Clinical Study Protocol

Drug Substance	AZD1222
Study Number	D8111C00010
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TITLE PAGE

A Phase IV Open-Label, Non-Randomized, Multi-Cohort, Multicenter Study in Previously Unvaccinated Immunocompromised Adults to Determine the Immunogenicity and Safety of AZD1222 Vaccine for the Prevention of COVID-19

Sponsor Name: **AstraZeneca AB**

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Regulatory Agency Identifier Number: NCT 05057897

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: D8111C00010

Amendment Number: 2

Study Intervention: AZD1222

Study Phase: IV

Short Title: A Phase IV Study of AZD1222, a Vaccine for the Prevention of COVID-19 in Immunocompromised Adults

Study Physician Name and Contact Information will be provided separately.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 2, Version 3.0	14 Dec 2021
Amendment 1, Version 2.0	13 Aug 2021
Version 1.0	06 Aug 2021

Amendment 2, Version 3.0:
The principal reasons for updating this protocol are to:

- Add a third dose in the primary vaccination series, four weeks after the second dose, for all immunocompromised cohorts and update the study design and schedule of activities.
- Add a third dose booster six months after the first dose for the immunocompetent cohort and update the study design and schedule of activities.
- Update the study objectives, endpoints, and statistical considerations.
- Additional minor clarifications and corrections.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase IV Open-Label, Non-Randomized, Multi-Cohort, Multicenter Study in Previously Unvaccinated Immunocompromised Adults to Determine the Immunogenicity and Safety of AZD1222 Vaccine for the Prevention of COVID-19

Short Title: Phase IV study of AZD1222, a Vaccine for the Prevention of COVID-19 in Immunocompromised Adults.

Rationale

The aim of this study is to assess the immunogenicity and safety of AZD1222 for prevention of COVID-19 in immunocompromised adults. Clinical studies supporting the emergency use authorizations of AZD1222 have, to date, generally excluded participants with significantly compromised immune systems. There remains an unmet need in determining the safety and immunogenicity of COVID-19 vaccines in a variety of immunocompromised populations, including primary immunocompromised adults. An immunocompetent group of participants will also be included.

Objectives and Endpoints:

The purpose of this study is to demonstrate the immunogenicity and safety of AZD1222, AstraZeneca's approved ChAdOx1 vector vaccine against SARS-CoV-2, in SARS-CoV-2 seronegative immunocompromised individuals who are unvaccinated.

The following table lists the primary and secondary endpoints:

Primary Immunogenicity Objectives	
• To characterize the immunogenicity of a 2-dose primary vaccination with AZD1222, with a 4-week dosing interval, in SARS-CoV-2 naïve immunocompromised adults and immunocompetent adults ≥ 18 years. Estimand:	
Endpoints [a]	1) SARS-CoV-2 specific titres 2) Seroresponse of SARS-CoV-2 specific titres (≥ 4-fold rise in titres from baseline [b])
Serotype	Wuhan-Hu-1
Timepoints	28 days after Dose 1; 28 days after Dose 2
Population	Immunogenicity analysis set
Cohort	Each of 5 immunocompromised cohorts, pooled immunocompromised cohorts, and immunocompetent cohort
Secondary Safety Objective	

