1222/AZD2816.

16 Receipt of immunoglobulins and/or any blood products within 90 days prior to administration of study intervention or expected receipt during the period of study follow-up

Other Exclusions

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

18 Women who are currently pregnant (confirmed with positive pregnancy test), breastfeeding, having given birth less than 90 days before or planning pregnancy during the study.

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

20 Participants with a history of chronic alcohol or drug abuse or any condition associated with poor compliance.

21 Judgment by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements or if vaccination would interfere with the participant's ongoing treatment.

22 Previous enrollment in the present study.

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 assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

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

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention, marketed product, or placebo intended to be administered to or medical device utilized by a study participant according to the study protocol. Study intervention is defined as AZD2816 or AZD1222 (Table 8).

6.1 Study Interventions Administered

6.1.1 Investigational Products

Table 8 Investigational Products

Intervention Name	AZD2816	AZD1222
Type	Vaccine	Vaccine
Dose Formulation	CCI [redacted]	CCI [redacted]
Unit Dose Strength	1×10^{11} viral particles/mL	1×10^{11} viral particles/mL
	$\geq 5 \times 10^{8}$ infectious units/mL	$\geq 5 \times 10^{8}$ infectious units/mL
Dosage Level	5×10^{10} viral particles (nominal, $\pm 1.5 \times 10^{10}$ viral particles)	5×10^{10} viral particles (nominal, $\pm 1.5 \times 10^{10}$ viral particles)
	$\geq 2.5 \times 10^{8}$ infectious units	$\geq 2.5 \times 10^{8}$ infectious units
Route	Intramuscular	Intramuscular
Use	Experimental	Experimental
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labelling	Will be provided in vials within a carton. Each carton and vial will be labelled as required per country requirement	Will be provided in vials within a carton. Each carton and vial will be labelled as required per country requirement
Current/Former Name	-	Previous clinical documentation: ChAdOx1 nCoV-19 Current tradename: Vaxzevria

IMP: investigational medicinal product; NIMP: non-investigational medical product; w/v: weight/volume.

AZD2816

AZD2816 will be supplied by the Sponsor as a vial solution for injection. It is a sterile, clear to slightly opaque solution, practically free from visible particles. Each vial of AZD2816 has a label-claim volume of 5 mL and can provide up to ten 0.5 mL doses.

AZD1222

AZD1222 will be supplied by the Sponsor as a vial solution for injection. It is a sterile, clear to slightly opaque solution, practically free from visible particles. Each vial of AZD1222 has a label-claim volume of 4 mL and can provide up to eight 0.5 mL doses.

Unopened vials of AZD2816 and AZD1222 must be stored at 2-8 ºC (36-46 ºF) for the duration of the assigned shelf-life and must not be frozen. Both investigational products must be kept in original packaging until use to prevent prolonged light exposure.

6.1.2 Dosing Instructions

Previously unvaccinated participants will receive 2 doses of either AZD1222, AZD2816, or AZD1222 plus AZD2816, with the first dose administered on Day 1 and the second dose on Day 29 (for a 4-week dosing interval) (Table 3) or Day 85 (for a 12-week dosing interval) (Table 4).

Previously vaccinated participants will receive 1 dose of either AZD1222 or AZD2816 (Table 2).

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

All study participants will be observed in the clinic for at least 15 minutes after vaccination. Allergic reactions to vaccines are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

6.2 Preparation/Handling/Storage/Accountability

The procedures for preparation, handling, storage, and accountability are identical for AZD2816 and AZD1222.

1 The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2 Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
3 The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

4 Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual or specified handling instructions.

6.2.1 Dose Preparation and Administration

Doses of AZD2816 and 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 AZD2816 or AZD1222 in a sterile syringe.

AZD2816 and AZD1222 do not contain preservatives. Each vial must be assigned a beyond-use-date of 6 hours at 2-30 °C (36-86 °F) from first needle puncture of the vial, after which any unused portion must be discarded.

Once an AZD2816 or AZD1222 dose is drawn into a syringe for administration, the dose must be administered within the beyond-use-date of the vial. If dose administration is not completed within the 6-hour vial beyond-use-date, a new dose must be prepared from a new vial.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization

The study contains 3 cohorts that are randomised to a total of 8 treatments:

- Participants that have previously been vaccinated with 2 doses of AZD1222 will be randomised 1:1 to 1 dose of AZD2816 or 1 dose of AZD1222.
- Participants that have been previously vaccinated with an mRNA COVID-19 vaccine will be randomised 1:1 to 1 dose of AZD2816 or AZD1222.
- Previously unvaccinated participants that will be randomised 2:2:2:1 to 2 doses of AZD2816 with a 4-week dosing interval, 2 doses of AZD1222 with a 4-week dosing interval, 1 dose of AZD1222 followed by 1 dose of AZD216 with a 4-week dosing interval, or 2 doses of AZD2816 with a 12-week dosing interval.

Separate populations of SARS-CoV-2 seronegative participants (supporting the primary and secondary objectives) and SARS-CoV-2 seropositive participants (supporting exploratory objectives) will be randomised/included in the above cohorts.

Randomization will be stratified based on age (less than 65, 65 and above), gender, and presence of at least one of the following comorbidities that are known risk factors for severe illness from COVID-19 (based on the participant's past and current medical history):

- Obesity (BMI $\geq$ 30 kg/m^2 at baseline)
- Significant cardiovascular disease (eg, heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, or pulmonary hypertension)

- Chronic lung disease (eg, chronic obstructive pulmonary disease, idiopathic pulmonary disease, cystic fibrosis, or moderate to severe asthma)
- Diabetes .

The randomised participants will be centrally assigned to randomised study intervention using an Interactive Response Technology (IRT)/Randomisation and Trial Supply Management. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information & directions for the Randomisation and Trial Supply Management will be provided to each site.

Where a participant does not meet all the eligibility criteria but incorrectly received study intervention, the investigator should inform the Study Physician immediately, and a discussion should occur between the Study Physician and the investigator regarding whether to continue or discontinue the participant.

6.3.2 Blinding

Treatment will be double-blinded for previously vaccinated participants randomised to a single dose of either AZD2816 or AZD1222. Treatment will also be double-blind for previously unvaccinated participants randomised to 2 dose vaccinations with a 4-week dosing interval (ie, homologous AZD2816 or AZD1222 vaccination or heterologous AZD1222/AZD2816 vaccination). Previously unvaccinated participants randomised to a homologous AZD2816 vaccination with a 12-week dosing interval will receive treatment in an open-label fashion due to the different dosing interval.

For the double-blinded treatments, neither the participant nor any of the investigators or Sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the study intervention received. Since AZD2816 and AZD1222 are visually distinct prior to dose preparation (due to differences in container closure), all investigational 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, AZD2816 and AZD1222 are not visually distinct from each other.

The IRT will provide the investigators with a dose tracking number to be allocated to the participant at the dispensing visit. Routines for this will be described in the IRT user manual that will be provided to each study site.

For participants receiving double-blinded treatments, the randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization. The investigator documents and reports the action to the Sponsor, without revealing the treatment given to participant to the Sponsor staff.

The Sponsor retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational medicinal product and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

6.3.3 Procedures for Unblinding

The IRT will be programmed with blind-breaking instructions. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition (eg, antidote available), the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded for safety, the Sponsor must be notified within 24 hours after breaking the blind.

In the event that a study participant is contacted about receiving a licensed and/or authorized COVID-19 vaccine outside of this clinical study, unblinding instructions are being provided to the sites. If the participant is unblinded, the Sponsor needs to be notified within 24 hours, and this should be documented in the site source documents.

6.4 Study Intervention Compliance

Participants are dosed at the study site, receiving study intervention directly from the investigator or designee, under medical supervision. The date, and time if applicable, of dose administered will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines) that the participant is receiving at the time of enrollment or receives during the period specified in the Schedule of Activities (Section 1.3), must be recorded in the eCRF along with the information listed below. Vitamins and/or herbal supplements are not to be recorded.

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Permitted Concomitant Medications

- Participants may take concomitant medications prescribed by their primary care provider for management of chronic medical conditions and/or for health maintenance.
- Primary care providers, or where appropriate investigators, should prescribe appropriate concomitant medications or treatments deemed necessary to provide full supportive care and comfort during the study.
- Participants who develop COVID-19 after receiving study intervention should be treated with licensed medications and interventions according to standard of care. All routine vaccinations other than influenza are permitted beginning > 30 days after last dose of study intervention. Licensed influenza vaccines are permitted 7 days before and 7 days after administration of study intervention.
- Topical/inhaled steroids or short-term oral steroids (course lasting ≤ 14 days) are permitted

6.5.2 Prohibited Concomitant Medications

The following medications are prohibited and the Sponsor must be notified if a participant receives any of these prohibited medications. The use of the following concomitant medications and/or vaccines, however, will not definitively require withdrawal of the participant from the study, but may determine a participant's eligibility to receive a second dose or evaluability in the per-protocol analysis set.

- Primary or booster vaccinations, other than AZD2816 or AZD1222, for prevention of SARS-CoV-2 or COVID-19**.**

  Note: Participants choosing to receive a licenced and/or authorized COVID-19 vaccine should inform the Investigator so it can be properly documented. Participants, who receive a licenced and/or authorized COVID-19 vaccine outside the study, should be encouraged to continue study conduct to be followed for safety reporting and all assessments.
- Receipt of any vaccine (licensed or investigational) other than licensed influenza vaccines within 30 days prior to and after administration of study intervention. Thirty days after the second vaccination, other routine vaccinations are permitted as clinically indicated.
- Glucocorticoids at a dose ≥ 20 mg/day of prednisone or equivalent given daily or on alternate days for ≥ 14 consecutive days between randomization and the participant's scheduled final visit
- Other systemically administered drugs with significant immunosuppressive activity, such as azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy between randomization and the participant's scheduled final visit
- Immunoglobulins and/or any blood product.

If a participant receives a prohibited concomitant medication, the investigator in consultation with the Sponsor will evaluate any potential impact on receipt of study intervention based on

time the medication was administered, the medication's pharmacology and pharmacokinetics, and whether the medication will compromise the participant's safety or interpretation of the data (see Section 7.1).

6.6 Dose Modification

Study intervention will be administered as described in Section 6.1. Dose modification is not permitted.

6.7 Intervention After the End of the Study

There is no intervention after the end of the study (see definition in Section 4.4).

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

An individual participant will not receive the first or second dose (if applicable) of study intervention if any of the following occur in the participant in question:

1 Withdrawal of consent after signing informed consent
2 Participant meets one or more of the exclusion criteria or fails to meet all inclusion criteria for study participation
3 Laboratory-confirmed SARS-CoV-2 infection
4 Participant is pregnant or nursing
5 Any grade 3 or greater allergic reaction including anaphylaxis that is assessed as related to study intervention
6 Occurrence of any thrombosis with concurrent thrombocytopenia
7 Any SAE assessed as related to study intervention
8 Any AE that, in the judgment of the site investigator, is related to study intervention and may jeopardize the safety of the study participant
9 Receipt of a prohibited concomitant medication that may jeopardize the safety of the study participant or interpretation of the data

Each participant who has received at least 1 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.