Objective	Endpoints
• To characterize the reactogenicity and safety of a 3-dose primary vaccination series with AZD1222, with a 4-week dosing interval, in SARS-CoV-2 naïve immunocompromised adults ≥ 18 years.	• Reactogenicity: Incidence of local and systemic solicited AEs for 7 days after each dose of AZD1222 by eDiary. • Incidence of unsolicited AEs for 28 days post dose after each vaccination • Incidence of SAEs, MAAEs and AESIs from Day 1 post treatment to last study visit. • Absolute and change from baseline [b] for safety laboratory measures.
Secondary Immunogenicity Objectives	
• To describe the immunogenicity of a 2-dose primary vaccination with AZD1222 in adults ≥ 18 years with a 4-week dosing interval between SARS-CoV-2 naïve participants with solid organ transplant compared to immunocompetent participants. Estimand:	
Endpoints [a]	1) Ratio of SARS-CoV-2 specific GMT titres 2) Difference in seroresponse rates of SARS-CoV-2 specific titres (≥ 4-fold rise in titres from baseline [b])
Serotype	Wuhan-Hu-1
Timepoint	28 days after Dose 2
Population	Immunogenicity analysis set
Comparator Cohort	Solid organ transplant
Reference Cohort	Immunocompetent
• To describe the immunogenicity of a 2-dose primary vaccination with AZD1222 in adults ≥ 18 years with a 4-week dosing interval between SARS-CoV-2 naïve participants with hematopoietic stem cell transplant compared to immunocompetent participants. Estimand:	
Endpoints [a]	1) Ratio of SARS-CoV-2 specific GMT titres 2) Difference in seroresponse rates of SARS-CoV-2 specific titres (≥ 4-fold rise in titres from baseline [b])
Serotype	Wuhan-Hu-1
Timepoint	28 days after Dose 2
Population	Immunogenicity analysis set
Comparator Cohort	Hematological stem cell transplant
Reference Cohort	Immunocompetent
• To describe the immunogenicity of a 2-dose primary vaccination with AZD1222 in adults ≥ 18 years with a 4-week dosing interval between SARS-CoV-2 naïve participants with solid organ cancer patients receiving cytotoxic chemotherapy compared to immunocompetent participants. Estimand:	
Endpoints	1) Ratio of SARS-CoV-2 specific GMT titres

	2) Difference in seroresponse rates of SARS-CoV-2 specific titres (≥ 4-fold rise in titres from baseline [b])
Serotype	Wuhan-Hu-1
Timepoint	28 days after Dose 2
Population	Immunogenicity analysis set
Comparator Cohort	Solid organ cancer patients receiving cytotoxic chemotherapy
Reference Cohort	Immunocompetent
• To describe the immunogenicity of a 2-dose primary vaccination with AZD1222 in adults ≥ 18 years with a 4-week dosing interval between SARS-CoV-2 naïve participants with chronic inflammatory disorders compared to immunocompetent participants. Estimand:	
Endpoints [a]	1) Ratio of SARS-CoV-2 specific GMT titres 2) Difference in seroresponse rates of SARS-CoV-2 specific titres (≥ 4-fold rise in titres from baseline [b])
Serotype	Wuhan-Hu-1
Timepoint	28 days after Dose 2
Population	Immunogenicity analysis set
Comparator Cohort	Chronic inflammatory disorders
Reference Cohort	Immunocompetent
• To describe the immunogenicity of a 2-dose primary vaccination with AZD1222 in adults ≥ 18 years with a 4-week dosing interval between SARS-CoV-2 naïve participants with primary immunodeficiency compared to immunocompetent participants. Estimand:	
Endpoints [a]	1) Ratio of SARS-CoV-2 specific GMT titres 2) Difference in seroresponse rates of SARS-CoV-2 specific titres (≥ 4-fold rise in titres from baseline [b])
Serotype	Wuhan-Hu-1
Timepoint	28 days after Dose 2
Population	Immunogenicity analysis set
Comparator Cohort	Primary immunodeficiency
Reference Cohort	Immunocompetent
• To describe the immunogenicity of a 2-dose primary vaccination with AZD1222 in adults ≥ 18 years with a 4-week dosing interval between SARS-CoV-2 naïve participants with any immunocompromised condition compared to immunocompetent participants. Estimand:	
Endpoints [a]	1) Ratio of SARS-CoV-2 specific GMT titres 2) Difference in seroresponse rates of SARS-CoV-2 specific titres (≥ 4-fold rise in titres from baseline [b])

Serotype	Wuhan-Hu-1
Timepoint	28 days after Dose 2
Population	Immunogenicity analysis set
Comparator Cohort	Pooled immunocompromised
Reference Cohort	Immunocompetent
• To characterize the immunogenicity after a 3rd-dose in a 3 dose primary vaccination series with AZD1222 in immunocompromised adults ≥ 18 years. Estimand:	
Endpoints [a]	1) SARS-CoV-2 specific titres 2) Seroresponse of SARS-CoV-2 specific titres (≥ 4-fold rise in titres from baseline [b])
Serotype	Wuhan-Hu-1
Timepoint	28 days after the 3rd dose
Population	Immunogenicity analysis set
Cohort	Each of 5 immunocompromised cohorts and pooled immunocompromised cohorts
• To describe the immunogenicity after the 3rd dose in a 3-dose primary vaccination series with AZD1222 in adults ≥ 18 years between SARS-CoV-2 naïve immunocompromised participants compared to immunocompetent participants after a 2-dose primary vaccination. Estimand:	
Endpoints [a]	1) Ratio of SARS-CoV-2 specific GMT titres 2) Difference in seroresponse rates of SARS-CoV-2 specific titres (≥ 4-fold rise in titres from baseline [b])
Serotype	Wuhan-Hu-1
Timepoint	28 days after Dose 3 (28 Days after Dose 2 for reference cohort)
Population	Immunogenicity analysis set
Comparator Cohort	Each of 5 immunocompromised cohorts and pooled immunocompromised cohorts
Reference Cohort	Immunocompetent

[a] Immunogenicity endpoints will be analysed for both binding (anti-S) and pseudo-neutralization titres.
[b] Baseline is defined as the last collection prior to the first dose.
AE = adverse event; AESI = adverse event of special interest; GMT = geometric mean titre; MAAE = medically attended adverse event; S = spike; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2

Overall Design: This study is a Phase IV, open-label, non-randomized, multi-cohort, multicenter study of the immunogenicity and safety of AZD1222 for the prevention of COVID-19 in previously unvaccinated immunocompromised adults ≥18 years. Immuncompromised participants will receive primary vaccination with 3 IM doses of AZD1222 separated by 4 weeks and will continue to be followed to the end of the study. Immunocompetent participants will receive a third dose booster 6 months after dose 1 and will continue to be followed to the end of the study.

Disclosure Statement: This is an open-label preventive treatment study with 6 cohorts that is non-randomized.

Number of Participants: Approximately 360 SARS-CoV-2 spike and nucleocapsid seronegative participants will be enrolled to support the primary and secondary objectives of this study.

Intervention Groups and Duration: Participants will include adults ≥ 18 years with stable immunocompromising conditions, or on stable doses of immunocompromising therapeutics, and will be enrolled in the following 5 disease cohorts of approximately 60 participants each: (1) solid organ transplant; (2) hematopoietic stem cell transplant; (3) solid organ cancer patients receiving cytotoxic chemotherapy; (4) chronic inflammatory disorders; and (5) primary immunodeficiency. A sixth cohort of immunocompetent individuals will also be recruited. Participants will be allocated to the immunocompromised cohorts according to the underlying aetiology of their immunocompromised status.

Data Monitoring Committee: Not applicable.

Statistical Methods:

[redacted]

The analysis sets will be:

- All participants analysis set (including all screened participants)
- Full analysis set (including all enrolled participants)
- Safety analysis set (including all participants who have received at least one dose of AZD1222)
- Immunogenicity analysis set (including all participants in the safety analysis set who have no protocol deviations judged to have the potential to interfere with the generation or interpretation of an immune response)

The primary analysis will occur when all participants within a cohort have completed visit 8 (i.e., 28 days after the second dose; see Table 2 and Table 3). Secondary analyses of a third dose (primary series) will occur when all participants within an immunocompromised cohort have completed visit 10 (i.e., 28 days after the third dose; see Table 2). The final analysis will occur when data from all vaccinated participants are available through completion of the last study visit (see Table 2 and Table 3).

For the primary objective, without a prespecified directional hypothesis, 2-sided 95% confidence intervals will be calculated as descriptive measures for each immunogenicity endpoint. Descriptive comparisons between groups will be included in secondary analyses.