In the event that a study participant receives a licensed and/or authorized COVID-19 vaccine during the study, AstraZeneca needs to be notified within 24 hours and this should be

documented in the site source documents. Participants who have received study intervention, regardless of reason, will be followed for the full study period.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Sponsor Study Team. If the participant does not specifically request withdrawal of consent for use of samples, then the samples collected prior to the consent withdrawal will be destroyed once per protocol analysis is complete.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The study site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Schedule of Activities (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 Schedule of Activities (Section 1.3) is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities.

8.1 Efficacy Assessments

Not applicable.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Activities (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 Schedule of Activities (Section 1.3).

- A complete physical examination will include, but not be limited to, assessment of height, weight, general appearance, head, ears, eyes, nose, throat, neck, skin, as well as cardiovascular, respiratory, abdominal, and nervous systems. Each clinically significant abnormal finding at screening will be recorded in the medical history.
- A targeted physical examination will include areas suggested by the medical history, clinical signs, and symptoms and will include signs of thrombosis and/or thrombocytopenia. Each clinically significant abnormal finding following vaccination will be recorded as an AE.
- All physical examinations will be performed by a licensed healthcare provider (eg, physician, physician assistant, or licensed nurse practitioner).

8.2.2 Vital Signs

Vital signs, including heart rate, pulse oximetry, blood pressure, and body temperature, will be performed as specified in the Schedule of Activities (Section 1.3). The participant should be resting prior to the collection of vital signs. On vaccination days, vital signs should be assessed prior to vaccine administration.

Situations in which vital sign results should be reported as AEs are described in Section 8.3.5.

8.2.3 Clinical Laboratory Assessments

Blood samples for determination of clinical chemistry and haematology will be taken at the visits indicated in the Schedule of Activities (Section 1.3). Additional unscheduled safety samples may be collected if clinically indicated at the discretion of the investigator, with the date and time of collection recorded in the appropriate eCRF.

The standard clinical chemistry and haematology analysis will be performed at a local laboratory at or near to the investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The following laboratory variables will be measured:

Table 9 Laboratory Safety Variables

Blood	Serum/Plasma
Haemoglobin	Activated partial thromboplastin time
Leukocyte count	Prothrombin time
Leukocyte differential count (absolute count)	Fibrinogen
Platelet count	D-dimer
-	Creatinine
-	Bilirubin, total
-	Alkaline phosphatase
-	Aspartate aminotransferase
-	Alanine aminotransferase

In case a participant shows an aspartate aminotransferase **or** alanine aminotransferase $\geq 3 \times$ upper limit of normal together with total bilirubin $\geq 2 \times$ the upper limit of normal, please refer to Section 8.3.6

For women participants of childbearing potential, a urine sample for pregnancy testing will be collected according to the Schedule of Activities (Section 1.3). Urine pregnancy tests for β-human chorionic gonadotropin may be performed at the site using a licensed dipstick test.

8.3 Adverse Events and Serious Adverse Events

The principal investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Solicited AEs are local or systemic predefined events for assessment of reactogenicity. Solicited AEs will be collected in a e-diary (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 the reporting of solicited AEs via e-diary unless otherwise noted..

All other AEs are considered to be unsolicited AEs (collected by 'open question' at study visits).

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

AEs will be recorded for 28 days after each dose of study intervention.

Solicited AEs will be recorded for 7 days after each dose of study intervention (ie, Day 1 through Day 8). If a solicited AE is not resolved within the e-diary reporting period, the event will be reported as a non-solicited adverse event in the eCRF, with a start date of when started and the actual stop date.

SAEs will be recorded from the time of signature of the informed consent form through the last participant contact.

Medically-attended AEs and AEs of special interest will be recorded from Day 1 through the last participant contact.

See the Schedule of Activities for the scheduled timepoints (Section 1.3).

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 Adverse Events and Serious Adverse Events

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. The Sponsor retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

AE variables

The following variables will be collected for each AE:

- AE (verbatim)
- Date when the AE started and stopped
- Severity grade/maximum severity grade/changes in severity grade
- Whether the AE is serious or not
- Investigator causality rating against the study intervention (yes or no)
- Action taken with regard to study intervention
- AE caused participant's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

A revised toxicity grading scale from US FDA guidance for healthy volunteers enrolled in a preventive vaccine clinical study (FDA 2007) will be utilized for all unsolicited events.

8.3.3 Causality Collection

The investigator should assess causal relationship between study intervention and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes.'

A guide to the interpretation of the causality question is found in Appendix B.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the Clinical Study Protocol-mandated vital signs and laboratory safety assessments will be summarized in the Clinical Study Report.

Deterioration as compared to baseline in protocol-mandated vital signs and laboratory safety assessment should therefore only be reported as AEs if they fulfil any of the SAE or medically-attended AE criteria or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required).

If deterioration in a vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an SAE or medically-attended AE, and the associated vital sign will be considered as additional information.

8.3.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation. Any occurrences of aspartate aminotransferase or alanine aminotransferase $\geq 3 \times$ the upper limit of normal together with total bilirubin $\geq 2 \times$ upper limit of normal at any point during the study following the administration of study medication should be reported to the Sponsor as a potential Hy's Law SAE within 1 day with a serious criteria of 'Important medical event' and causality assessment 'yes/related'.

The study physician will contact the investigator to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.

8.3.7 Solicited Adverse Events

Local and systemic predefined solicited AEs for reactogenicity assessment (Table 10) will be collected in a Solicited AE e-Diary for 7 days following administration of each dose of study intervention via e-diary collection. If a solicited AE is not resolved within the e-diary reporting period, the event will be also reported as a non-solicited adverse event in the eCRF, with a start date of when started and the actual stop date.

Solicited AEs should not be reported as unsolicited AEs unless they fulfil the criteria for SAEs or medically-attended AEs(see Sections 8.3 and 8.3.8, respectively).

Table 10 Predefined Solicited Adverse Events for Reactogenicity Assessment

Local	Systemic
Pain at the site of the injection	Fever (> 100 °F/37.8 °C)
Redness/erythema at the site of the injection	Chills
Tenderness at the site of the injection	Muscle pains
Induration/swelling at the site of the injection	Fatigue (physical or mental tiredness/exhaustion)
-	Headache
-	Malaise (general feeling of discomfort or uneasiness)
-	Nausea
-	Vomiting

Solicited AE e-Diary

On Day 1, participants (or, if applicable, their caregiver, surrogate, or legally authorized representative) will be given a thermometer, tape measure or ruler, and access to the Solicited AE e-Diary, with instructions on use, along with the emergency 24-hour telephone number to contact the on-call study physician if needed.

Participants will be instructed to record for 7 days following administration of each dose of study intervention, the timing and severity of local and systemic solicited AEs, if applicable, and whether medication was taken to relieve the symptoms.

Severity Assessment of Solicited AEs

Severity will be assessed for solicited AEs by the participant (or, if applicable, their caregiver, surrogate, or legally authorized representative) according to toxicity grading scales modified and abridged from the US FDA guidance (FDA 2007) as defined in Appendix D. Because

solicited AEs are expected to occur after vaccination, they will not be assessed for relationship to study intervention.

8.3.8 COVID-19 Assessment

This study will describe the incidence of COVID-19 adverse events reported from Day 1 to 180 days after the participant's last/only dose of vaccine.

COVID-19 is defined as SARS-CoV 2-RT-PCR positive symptomatic illness. At all clinic visits following the initial vaccination, participants will be asked if they have had a diagnosis of COVID-19 since their last clinic visit (see Schedule of Activities in Section 1.3). Medical records will be obtained for confirmation of a participant-reported diagnoses of COVID-19. Qualifying symptoms are fever, shortness of breath, difficulty breathing, chills, cough, fatigue, muscle/body aches, headache, new loss of taste or smell, sore throat, congestion, runny nose, nausea, vomiting, or diarrhoea. Events will be reported as AEs/SAEs.

If a participant presents at clinic visit with COVID symptoms, diagnosis will be confirmed using RT-PCR.

8.3.9 Medically-Attended Adverse Events

Medically-attended AEs will be collected according to the timepoints specified in the Schedule of Activities (Section 1.3).

Medically-attended AEs are defined as AEs leading to medically-attended visits that were not routine visits for physical examination or vaccination, such as an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. AEs, including abnormal vital signs, identified on a routine study visit or during the scheduled illness visits will not be considered medically-attended AEs.

8.3.10 Adverse Events of Special Interest

AEs of special interest will be collected according to the timepoints specified in the Schedule of Activities (Section 1.3).

AEs of special interest 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. AEs of special interest are based on Brighton Collaboration case definitions (SPEAC 2020), clinical experience, and scientific interest. A list of events is provided in Appendix E.

An AE of special interest can be serious or non-serious. All AEs of special interest will be recorded in the eCRF. If any AE of special interest occurs in the course of the study, investigators or other site personnel will inform the appropriate Sponsor representatives within

1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it. Serious AEs of special interest will be recorded and reported as per Section 8.3.11.

8.3.10.1 Vascular/Hematologic Adverse Events of Special Interest

Both thrombotic, thromboembolic, and neurovascular events and thrombocytopenia events are considered to be adverse events of special interest. The investigator should remain vigilant for the occurrence of thrombotic events with thrombocytopenia and/or bleeding. If a participant experiences new onset thromboembolic events with thrombocytopenia, there should be prompt evaluation with a thorough haematological investigation. COVID-19 testing, including PCR and serology (nucleoprotein antibodies), should also be performed. See Appendix F for further guidance on investigation and management of suspected events.