1.2 Schema

Figure 1 Study Design for Immunocompromised Participants

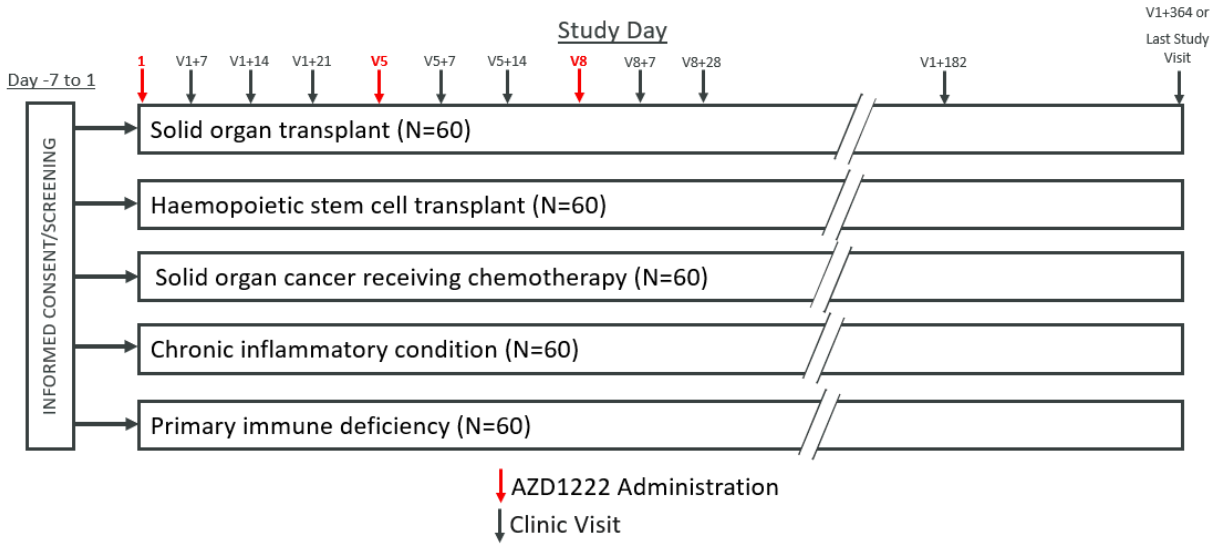
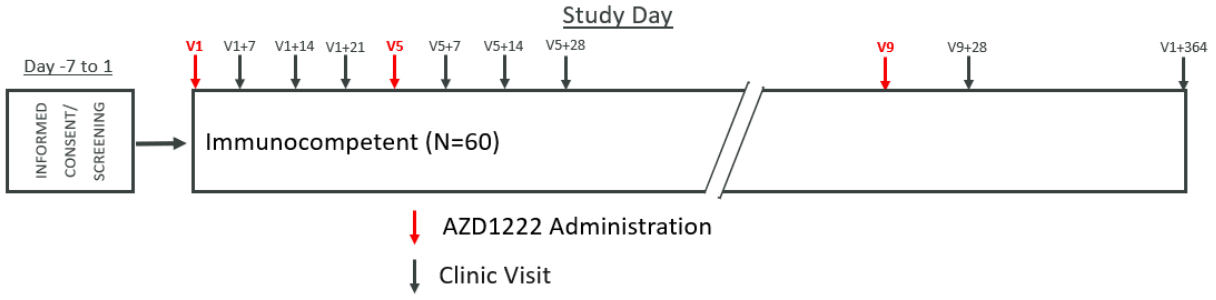


Figure 2 Study Design for Immunocompetent Participants



1.3 Schedule of Activities

The Schedule of Activities are shown in Table 1, Table 2 and Table 3.