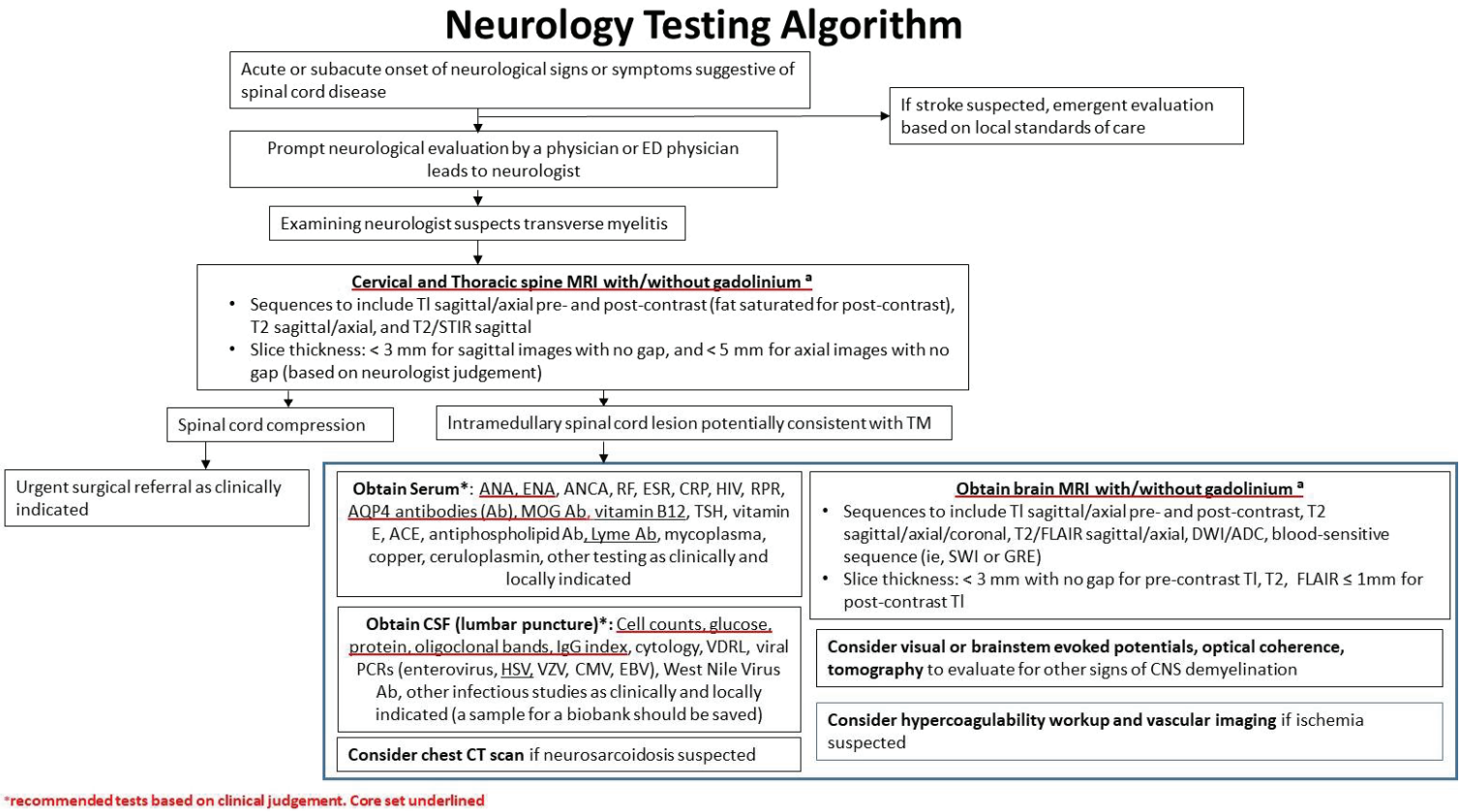
In the event of such a case of thrombosis and in accordance with local laws and ethical procedures, one blood sample may be taken from the participant and whole genome sequencing performed in order to enable investigations into the possible role of genetic polymorphisms as risk factors for these events.

8.3.10.2 Potential Neurological Adverse Events of Special Interest

If a participant experiences new onset (acute or subacute) motor and sensory disturbances (eg, weakness, numbness, paraesthesia, 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, including referral to a neurology specialist for further evaluation and testing, as clinically indicated. Testing can include evaluation for peripheral demyelinating conditions (eg, electromyography). In cases of concern for spinal cord disease, see Figure 3 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 AEs of special interest occurring in the AZD1222 clinical development program (see Appendix A 5).

Figure 3 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.

8.3.11 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the study intervention, or to the study procedures. All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, investigators or other site personnel will inform the appropriate Sponsor representatives within 1 day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform Sponsor representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but no later than 24 hours of when he or she becomes aware.

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 Sponsor representative.

If the Electronic Data Capture system is not available, then the investigator or other study site staff reports an SAE to the appropriate Sponsor representative by telephone or other method and the event is entered into the Electronic Data Capture system when available.

The Sponsor representative will advise the investigator/study site staff how to proceed.

For further guidance on the definition of an SAE, see Appendix B.

The reference document for definition of expectedness is the AZD1222 Investigators Brochure, Section 5.6.

8.3.12 Pregnancy

All pregnancies and outcomes of pregnancy with conception dates following administration of study intervention should be reported to the Sponsor, except if the pregnancy is discovered before the participant has received any study intervention.

8.3.12.1 Maternal Exposure

Female participants who are pregnant or have a confirmed positive pregnancy test at screening or Day 1 will be excluded from the study (see Section 5.2). Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and

spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate Sponsor representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (see Section 8.3.11) and **within 30 days** for all other pregnancies that are not associated with an SAEs.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the paper-based PREGOUT module may be used to report the outcome of the pregnancy.

8.3.13 Medication Error

If a medication error occurs, then the investigator or other site personnel informs the appropriate Sponsor representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative works with the investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) **or 5** (other serious initial and follow up) **calendar days** if there is an SAE associated with the medication error (see Section 8.3.11) and **within 30 days** for all other medication errors.

The definition of a Medication Error can be found in Appendix B 3.

8.4 Overdose

For this study, any dose of study intervention exceeding that specified in the protocol will be considered an overdose.

There is no specific treatment for an overdose with AZD2816 or AZD1222. If overdose occurs, the participant should be treated supportively with appropriate monitoring as necessary.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module
- An overdose without associated symptoms is only reported on the Overdose eCRF module

If an overdose occurs in the course of the study, the investigator or other site personnel inform appropriate Sponsor representatives immediately, but **no later than 24 hours** after when he or she becomes aware of it.

The designated Sponsor representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within 1 or 5 calendar days** for overdoses associated with an SAE (see Section 8.3.11) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study-specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. Further details on Handling of Human Biological Samples are provided in Appendix C.

Samples will be stored for a maximum of 15 years from the date of the issue of the Clinical Study Report in line with consent and local requirements, after which they will be destroyed/repatriated.

Remaining biological sample aliquots will be retained at the Sponsor or its designee for a maximum of 15 years following issue of the Clinical Study Report. Additional use excludes genetic analysis and includes but is not limited to, analysis of COVID-19 and other coronavirus-related diseases or vaccine-related responses, eg, exploratory immunology, such as systems serology and profiling of B- and T-cell repertoire. The results from further analysis will not be reported in the Clinical Study Report.

8.5.1 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.5.2 Immunogenicity Assessments

Serum and blood samples for immunogenicity assessments will be collected according to the Schedule of Activities (Section 1.3). Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual. Results for exploratory immunogenicity analyses may be reported separately from the CSR.

8.5.2.1 SARS-CoV-2 Serology Assessments

Serum samples will be collected to assess SARS-CoV-2 antigen-specific antibody levels from all participants according to the Schedule of Activities (Section 1.3). Authorized laboratories will assess serologic responses to AZD1222 and AZD2816 using validated (or qualified, where appropriate) assays. Serologic assessment to the S protein from different SARS-CoV-2 variants (which include Wuhan-Hu-1, B.1.351, B.1.1.7, and P.1) will be assessed quantitatively using a validated multiplexed ECL based immunoassay. Additionally, seroresponse will be assessed for each antigen over time. The rate of SARS-CoV-2 infection in participants receiving AZD2816 versus AZD1222 will be determined by seroresponse in a SARS-CoV-2 nucleocapsid antigen in a multiplexed electrochemiluminescence-based assay performed at an authorized laboratory. Additional exploratory assessments may be performed to measure binding antibodies to SARS-CoV-2 variants of interest (which may include B.1.429, B.1.525, B.1.526, P.2, P.3, B.1.617, and the Q677H mutation observed in multiple variants).

8.5.2.2 CCI

CCI

8.5.2.3 CCI

CCI

CCI

8.5.2.4 CCI

CCI

8.5.3 Pharmacodynamics

Pharmacodynamics are not evaluated in this study.

8.6 Human Biological Sample Biomarkers

Already collected samples may be analysed for biomarkers thought to play a role in COVID-19 severity or outcomes based upon emerging immunogenicity and pharmacodynamic analysis from this or other studies involving the study interventions. These analyses include but are not limited to serum or plasma cytokines, quantification of RNA, micro-RNA, and/or non-coding RNA using quantitative reverse transcriptase polymerase chain reaction (RT-PCR), microarray, sequencing, or other technologies in blood, or peripheral blood mononuclear cells to evaluate their association with AZD1222/2816 and observed clinical responses to these study interventions.

8.7 Optional Genomics Initiative Sample

Not applicable.

8.8 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics are not applicable in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The overall hypothesis for this 8-armed study is that 28 days after vaccination (ie, following a single booster dose for the previously vaccinated participants or a second vaccination dose for previously unvaccinated participants), AZD2816 will be non-inferior to AZD1222 in terms of immunogenicity (ie, neutralising antibodies GMT ratio and difference in seroresponse). The specific null and alternative hypotheses for each objective are presented in Section 9.4.3

9.2 Sample Size Determination

Immunogenicity response

Historical data were available for the immunogenicity responses (ie, pseudovirus neutralising antibodies, live virus neutralising antibodies, and spike protein binding antibodies) to AZD1222 from the pooled COV001/002/003/005 studies. Table 11 presents the log transformed immunogenicity responses (ie, geometric mean titres) by assay for participants that received 2 standard doses of AZD1222. These results indicate that the pseudo-neutralising antibodies exhibited the largest variation (standard deviation of 1.20 and 1.10 for the 4-week and 12-week dosing intervals respectively), while live-neutralising antibodies had the lowest (standard deviation of 0.72 for the 4-week dosing interval).

Table 11 Historic Immunogenicity Responses by Dosing Interval (Geometric Mean Antibody Titres, Standard Dose Immunogenicity Analysis Set)

	Post-1st Dose			Post-2nd dose with a 4-week dosing interval[a]			Post-2nd dose with a 12-week dosing interval[b]		
Assay	**N**	**Mean**	**Std Dev**	**N**	**Mean**	**Std Dev**	**N**	**Mean**	**Std Dev**
Pseudo	476	4.3	1.34	166	5.3	1.20	113	5.4	1.10
Live	51	4.9	1.15	42	6.2	0.72	0	-	-
Spike protein	1139	9.1	1.14	293	10.1	0.96	302	10.7	0.83

[a] Estimates from pooled COV001/002/003/005 study data from participants with 2- to 6-week dosing interval
[b] Estimates from pooled COV001/002/003/005 study data from participants with 10- to 14-week dosing interval

Table 12 presents the seroresponse (ie, ≥ 4 fold increase from baseline) by assay. These results indicate that the pseudo-neutralising antibodies exhibited the lowest proportion of seroresponse (59.7% and 85.5% for the 4-week and 12-week dosing intervals respectively), while both live-neutralising and spike-binding seroresponse rates exceeded 95%.

Table 12 Historic Seroresponse Rates by Dosing Interval (≥4-fold Increase from Baseline, Standard Dose Immunogenicity Analysis Set)

	Post-1st Dose		Post-2nd dose with a 4-week dosing interval[a]		Post-2nd dose with a 12-dose week interval[b]	
Assay	**N**	**Proportion**	**N**	**Proportion**	**N**	**Proportion**
Pseudo	499	32%	382	59.7%	117	85.5%
Live	96	75%	95	96.8%	-	-
Spike protein	940	96.6%	636	95.9%	304	99.3%

[a] Estimates from pooled COV001/002/003/005 study data from participants with 2- to 6-week dosing interval
[b] Estimates from pooled COV001/002/003/005 study data from participants with 10- to 14-week dosing interval

Under the assumption that the immunogenicity responses (ie, geometric mean antibody titres) associated with AZD2816 will be similar to the responses associated with AZD1222 in participants that received 2 standard doses in the pooled COV001/002/003/005 studies, in which standard deviations ranged from 0.72 to 1.2 (Table 11), 150 participants will provide a 95% confidence interval half-width between 0.115 and 0.192 (see Table 13). Similarly, 380 participants will provide a 95% confidence interval half-width between 0.072 and 0.120.

Under the assumption that the seroresponse rates associated with AZD2816 will be similar to the response rates in adults that received 2 standard doses of AZD1222 in the pooled COV001/002/003/005 studies (Table 12), 150 participants will provide a 95% confidence interval half-width between 1.33% and 7.85%, and 380 participants will provide a 95% confidence interval half-width between 0.84 % and 4.93 % (Table 14).

Table 13 Estimated Half-width of the 95% Confidence Intervals for Immunogenicity Responses (Geometric Mean Titres) Based on Historic Immunogenicity Assay Variances and the Proposed Sample Sizes

Standard Deviation	Number of participants	Estimated half-width of the 95% confidence interval (natural log scale)
0.72	150	0.115
	300	0.081
	350	0.075
	380	0.072
0.83	150	0.133
	300	0.094
	350	0.087
	380	0.084
0.96	150	0.154
	300	0.109
	350	0.101
	380	0.097
1.1	150	0.176
	300	0.124
	350	0.115
	380	0.111
1.2	150	0.192
	300	0.136
	350	0.126
	380	0.120

Table 14 Estimated Half-Width of the 95% Confidence Interval for the Seroresponse Rates based on Historic Seroresponse Rates and Proposed Sample Sizes

Observed seroresponse rate	Number of participants	Estimated half-width of the 95% confidence interval
59.7%	150	7.85%
	300	5.55%
	350	5.14%
	380	4.93%
85.5%	150	5.63%
	300	3.98%
	350	3.69%
	380	3.54%
95.9%	150	3.17%
	300	2.24%
	350	2.08%
	380	1.99%
96.8%	150	2.82%
	300	1.99%
	350	1.84%
	380	1.77%
99.3%	150	1.33%
	300	0.94%
	350	0.87%
	380	0.84%

For a fixed sample size, the precision with which the 95% confidence interval of the binary seroresponse rate can be estimated is a function of the response rate. Table 14 provides the lower bounds of the 95% confidence interval for selected response proportions for alternate sample sizes. For a given response rate, we can be 95% confident that the true seroresponse rate is at least as large as the lower bound of the confidence interval.

Immunogenicity Comparisons: Non-inferiority

Under the assumption that there is no difference between treatment arms of interest (ie, a ratio of 1, difference on the log scale of 0), the power conferred by 150 and 380 participants respectively for the comparison of geometric mean titre ratio using a noninferiority margin of 1.5 (equivalent to a difference on the log scale of 0.405) is presented in Table 15 and for the comparison of seroresponse rate using the non-inferiority margin of -15% as the upper bound of the difference is presented in Table 16.

If there is no difference between treatment arms of interest (ie, a ratio of 1) in the proportion of seroresponders, 300 participants provides 98% power for to establish non-inferiority to within margin of -15% if the seroresponse rate is >50%. The observed pseudo-neutralising response rates (≥ 4 fold increase from baseline) from the COV001/002/003/005 studies for AZD1222 were 59.7% and 85.5% for the 4-week and 12-week dosing interval respectively (Table 12). A population of 300 participants provides >90% power to detect non-inferiority (using a non-inferiority margin of -15%) if the observed response rate is 59.7% (Table 16).

Table 15 Power for Non-inferiority Using 1.5 as the Upper Bound of the Geometric Mean Titre Ratio

Sides	Null difference	Assumed mean treatment difference	Assumed standard deviation	Number in comparator group	Number in reference group	Alpha	Power
Upper	ln1.5 = 0.405	0	0.72	150	300	0.025	>.999
				150	350		>.999
				150	380		>.999
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999
			0.83	150	300		0.998
				150	350		0.999
				150	380		>.999
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999
			0.96	150	300		0.988
				150	350		0.991
				150	380		0.992
				300	300		>.999
				300	350		>.999
				300	380		>.999

				350	380		>.999
				350	350		>.999
				380	380		>.999
			1.10	150	300		0.957
				150	350		0.965
				150	380		0.968
				300	300		0.994
				300	350		0.997
				300	380		0.997
				350	380		0.999
				350	350		0.998
				380	380		>.999
			1.20	150	300		0.920
				150	350		0.932
				150	380		0.937
				300	300		0.985
				300	350		0.990
				300	380		0.992
				350	380		0.995
				350	350		0.994
				380	380		0.996

Table 16 Power for Non-inferiority Using -15% as the Upper Bound of the Difference in Seroresponse Rate

Sides	Null proportion difference	Assumed difference in proportion of seroresponders	Assumed proportion of seroresponders in both groups	Number in comparator group	Number in reference group	Alpha	Power
Lower	-0.15	0	0.597	150	300	0.025	0.878
				150	350		0.894
				150	380		0.902
				300	300		0.964
				300	350		0.975
				300	380		0.979
				350	380		0.986
				350	350		0.982
				380	380		0.989
			0.855	150	300		0.993
				150	350		0.995
				150	380		0.996
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999
			0.959	150	300		>.999
				150	350		>.999
				150	380		>.999
				300	300		>.999
				300	350		>.999
				300	380		>.999

				350	380		>.999
				350	350		>.999
				380	380		>.999
			0.968	150	300		>.999
				150	350		>.999
				150	380		>.999
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999
			0.993	150	300		>.999
				150	350		>.999
				150	380		>.999
				300	300		>.999
				300	350		>.999
				300	380		>.999
				350	380		>.999
				350	350		>.999
				380	380		>.999

Primary Objective: Safety

Table 17 indicates the probability of observing 1 or more safety events, such as solicited injection site or systemic reactogenicity events or an unsolicited non-serious AE of a particular type for participants in each treatment arm. With the sample size of 300 participants, at least 1 participant with an AE of incidence rate of 1% can be detected with probability of about 95%.

Table 17 Probability of detecting 1 or more safety events (N = 300)

Event Frequency	Probability (> 1 event)
≥ 10% (Very Common)	> 99%
≥ 1% (Common)	95%
≥ 0.1% (Uncommon)	26%
≥ 0.01% (Rare)	3%

9.3 Populations for Analyses

The following populations are defined:

Table 18 Populations for Analysis

Population	Description
All participants analysis set	All participants screened for the study, to be used for reporting disposition and screening failures.
Full analysis set	All randomised participants who received study treatment, irrespective of their protocol adherence and continued participation in the study. Participants will be analysed according to their randomised treatment, irrespective of whether or not they have prematurely discontinued, according to the intent-to-treat principle. Participants who withdraw consent or assent to participate in the study will be included up to the date of their study termination.
Safety analysis set	The safety analysis set consists of all participants who have received study treatment. Erroneously-treated participants (eg, those randomised to AZD2816, but were actually given treatment AZD12222) are accounted for in this analysis set by assigning them to the treatment they actually received.
Immunogenicity analysis set	The vaccine immunogenicity analysis set will include all randomised participants, received at least 1 dose of planned study treatment (ie, 1 dose of either AZD2816 or 1 dose of AZD1222), had baseline and post-dose antibody measurements, have at least 1 post-dose quantifiable serum titre, and had no protocol deviations judged to have the potential to interfere with the generation or interpretation of an antibody response. The analyses conducted using this analysis set will be based on the actual treatment received.
Seronegative immunogenicity analysis set	The subset of the immunogenicity analysis set who were seronegative at baseline.
Seropositive immunogenicity analysis set	The subset of the immunogenicity analysis set who were seropositive at baseline.

Participants that are SARS-CoV-2 seropositive at screening will be included in seropositive analysis sets analogous to the above seronegative analysis sets. Further definition is provided in the Statistical Analysis Plan.

9.4 Statistical Analyses

This section provides a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints. A more technical and detailed description of the statistical analyses will be described in the Statistical Analysis Plan, and an approved version will be finalized prior to the interim analyses.

9.4.1 General Considerations

An initial interim analysis will occur when a subset of participants previously vaccinated with AZD1222 have completed their Day 29 visit (ie, 28 days after booster dose). This sample will include both participants randomised to receive both a booster dose of AZD2816 as well as those randomised to receive a booster dose of AZD1222. Analyses presenting treatment arm summaries of both the raw and model adjusted immunogenicity will be reviewed by an unblinded team within AstraZeneca to make a decision regarding the potential need for sample size re-estimation. Full details of this analyses are provided in the Interim Analysis Charter to be finalized prior to any interim analysis.

An second interim analysis will occur when all participants previously vaccinated with AZD1222 have completed their Day 29 visit (ie, 28 days after booster dose). It is estimated that this early analysis has the potential to provide clear signals about whether AZD2816 provides a strong neutralizing response against the B.1.351 strain while retaining immunogenicity against the Wuhan strain, and thereby influence programmatic decisions early. Analyses results will present treatment arm specific summaries of both the raw and model adjusted (baseline age and co-morbidities). The raw data outputs will be stratified by age group (<65, ≥ 65) while the model adjusted summaries will pool data across age groups. Full details of this analyses are provided in the Interim Analysis Statistical analysis Plan to be finalized prior to any interim analysis.

A third interim analysis may be performed when a subset of previously unvaccinated participants have completed their Day 57 visit (ie, 56 days after fist dose). The participant sample will include both participants randomised to AZD2816 as well as those randomised to AZD1222. This analysis is intended to assess immunogenicity variability. The number of previously unvaccinated participants per treatment arm may be increased based upon the results of this analysis. The details of this interim analysis, including the trigger and methods, will be specified in the Interim Analysis Charter Plan-The primary analysis will occur when all participants have completed their Day 29 visit and safety and immunogenicity data from all unvaccinated participants randomised to a 4-week dosing interval are available through completion of their visit 28 days after the second priming dose.

A secondary analysis will occur when all participants have completed their Day 29 visit and safety and immunogenicity data from all unvaccinated participants (including those randomised to a 12-week dosing interval) are available through completion of the visit 28 days after the second dose.

The final analysis will occur when data from all vaccinated participants is available through completion of the last study visit (180 days after the single dose for previously vaccinated participants / 180 days after the second dose for unvaccinated participants).

Further details of the primary analysis, secondary analysis and final analysis are contained within the Statistical Analysis Plan.

To maintain trial integrity sponsor roles with direct input into participant management and safety monitoring will not have access to unblinded participant level data or associated outputs from the interim analyses until end of study.

Further details on the tools and processes to maintain the blind will be presented in the Study Integrity Plan.

9.4.2 Safety

9.4.2.1 Primary Endpoints

Overview

Descriptive analyses will support evaluation of safety, reactogenicity and immunogenicity. The primary safety analysis includes:

- Incidence of local and systemic solicited AEs for 7 days following each vaccination will be summarised by day and overall.
- Incidence of unsolicited AEs for 28 days following each vaccination will be summarised by system organ class and preferred term, and by relationship to vaccination as assessed by the investigator.
- MAAEs, SAEs, and AESIs following the first vaccination and throughout the study duration will be summarised by system organ class and preferred term and by relationship to vaccination as assessed by the investigator.
- The change from baseline for safety laboratory measures at 7 and 28 days after vaccination.

AE severity will be graded according to a revised toxicity grading scale from the US FDA guidance (FDA 2007) and coded using the most recent version of the Medical Dictionary for Regulatory Activities. AEs will be presented for each treatment group by system organ class and preferred term. Summaries will include the number and percentage of participants reporting at least one event, number of events and exposure adjusted rates, where appropriate.

An overview of AEs will be presented for each treatment group, including the number and percentage of participants with any AE and SAEs. Summaries will present the relationship to study intervention as assessed by the investigator, maximum intensity, seriousness, and death.

A listing will cover details for each individual AE. Full details of all AE analyses will be provided in the Statistical Analysis Plan, including intercurrent events for safety due to potential unblinding of participants for administration of licensed and/or approved SARS-CoV-2 or COVID-19 vaccine.

At the time of the interim analyses, group assignment will not be presented when safety event data has the potential to unblind participant's study group attribution.

9.4.2.2 Other Safety Endpoints

Vital Signs

Vital sign measurements will be performed as specified in the Schedule of Activities (Section 1.3). The set of assessments will include pulse oximetry, blood pressure, and body temperature.

Details of all vital sign analyses will be provided in the Statistical Analysis Plan, which will include descriptive statistics presented for observed values for all vital sign parameters.

COVID-19

This study will describe the incidence of COVID-19 adverse events from the first dose of the vaccine to study end (180 days post-vaccination). Descriptive statistics will be produced based on the safety analysis set. Full details will be documented in the statistical analysis plan.

9.4.3 Immunogenicity

9.4.3.1 Immunogenicity Endpoints

The immunogenicity endpoints of interest in this study are:

- Geometric mean antibody titre.
- Seroresponse, defined as ≥ 4-fold increase in the geometric mean antibody titre from baseline

Both the geometric mean antibody titre and seroresponse of participants will be summarized descriptively by strain, treatment arm, and timepoint for the immunogenicity population.

9.4.3.1.1 Estimand framework for immunogenicity descriptions and comparisons

Target populations:

1) Previously unvaccinated participants

    a. Seronegative Analysis Set: and with no evidence of prior or current infection

2) Participants who previously received SARS-CoV-2 vaccination with either AZD1222 or a licensed mRNA vaccine according to the authorized dose and dosing regimen at least 90 days prior to first study intervention (see Section 5.1.2).

Outcome variable: neutralizing antibody and binding titres to SARS-CoV-2 at 28 days after each treatment administration (1 treatment administration for the previously vaccinated population and 2 planned treatment administrations for the unvaccinated population).

Treatment conditions:

Previously unvaccinated population

- 2 doses of AZD1222 given on Day 1 and on Day 29 (4-week dosing interval)
- 2 doses of AZD2816 given on Day 1 and on Day 29 (4-week dosing interval)
- 1 dose of AZD1222 given on Day 1 and 1 dose of AZD2816 on Day 29 (4-week dosing interval)
- 2 doses of AZD2816 given on Day 1 and on Day 85 (12-week dosing interval)

Previously vaccinated population

- 1 dose of AZD1222 given on Day 1.
- 1 dose of AZD2816 given on Day 1.

Intercurrent events: the following intercurrent events could impact the antibody levels achieved:

- missing the second vaccination (for the unvaccinated population)
- receiving of immune-modifying drugs or vaccines
- subsequent infection with SARS-CoV-2.

All immunogenicity descriptions and comparisons will use the principal stratum strategy, ie, all analyses will exclude participants who experience any of the above intercurrent events

Population-level summary:

Descriptive Analyses (see Table 20 and Table 21)

- geometric means of the antibody titres
- seroresponse proportions

Comparative Analyses (see Table 22 and Table 23)

- ratio of geometric means of the antibody titres.
- difference in seroresponse proportion

Planned Descriptive Analyses:

Table 20 and Table 21 present planned descriptive immunogenicity analyses for the unvaccinated and previously vaccinated populations respectively (each one exploring an individual treatment arm at a specific timepoint against a particular strain).

The tables show that without introduction of further variants, there are 24 planned descriptive analyses for the unvaccinated population and 16 planned descriptive analyses for the previously immunised population (index). Within each table there is an analysis key which describes the population (see Table 19). The descriptive analyses presented in Tables 19 and 20 will be repeated for the subset of participants who are seropositive at screening.

Table 19 Description of the Analysis Keys for Tables 19 and 20

Population	Analysis Key	Example
Previously unvaccinated	Vaccination treatment received: V1222 (2 doses of AZD1222) or V2816 (2 doses of AZD2816) or V1222/2816 (1 dose of AZD1222 followed by 1 dose of AZD2816) or HV1222: ([historical] 2 doses of AZD1222 from study D8110C00001) Dosing interval: (4): 4-week dosing interval or (12): 12-week dosing interval Strain: Wuhan: Wuhan-Hu-1 or Beta: Variant B.1.351 Analysis Timepoint: D1: 28 days post-dose 1 D2 (28 days post-dose 2	[V1222 (4):Wuhan:D2] = Immunogenicity following primary vaccination with 2 doses of AZD1222 using a 4-week dosing interval against Wuhan-Hu-1 28 days post-dose 2
Previously vaccinated	Pre-study primary vaccination: V1222: 2 doses of AZD1222 or VmRNA: 2 doses of an mRNA vaccine Treatment received: B1222: 1 booster dose of AZD122) or B2816: 1 booster dose of AZD2816 Strain: Wuhan:Wuhan-Hu-1 or Beta: Variant B.1.351	[V1222:B1222:Beta] = Immunogenicity in participants who were previously vaccinated with 2 doses of AZD1222 as primary vaccination series and received a single boost dose of AZD1222 against the B.1.351 variant

Table 20 Immunogenicity Descriptive Analysis for Previously Unvaccinated Treatment Groups (with Separate Seronegative and Seropositive Analyses)

Treatment	Dosing interval	Strain	Timepoint	Endpoint	Index	Analysis Key
AZD1222	4 weeks	Wuhan-Hu-1	28 days after 1st dose	GMT	1	[V1222(4):Wuhan:D1]†
				Seroresponse	2	
			28 days after 2nd dose	GMT	3	[V1222(4):Wuhan:D2]
				Seroresponse	4	
		B.1.351	28 days after 1st dose	GMT	5	[V1222(4):Beta:D1] †
				Seroresponse	6	
			28 days after 2nd dose	GMT	7	[V1222(4):Beta:D2]
				Seroresponse	8	
AZD2816	4 weeks	Wuhan-Hu-1	28 days after 1st dose	GMT	9	[V2816(4):Wuhan:D1] ‡
				Seroresponse	10	
			28 days after 2nd dose	GMT	11	[V2816(4):Wuhan:D2]
				Seroresponse	12	
		B.1.351	28 days after 1st dose	GMT	13	[V2816(4):Beta:D1] ‡
				Seroresponse	14	
			28 days after 2nd dose	GMT	15	[V2816(4):Beta:D2]
				Seroresponse	16	
AZD1222/ AZD2816	4 weeks	Wuhan-Hu-1	28 days after 2nd dose	GMT	17	[V1222/2816(4):Wuhan:D2]
				Seroresponse	18	
		B.1.351	28 days after 2nd dose	GMT	19	[V1222/2816(4):Beta:D2]
				Seroresponse	20	
AZD2816	12 weeks	Wuhan-Hu-1	28 days after 2nd dose	GMT	21	[V2816(12):Wuhan:D2]
				Seroresponse	22	
		B.1.351	28 days after 2nd dose	GMT	23	[V2816(12):Beta:D2]
				Seroresponse	24	

† descriptive summaries for 28 days after 1st dose will pool all treatment groups who received AZD1222 as their first dose (ie, homologous and heterologous series).
‡ descriptive summaries for 28 days after 1st dose will pool all treatment groups who received AZD2816 as their first dose (4-week interval and 12-week interval treatment arms).

GMT: Geometric mean titre

Table 21 Immunogenicity Descriptive Analysis for Previously Vaccinated Treatment Groups (with Separate Seronegative and Seropositive Analyses)

Primary vaccination	Booster Treatment	Strain	Timepoint	Endpoint	Index	Analysis Key
AZD1222	AZD1222	Wuhan-Hu-1	28 days after booster dose	GMT	1	[V1222:B1222:Wuhan]
				Seroresponse	2	
		B.1.351	28 days after booster dose	GMT	3	[V1222:B1222:Beta]
				Seroresponse	4	
	AZD2816	Wuhan-Hu-1	28 days after booster dose	GMT	5	[V1222:B2816:Wuhan]
				Seroresponse	6	
		B.1.351	28 days after booster dose	GMT	7	[V1222:B2816:Beta]
				Seroresponse	8	
mRNA	AZD2816	Wuhan-Hu-1	28 days after booster dose	GMT	9	[VmRNA:B2816:Wuhan]
				Seroresponse	10	
		B.1.351	28 days after booster dose	GMT	11	[VmRNA:B2816:Beta]
				Seroresponse	12	
	AZD1222	Wuhan-Hu-1	28 days after booster dose	GMT	13	[VmRNA:B1222:Wuhan]
				Seroresponse	14	
		B.1.351	28 days after booster dose	GMT	15	[VmRNA:B1222:Beta]
				Seroresponse	16	

GMT: Geometric mean titre

Immunogenicity comparisons:

Immunogenicity analysis

A number of comparisons of geometric mean titres and seroresponse rates between vaccine regimens and vaccine types are intended to be made.

All non-inferiority comparisons of geometric mean titre ratios will be made utilizing the lower bound of two-sided score-based confidence intervals ($\alpha = 0.05$) with non-inferiority margin 0.67

All non-inferiority comparisons of seroresponse rates will be made utilizing the lower bound of two-sided score-based confidence intervals ($\alpha = 0.05$) with non-inferiority margin 15%, and superiority comparisons of seroresponse rates will be made using one-sided Fisher's exact test ($\alpha = 0.025$). Comparisons of antibody titres between treatment groups will be conducted using geometric mean titre (GMT) ratios and seroresponse rates, facilitated by an analysis of covariance (ANCOVA) model of the log2 titre, which adjusts for the baseline level, time since previous vaccination (for previously vaccinated individuals), baseline co-morbidities and

gender as fixed effects. All analyses of antibody titres (GMT ratios and differences in seroresponse) will be repeated using the unadjusted (raw observed) concentration values.

Geometric Mean Titres

The statistical methodology will be based on a 2-sided 95% CI of the ratio of the GMTs. Non-inferiority will be demonstrated if the lower limit of the 2-sided 95% CI of the GMT ratio of the reference group and comparator group is >0.67 (see Table 22 and Table 23). The 2-sided 95% CI for the ratio of GMTs will be calculated using normal approximation of log-transformed concentrations.

The 95% CI for the GMT ratio between 2 groups will be constructed as follows:

Logarithm transformation of the individual concentrations will be calculated.

The 95% CI for the difference in log(GMT) between 2 groups: Group$_C$ and Group$_R$ will be in the form:

$$\bar{X}_C - \bar{X}_R \pm t\left(1 - {}^{\alpha}/_{2}, n_C + n_R - 2\right) \times S\sqrt{{}^{1}/_{n_C} + {}^{1}/_{n_R}}$$

Where $\bar{X}_C$ and $\bar{X}_R = \log(GMT)$ are the means of the log-transformed concentration for $Group_C$ and $Group_R$, respectively,

$S^2 = {}^{[(n_C - 1)S_C^2 + (n_R - 1)S_R^2]}/_{(n_C + n_R - 2)}$ is the pooled sample variance,

n_C and n_R are the sample sizes for $Group_C$ and $Group_R$, respectively,

S_C and S_R are the sample variances for $Group_C$ and $Group_R$, respectively,

$t\left(1 - {}^{\alpha}/_{2}, n_C + n_R - 2\right)$ is the $100\left(1 - \frac{\alpha}{2}\right)$ percentile of the t-distribution with degrees of freedom $df = n_C + n_R - 2$

To test this hypothesis, a 2- sided 95% CI will be constructed around the ratio $\frac{GMT_C}{GMT_R}$, where GMT_C and GMT_R are the geometric mean of the antibody titres in the comparator and reference groups respectively, at the timepoints post vaccination for which the groups are being compared.

The hypothesis will be supported by the data, if the lower bound of the calculated of the calculated 95% CI is > 0.67. This is equivalent to testing the null hypothesis using a 1-sided type-I error rate of 0.025.

$$H_0: {GMT_C}/{GMT_R} \leq 0.67$$

$$H_A: {GMT_C}/{GMT_R} > 0.67$$

Or equivalently

$$H_0: \log(GMT_C) - \log(GMT_R) \leq \log(0.67)$$

$$H_A: \log(GMT_C) - \log(GMT_R) > \log(0.67)$$

For the separately considered GMT hypotheses, if the null hypothesis is rejected, then the alternative hypothesis of non-inferiority will be supported.

Seroresponse

The statistical methodology will be based on a 2-sided 95% CI of the difference in seroresponse. Non-inferiority will be demonstrated if the upper bound of the 2-sided 95% CI rate difference in seroresponse between the reference group and comparator group is <15%. The 95% CI of the difference in proportions $P_C - P_R$ will be computed using the Wilson score without continuity correction.

To test this hypothesis, a 2- sided 95% CI will be constructed around the difference $P_C - P_R$, whereP_C and P_R are the proportions of participants in the comparator and reference groups respectively who are classified as seroresponders ($\geq$ 4 fold increase from baseline) at the timepoints post vaccination for which the groups are being compared.

The hypothesis will be supported by the data, if the lower bound of the calculated of the calculated 95% CI is > 15%. This is equivalent to testing the null hypothesis using a 1-sided type-I error rate of 0.025.

$$H_0: P_C - P_R < -15\%$$

$$H_A: P_C - P_R \geq 15\%$$

If the null hypothesis is rejected, then the alternative hypothesis of non-inferiority will be supported.

Comparisons

The primary and secondary immunogenicity objectives and the GMT and seroresponse comparisons for the previously unvaccinated participants receiving a 2-dose primary vaccination are presented in Table 22.

The immunogenicity objectives and the GMT and seroresponse comparisons for the previously vaccinated participants receiving a 1-dose booster vaccination are presented in Table 23.

Owing to national vaccine rollout in the recruitment countries, including the prioritization of elderly populations, it is anticipated that there will be critical differences between the previously vaccinated and previously unvaccinated cohorts with respect to age and presence of important underlying comorbidities that may confound the interpretation of the results. Consequently, the primary and key secondary non-inferiority analyses across these two cohorts will compare the previously vaccinated participants that received a booster dose in this study with a subset of matched participants from the previously unvaccinated participants that received the 2-dose AZD1222 primary vaccine series in the AZD1222 Phase 3 trial Study D8110C00001, which was performed in the US, Chile, and Peru.

This historical control group will be matched, at a minimum, to the previously vaccinated AZD1222 booster cohort in the D7220C00001 study based on age, gender, and presence of baseline comorbidities. These matched samples will then serve as the control arm for all planned non-inferiority analyses (both geometric mean titre [GMT] ratio and difference in seroresponse) of the previously vaccinated cohort treatment arms to the primary series vaccination. Comparisons of antibody titres between the previously vaccinated cohort in this study and the historical controls from Study D8110C00001 will be conducted using the immunogenicity analysis described above (ie, using an adjusted ANCOVA model to calculated adjusted means and standard errors for the historical comparators).

For immunogenicity data not already available, preserved sera samples from the matched controls will be used to generate immune response by the primary series parent vaccine against variant strains. AstraZeneca confirms that study D8110C00001 utilizes the same validated pseudovirus neutralising antibody assay for the Wuhan-Hu-1 strain and that residual sera are available from these study participants that will be tested in a pseudovirus neutralising antibody assay against the beta (B.1.351) variant (Monogram Biosciences, South San Francisco, USA).

Further details on the matching procedures and reporting of historical samples are provided in the Statistical Analysis Plan.

Table 22 Immunogenicity Comparisons for Previously Unvaccinated Groups

Objective	$\frac{[\mathbf{GMT}_{\mathbf{comparator}}]}{[\mathbf{GMT}_{\mathbf{reference}}]}$	$\Delta = [\mathbf{Seroresponse}_{\mathbf{comparator}}] - [\mathbf{Seroresponse}_{\mathbf{reference}}]$
To determine if the neutralizing antibody GMT response/seroresponse elicited by a 2-dose AZD2816 primary vaccination is non-inferior to the response elicited by a 2-dose AZD1222 primary vaccination	[V2816(4): Beta: D2]/[V1222(4): Wuhan: D2] (Primary)	[V2816(4): Beta: D2] − [V1222(4): Wuhan: D2] (Key Secondary 2.1)
	[V2816(4): Beta: D1]/[V1222(4): Wuhan: D1]	[V2816(4): Beta: D1] − [V1222(4): Wuhan: D1]
	[V2816(4): Wuhan: D2]/[V1222(4): Wuhan: D2] (Key Secondary 2.4)	[V2816(4): Wuhan: D2] − [V1222(4): Wuhan: D2] (Other Secondary)
	[V2816(4): Wuhan: D1]/[V1222(4): Wuhan: D1]	[V2816(4): Wuhan: D1] − [V1222(4): Wuhan: D1]
	[V2816(4): Beta: D2]/[V1222(4): Beta: D2] (Key Secondary 2.2)	[V2816(4): Beta: D2] − [V1222(4): Beta: D2] (Other Secondary)
	[V2816(4): Beta: D1]/[V1222(4): Beta: D1]	[V2816(4): Beta: D1] − [V1222(4): Beta: D1]
To determine if the neutralizing antibody GMT response/seroresponse elicited by a 2-dose AZD1222 + AZD2816 heterologous primary vaccination is non-inferior to the response elicited by a 2-dose AZD1222 primary vaccination	[V1222/2816(4): Beta: D2]/[V1222(4): Wuhan: D2] (Key Secondary 2.3)	[V1222/2816(4): Beta: D2] − [V1222(4): Wuhan: D2] (Other Secondary)
	[V1222/2816(4): Wuhan: D2]/[V1222(4): Wuhan: D2] (Other Secondary)	V1222/2816(4): Wuhan: D2] − [V1222(4): Wuhan: D2] (Other Secondary)
	[V1222/2816(4): Wuhan: D2]/[V1222(4): Wuhan: D2] (Other Secondary)	[V1222/2816(4): Wuhan: D2] − [V1222(4): Wuhan: D2] (Other Secondary)

Table 22 Immunogenicity Comparisons for Previously Unvaccinated Groups

Objective	$\frac{[\mathbf{GMT}_{\mathbf{comparator}}]}{[\mathbf{GMT}_{\mathbf{reference}}]}$	$\Delta = [\mathbf{Seroresponse}_{\mathbf{comparator}}] - [\mathbf{Seroresponse}_{\mathbf{reference}}]$
To determine if the neutralizing antibody GMT response/seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following a 2-dose AZD2816 primary vaccination	[V2816(4): Beta: D2]/[V2816(4): Wuhan: D2] (Other Secondary)	[V2816(4): Beta: D2] − [V2816(4): Wuhan: D2] (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following a 2-dose AZD1222/AZD2816 primary heterologous vaccination	[V1222/2816(4): Beta: D2]/[V1222/2816(4): Wuhan: D2] (Other Secondary)	[V1222/2816(4): Beta: D2] − [V1222/2816(4): Wuhan: D2] (Other Secondary)

Table 23 Immunogenicity Comparisons for Previously Vaccinated Group

Objective	$\frac{[\![\mathbf{GMT}]\!]_{\mathbf{comparator}}}{[\![\mathbf{GMT}]\!]_{\mathbf{reference}}}$	$[\![\mathbf{Seroresponse}]\!]_{\mathbf{comparator}} - [\![\mathbf{Seroresponse}]\!]_{\mathbf{reference}}$
To determine if the neutralizing antibody GMT response/seroresponse elicited by an AZD2816 booster dose in participants previously vaccinated with AZD1222 is non-inferior to response elicited by a 2-dose AZD1222 vaccination	V1222: B2816: Beta]/[HV1222(4): Wuhan: D2] (Primary)	[V1222: B2816: Beta] − [HV1222(4): Wuhan: D2] (Other Secondary)
	[V1222: B2816: Beta]/[HV1222(4): Beta: D2] (Key Secondary 2.1)	[V1222: B2816: Beta] − [HV1222(4): Beta: D2] (Other Secondary)
	[V1222: B2816: Wuhan]/[HV1222(4): Wuhan: D2] (Key Secondary 2.3)	[V1222: B2816: Wuhan] − [HV1222(4): Wuhan: D2 (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse elicited by an AZD2816 booster dose is non-inferior to response elicited by an AZD1222 booster dose in participants previously vaccinated with AZD1222	[V1222: B2816: Beta]/[V1222: B1222: Beta] (Key Secondary 2.2)	[V1222: B2816: Beta] − [V1222: B1222: Beta] (Other Secondary)
	[V1222: B2816: Wuhan]/[V1222: B1222: Wuhan] (Key Secondary 2.5)	[V1222: B2816: Wuhan] − [V1222: B1222: Wuhan] (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse elicited by an AZD1222 booster dose in patients previously vaccinated with AZD1222 is non-inferior to the response elicited by a 2-dose AZD1222 vaccination	[V1222: B1222: Wuhan]/[HV1222(4): Wuhan: D2] (Key Secondary 2.4)	[V1222: B1222: Wuhan] − [HV1222(4): Wuhan: D2 (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse elicited by an AZD2816 booster dose in participants previously vaccinated with an mRNA-based vaccine is non-	[VmRNA: B2816: Beta]/[HV1222(4): Wuhan: D2] (Other Secondary)	[VmRNA: B2816: Beta] − [HV1222(4): Wuhan: D2] (Other Secondary)
	[VmRNA: B2816: Beta]/[HV1222(4): Beta: D2] (Other Secondary)	[VmRNA: B2816: Beta] − [HV1222(4): Beta: D2] (Other Secondary)

Table 23 Immunogenicity Comparisons for Previously Vaccinated Group

Objective	$\frac{[\![\mathbf{[GMT]}]\!]_{\mathbf{comparator}}]}{[\![\mathbf{[GMT]}]\!]_{\mathbf{reference}}]}$	$[\![\mathbf{[Seroresponse]}]\!]_{\mathbf{comparator}}] - [\![\mathbf{[Seroresponse]}]\!]_{\mathbf{reference}}]$
inferior to response elicited by a 2-dose AZD1222 vaccination	[VmRNA: B2816: Wuhan] /[HV1222(4): Wuhan: D2] (Other Secondary)	[VmRNA: B2816: Wuhan] − [HV1222(4): Wuhan: D2] (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse elicited by an AZD2816 booster dose is non-inferior to the response elicited by an AZD1222 booster dose in participants previously vaccinated with an mRNA-based vaccine	[VmRNA: B2816: Wuhan]) /[VmRNA: B1222: Wuhan] (Other Secondary)	[VmRNA: B2816: Wuhan] − [VmRNA: B1222: Wuhan] (Other Secondary)
	[VmRNA: B2816: Beta])/[VmRNA: B1222: Beta] (Other Secondary)	[V1222: B2816: Beta]/[V1222: B2816: Wuhan] (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following an AZD2816 booster dose	[V1222: B2816: Beta]/[V1222: B2816: Wuhan] (Other Secondary)	[V1222: B2816: Beta] − [V1222: B2816: Wuhan] (Other Secondary)
To determine if the neutralizing antibody GMT response/seroresponse rate against the B.1.351 variant is non-inferior to the rate against the original Wuhan-Hu-1 strain following an AZD1222 booster dose	[V1222: B1222: Beta]/[V1222: B1222: Wuhan] (Other Secondary)	[V1222: B1222: Beta] − [V1222: B1222: Wuhan] (Other Secondary)

9.4.4 Multiple Comparisons

A hierarchical approach will be used to control for multiplicity of the primary and key secondary immunogenicity endpoints. That is, the null hypotheses for the immunogenicity endpoints will be tested in a hierarchical order, and the subsequent null hypothesis will be tested only if the prior null hypothesis is rejected. Consequently, no adjustment to alpha for multiplicity will be made in the analysis of immune response. The primary Statistical comparisons of safety data will not be adjusted for multiple comparisons. Further details are provided in the statistical analysis plan.

9.4.5 Data Safety Monitoring Board

An independent COVID-19 Vaccine Data Safety Monitoring Board will provide oversight, to ensure safe and ethical conduct of the study. During the study, the benefit/risk assessment will be continuously monitored by the Board to ensure that the balance remains favourable. Further details, composition, and operation of the COVID-19 Vaccine Data Safety Monitoring Board will be described in a separate charter. For further details, see Appendix A 5.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Not applicable.

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH/GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigators Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Sponsor will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a contract research organization but the accountability remains with the Sponsor.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH/GCP guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all Food and Drug Administration (FDA) Regulations, as applicable and all other applicable local regulations

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
  - European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH/GCP guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The study medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study if required by the IRB.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committee Structure

The safety of all Sponsor clinical studies is closely monitored on an ongoing basis by Sponsor representatives in consultation with AstraZeneca Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the Clinical Study Protocol and letters to investigators.

A COVID-19 Vaccine Data Safety Monitoring Board comprised of independent experts will be convened to provide oversight and to ensure safe and ethical conduct of the study. The COVID 19 Vaccine Data Safety Monitoring Board will have the responsibility of evaluating cumulative safety and other clinical study data at regular intervals and making appropriate recommendations based on the available data. During the study, the benefit/risk assessment will be continuously monitored by the COVID-19 Vaccine Data Safety Monitoring Board to ensure that the balance remains favourable. Full details of the COVID-19 Vaccine Data Safety Monitoring Board composition and operations can be found in the COVID-19 Vaccine Data Safety Monitoring Board Charter.

An independent Neurological AESI Expert Committee will be available to review and provide on request about the diagnosis and causality assessment of selected neurological AEs of special interest occurring in the study. Details on the composition and operation of this committee are described in the Neurological AESI Expert Committee Charter.

A 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the relevant study plans.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data review to confirm that the safety and rights of participants are being protected, and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH/GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A 9 Study and Site Start and Closure

The first act of recruitment is the first participant screened and will be the study start date.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or ICH/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 IRB/IECs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites may have the opportunity to be transferred to another site to continue the study.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of 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 SAEs and non-SAEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of Serious Adverse Events

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

AEs for **malignant tumours** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-SAE**. 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 hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life Threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the study intervention would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability, or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used. Examples of important medical events include such events as listed below:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by acetaminophen overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

Intensity Rating Scale

A revised toxicity grading scale found in the US FDA guidance for healthy volunteers enrolled in a preventive vaccine clinical study (FDA 2007) will be utilized for all events.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for

several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B 2.

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 investigational product.

- 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 investigational product?
- Consistency with known investigational product profile. Was the AE consistent with the previous knowledge of the suspect investigational product (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 investigational product?
- 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 investigational product was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the investigational medicinal product?
- 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 3 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 investigational product, but rather a human or process related failure while the investigational product 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 investigational product
- 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:

- Investigational product name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the participant
- Investigational product not administered as indicated, for example, wrong route or wrong site of administration
- Investigational product not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Investigational product not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT errors)
- Wrong investigational product administered to participant (excluding IRT errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT - including those which lead to one of the above listed events that would otherwise have been a medication error
- Accidental overdose (will be captured as an overdose)
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each study site keeps full traceability of collected biological samples from the participants while in storage at the study site until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps record of receipt of arrival and onward shipment or disposal.

The Sponsor or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

The Sponsor ensures that biological samples are destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, the Sponsor is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes.

The investigator:

- Ensures participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to the Sponsor or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and the Sponsor are informed about the sample disposal.

The Sponsor ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

Appendix D 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 24: Clinical Abnormalities, Local Reactions to Injectable Product
- Table 25: Clinical Abnormalities, Vital Signs
- Table 26: Clinical Abnormalities, Systemic (General or Illness)

Table 24 Tables for Clinical Abnormalities: Local Reactions to Injectable Product

Local Reaction to Injectable Product	Reaction Grade			
	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Life Threatening (Grade 4)**
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/redness [a, b]	1-2 inches (2.5–5 cm)	> 2-4 inches (5.1–10 cm)	> 4 inches (> 10 cm)	Necrosis or exfoliative dermatitis
Induration/swelling [a, b]	1-2 inches (2.5–5 cm)	> 2-4 inches (5.1–10 cm)	> 4 inches (> 10 cm)	Necrosis

[a] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable. Reactions < 0.25 inches (< 0.6 centimetres) in diameter will not be recorded.

[b] Grade 4 erythema or induration is determined by study site with participant input rather than being recorded directly in Solicited AE e-Diary.

ER: emergency room.

Table 25 Tables for Clinical Abnormalities: Vital Signs

Vital Sign	Vital Signs Grade			
	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)a**
Fever (°C/°F)	37.9-38.4 100.1-101.1	38.5-38.9 101.2-102.0	39.0-40 102.1-104	> 40 > 104
Tachycardia (beats/minute)	101-115	116- 130	> 130	Emergency room visit or hospitalization for arrhythmia
Bradycardia (beats/minute)	50-54	45-49	< 45	Emergency room visit or hospitalization for arrhythmia
Hypertension; systolic (mm Hg)	141-150	151-155	> 155	Emergency room visit or hospitalization for malignant hypertension
Hypertension; diastolic (mm Hg)	91-95	96-100	> 100	Emergency room visit or hospitalization for malignant hypertension
Hypotension; systolic (mm Hg)	85-89	80-84	< 80	Emergency room visit or hospitalization for hypotensive shock
Respiratory rate (breaths/minute)	17-20	21-25	> 25	Intubation

Grade 4 vital signs other than fever are reported as adverse events. Use clinical judgment when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.

Table 26 Tables for Clinical Abnormalities: Systemic (General or Illness)

Systemic (General)	Systemic Grade[a]			
	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Nausea/ vomiting	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, required outpatient intravenous hydration	Emergency room visit or hospitalization for hypotensive shock
Chills	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalization
Systemic Illness				
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring intervention	Prevents daily activity and required medical intervention	Emergency room visit or hospitalization

Appendix E Adverse Events of Special Interest

Adverse events of special interest for this study are based on Brighton Collaboration case definitions (SPEAC 2020), clinical experience, and scientific interest. There is no current evidence to suggest that AZD1222 is associated with these AEs of special interest.

Table 27 Adverse Events of Special Interest

Category	Medical Concept
Neurologic	Generalized convulsion: episodes of neuronal hyperactivity most commonly resulting in sudden, involuntary muscular contractions. They may also manifest as sensory disturbances, autonomic dysfunction and behavioural abnormalities, and impairment or loss of consciousness.
	Guillain-Barré syndrome: a peripheral nerve demyelinating disease, which can present as temporary ascending paralysis.
	Acute disseminated encephalomyelitis: defined as a uniphasic syndrome of brain inflammation and demyelination occurring in temporal association with an antecedent immunologic challenge, such as infection or an immunization. ADEM most commonly occurs in the paediatric population.
	Other neurologic events: include new onset event (acute or subacute) motor and sensory disturbances (eg, weakness, numbness, paraesthesia, hypoesthesia, hyperesthesia, dysesthesias), bowel/bladder dysfunction, gait impairment, or visual disturbance, or any event of myelitis, encephalomyelitis, myelitis transverse, or other sudden neurological deficit.
Vascular	Thrombotic, thromboembolic, and neurovascular events: events that can manifest as transient or permanent vision problems, dizziness, trouble understanding, facial droop, slurred speech, unilateral weakness, deep vein thrombosis with swollen, warm or painful leg, pulmonary embolism with shortness of breath, chest pain or irregular heart rate.
Hematologic	Thrombocytopenia: a disorder in which there is an abnormally low platelet count; a normal platelet count ranges from 150 000 to 450 000 platelets per µL.
Immunologic	Vasculitides: a group of related disorders characterized by inflammation of blood vessels (vasculitis) leading to tissue or end-organ injury.
	Anaphylaxis: an acute hypersensitivity reaction with multi-organ-system involvement that can present as, or rapidly progress to, a severe life-threatening reaction requiring immediate medical attention.
	Vaccine-associated enhanced respiratory disease: pathogenicity has been linked to a vaccine immune response characterized by induction of non-neutralizing antibodies, and a T-cell response of the Th2 type with hypereosinophilia (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: 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 28.

Table 28 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

Table 28 List of Potential Immune-mediated Medical Conditions

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, Bechet's syndrome, leukocytoclastic vasculitis

Table 28 List of Potential Immune-mediated Medical Conditions

Category	Condition
Other	Antiphospholipid syndrome
	Autoimmune haemolytic anaemia
	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 anaemia
	Raynaud's phenomenon
	Sarcoidosis
	Sjögren's syndrome
	Stevens-Johnson syndrome
	Uveitis

Appendix F Actions Required in Cases of Thrombotic Events With Thrombocytopenia and/or Bleeding

F 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of thrombotic events with thrombocytopenia and/or bleeding. It is not intended to be a comprehensive guide to the management of all venous thromboembolic events.

During the course of the study, the investigator will remain vigilant for occurrence of thrombotic events with thrombocytopenia and/or bleeding. Appropriate investigations (eg, imaging) to diagnose these events should be made on a case-by-case basis. The investigator is responsible for determining whether a participant meets criteria for thrombotic events with thrombocytopenia and/or bleeding at any point during the study.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting criteria for thrombotic events with thrombocytopenia and/or bleeding. The Study Physician contacts the investigator to provide guidance, discuss, and agree an approach for the participant's follow-up and the continuous review of data. Guidance from the International Society of Thrombosis and Haemostasis for management of thrombocytopenic thromboembolism occurring after vaccination can be found at www.isth.org. Notably, participants should only be treated with heparin if a test for heparin-induced thrombocytopenia antibodies is negative. An alternative explanation for thrombocytopenia should be considered (eg, alcohol use, liver cirrhosis, concomitant medications, exposure to toxic chemicals, viral infections).

The investigator is responsible for recording data pertaining to thrombotic events with thrombocytopenia and/or bleeding and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

F 2 Tests that Should Be Considered if Thrombotic Events With Thrombocytopenia and/or Bleeding Are Suspected

The following tests should be considered, but not limited to:

1. Measurement of platelet levels, prothrombin time, activated partial thromboplastin time, D-dimer levels, and fibrinogen levels

2. Complete blood count, reticulocyte count, blood film, haptoglobins

3. Anti-platelet factor 4 antibodies

4. Anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies, rheumatoid factor, human leucocyte antigen B27, ADAMTS13 activity, anti-cardiolipin antibodies IgG + IgM, and anti-B2GPI antibodies IgG + IgM

5. Complement (eg, C3, C4, complement complex C5b-9, C5a), autoantibodies (eg, antinuclear IgG, anti-double stranded DNA IgG, anti-Smith IgG, anti-SSA IgG, anti-SSB IgG, anti-Jo1 IgG, anti-MPO IgG, anti-PR3 IgG, anti-glomerular basement membrane IgG)

6. Factor V Leiden, Factor II (prothrombin) variant

7. Platelet activation markers and functional assays (eg: sCD40L, soluble glycoproteins, degranulation markers [PF4, vWF, P-selectin, annexin V]), anti-PF4-plasma-serotonin release assay (if anti-PF4 ELISA positive)

8. Inflammatory markers: TNFa, IL-1, IL-4, IL-6, IL-10, IL-13

9. Cell adhesion molecules: VCAM, ICAM, E-selectin

10. Adenovirus serology

11. Additional viral serology: Cytomegalovirus (IgG and IgM), Ebstein-Barr virus (IgG and IgM), HIV, Parvo virus B19

12. COVID-19 testing, including PCR and serology

13. Calculation of an International Society of Thrombosis and Haemostatis score for Disseminated Intravascular Coagulation (derived from platelet levels, fibrinogen, and D-Dimer)

Appendix G Abbreviations

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ChAdOx1 MERS	Chimpanzee adenovirus Ox1 with MERS Spike antigen
ChAdOx1 nCoV-19	AZD1222 when initially developed by the University of Oxford
COVID-19	Coronavirus disease 2019
eCRF	Electronic case report form
e-Diary	Electronic diary
GMT	Geometric mean titre
ICF	Informed consent form
ICH/GCP	International Council for Harmonisation/Good Clinical Practice
IRB/IEC	Institutional Review Board/ Independent Ethics Committee
IRT	Interactive Response Technology
MAAEs	Medically attended adverse events
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
S	Spike
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome-coronavirus-2

Appendix H Protocol Amendment History

DOCUMENT HISTORY	
Document	**Date**
Amendment GBR-3	13 October 2021
Amendment GBR-2	30 July 2021
Amendment GBR-1	3 June 2021
Amendment 1	2 June 2021
Version 1	14 May 2021

Amendment GBR-3: 13 October 2021

The principal reason for this amendment was to remove the age cap and revise the primary and key secondary non-inferiority analyses to included historical controls due to difficulties in recruiting the previously unvaccinated cohort.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Synopsis Section 4.1 Section 9.4..3.1.1	Inserted information on use of historical controls	Required based on anticipated confounding between previously vaccinated and previously unvaccinated cohorts.	Substantial
Section 3.2, Table 6	Inserted exploratory objectives on exploration of humoral immune response with live virus neutralization assay and exploration of additional immune response based on emerging data	Omitted in error	Non-substantial
Section 4.1	Deleted age cap ensuring at least 25% enrolled participants were >65 years of age.	Due to enrollment difficulties in finding previously unvaccinated elderly	Substantial
Section 7.1	Inserted laboratory-confirmed SARS-CoV-2 infection as discontinuation of study intervention	To explicitly state this criterion (which is implicitly included in criteria 2) as a discontinuation of treatment criterion.	Non-substantial
Section 9.2	Section on immunogenicity comparisons and previous Table 16 and Table 17 were moved up under the Primary Objective sub-heading	Had been placed under Secondary Objective in error	Non-substantial
Section 9.4.3.1.1 Table 19 Table 20 Table 21 Table 22 Table 23	Analysis key (abbreviations) revised	Improvements in abbreviations for clarity	Non-substantial
Section 9.4..3.1.1	Description of statistical approach to be used with historical control comparisons added.	Inclusion of historical controls requires description of statistical methodology to be used.	Substantial

In addition, the protocol has been revised with minor rewordings, corrections, and clarifications which are all considered to be non-substantial.

Amendment GBR-2: 30 July 2021

The principal reason for this amendment was to

1) add an additional interim analysis to evaluate immunogenicity in a subset of AZD1222 previously vaccinated subjects boosted with AZD1222 or AZD2816

2) revise Objectives/Endpoints from descriptive to comparative, with ranking of primary, key secondary, other secondary, and exploratory objectives

3) add non-inferiority margins to primary analysis and add additional participants to maintain power

This amendment has also been implemented in the global version of the study D7220C00001 Clinical Study Protocol.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.1 Synopsis (Objectives and Endpoints)	Revised this section from primarily descriptive to primarily comparative. Comparative immunogenicity objectives created and ranked as primary, key secondary, other secondary.	Objectives of study changed from descriptive to comparative, testing for non-inferiority across treatment comparisons	Substantial
1.1 Synopsis (Number of Participants; Statistical Methods)	Overall size increased to 2590 participants	Adjustments made to maintain power with the added non-inferiority margins	Substantial
1.1 Synopsis (Statistical Methods)	An additional interim analysis added. Second interim analysis changed to include only the previously vaccinated with AZD1222 cohort.	Interim analysis plan was reviewed and revised.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
1.2 Schema	Figures updated with increased participant numbers	Adjustments made to maintain power with the added non-inferiority margins	Substantial
1.3 Schedule of Activities	Table 2: footnote clarification added Table 3: minor corrections	Clarification/Correction	Non-substantial
2.1 Study Rationale (and elsewhere in protocol)	Clarification on previous vaccination criteria	Clarification	Non-substantial
3 Objectives	Section completely rewritten. Divided into 2 sections: Previously unvaccinated and previously vaccinated. Immunogenicity objectives created for comparisons. Objectives ranked as primary, key secondary, other secondary, or exploratory.	Objectives of study changed to show non-inferiority across treatments.	Substantial
4.1 Overall design	Participant numbers increased	Adjustments made to maintain power with the added non-inferiority margins	Substantial
4.1 Overall design	Cap on age added	To ensure good representation across age groups	Substantial
8.3.2	Removal of severity grade 5	Correction	Non-substantial
8.5.2.3 CCI [redacted]	Addition of information on number of patients sampled for CCI [redacted]	Clarification	Non-substantial
9.1 Statistical Hypotheses	Addition of statistical hypotheses	Include hypothesis being tested.	Substantial
9.2 Sample size determination	Confidence intervals for populations of 350 and 380 added to Table 14 and Table 15	Updated to include current populations of 350 and 380 participants	Non-substantial
9.2 Sample size determination	Power estimates for populations of 350 and 380 added to Table 17 and Table 18	Updated to include current populations of 350 and 380 participants	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
9.4.1 General considerations	Details on the initial interim, second interim, and third interim analysis added	Include revised information on the analysis plan, including interim analyses	Substantial
9.4.3.1.1 Estimand framework for immunogenicity descriptions and comparisons	Objectives removed from descriptive analysis Table 23 and Table 24	Objectives of study changed from descriptive to comparative, showing non-inferiority across treatments	Substantial
9.4.3.1.1 Estimand framework for immunogenicity descriptions and comparisons	Section of Immunogenicity Comparisons added.	Objectives of study changed from descriptive to comparative, showing non-inferiority across treatments	Substantial
9.4.3.1.1 Estimand framework for immunogenicity descriptions and comparisons	Table 25 and Table 26 on immunogenicity comparisons revised, aligned with the revised objectives/endpoints.	Objectives of study changed from descriptive to comparative, showing non-inferiority across treatments	Substantial
9.4.4 Multiple Comparisons	Section added.	Objectives of study changed from descriptive to comparative, showing non-inferiority across treatments	Substantial

In addition, the protocol has been revised with minor corrections and clarifications.

Amendment GBR-1 (Protocol Version 2): 1 June 2021

Version 1 of the protocol was amended prior to the commencement of the study (ie, prior to approval of the protocol by an ethics committee) based on feedback from internal and regulatory authority reviews. The most substantial changes were as follows:

- addition of 2 treatment arms: 1) AZD1222 as a single booster vaccination in participants previously vaccinated with an mRNA COVID-19 vaccine and 2) heterologous vaccination with AZD1222 plus AZD2816 in previously unvaccinated participants
- further definition of analysis sets
- addition of thrombotic events with thrombocytopenia as a discontinuation criteria

In addition, corrections and revisions to text to improve readability were made.

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