Table 1 Schedule of Activities: Screening

Study Procedure	Day -7 to Day 1[a]	For Details See Section
Informed consent	X	5.1, Appendix A 1
Demography	X	-
Medical and surgical history	X	-
Prior and concomitant medications	X	6.5
Complete physical examination	X	8.2.1
Vital signs	X	8.2.2
Urine pregnancy test (for women of childbearing potential only)	X	8.2.3
HIV Testing (local laboratory)	X	-
Clinical safety laboratory assessments	X	8.2.3
Serious Adverse Events (SAEs)	X	8.3, Appendix B
Assessment of SARS-CoV-2 infection [b]	X	8.2.4
Test for antibody against SARS-CoV-2 (lateral flow test)	X	8.5.2
Verify eligibility criteria	X	5.1, 5.2

[a] Screening activities can occur up to 7 days prior to Visit 1. Screening activities can occur on the same day as initial vaccination (Day 1, see Table 2 and Table 3) **only if laboratory results for HIV, urine pregnancy test, complete blood count, and SARS-CoV-2 assessments are obtained prior to vaccination**. Vaccine administration cannot occur until screening safety lab results are available and verification of participant eligibility is confirmed.

[b] Local assessment of SARS-CoV-2 infection should be conducted using a nucleic acid amplification test (e.g., RT-PCR) and is required prior to vaccine administration (Day 1, see Table 2 and Table 3) in order to confirm participant eligibility (Section 8.2.4).

Table 2 Schedule of Activities: Vaccination/Follow-up Period for Immunocompromised Cohorts

Study procedure	Vaccination/Follow-up												For Details see Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8 [a]**	**V9**	**V10**	**V11**	**V12 [b]**	
Timeline (days)	**1**	**V1+7**	**V1+14**	**V1+21**	**V1+28**	**V5+7**	**V5+14**	**V5+28**	**V8+7**	**V8+28**	**V1+ 182**	**V1+ 364**	
Time window (days)	**-**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 14**	**± 30**	
General Procedures													
Verify eligibility criteria	X	-	-	-	-	-	-	-	-	-	-	-	4.1.1, 5
Medical and surgical history	X	-	-	-	-	-	-	-	-	-	-	-	-
Urine pregnancy test (WOCBP only)	X [c]	-	-	-	X [c]	-	-	X [c]	-	-	-	-	8.2.3
Prior/concomitant medication(s)	X	X	X	X	X	X	X	X	X	X	X	X	6.5
Vaccine administration (after screening activities, the activities listed above, and the pre-doses sampling activities listed below are completed)	X	-	-	-	X	-	-	X [a]	-	-	-	-	6
eDiary provided	X	-	-	-	X	-	-	X	-	-	-	-	8.3.6.1

Table 2 Schedule of Activities: Vaccination/Follow-up Period for Immunocompromised Cohorts

Study procedure	Vaccination/Follow-up												For Details see Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8** [a]	**V9**	**V10**	**V11**	**V12** [b]	
Timeline (days)	**1**	**V1+7**	**V1+14**	**V1+21**	**V1+28**	**V5+7**	**V5+14**	**V5+28**	**V8+7**	**V8+28**	**V1+ 182**	**V1+ 364**	
Time window (days)	**-**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 14**	**± 30**	
eDiary with solicited AEs returned	-	X	-	-	-	X	-	-	X	-	-	-	8.3.6.1
Safety Assessments													
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	8.2.2
Targeted physical examination	X	X	X	X	X	X	X	X	X	X	X	X	8.2.1
Unsolicited AEs	X	X	X	X	X	X	X	X	X	X	-	-	8.3
SAEs, AESIs and MAAEs	X	X	X	X	X	X	X	X	X	X	X	X [b]	8.3, Appendix B
Clinical safety laboratory assessments (local assessments)	X [c]	X	X [f]	X [f]	X [c]	X	X [f]	X [c]	X	X [f]	-	-	8.2.3
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunogenicity Assessments													

Table 2 Schedule of Activities: Vaccination/Follow-up Period for Immunocompromised Cohorts

Study procedure	**Vaccination/Follow-up**												**For Details see Section**
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8 [a]**	**V9**	**V10**	**V11**	**V12 [b]**	
Timeline (days)	**1**	**V1+7**	**V1+14**	**V1+21**	**V1+28**	**V5+7**	**V5+14**	**V5+28**	**V8+7**	**V8+28**	**V1+ 182**	**V1+ 364**	
Time window (days)	**-**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 14**	**± 30**	
Symptomatic assessment of SARS-CoV-2 infection [d]	X	X	X	X	X	X	X	X	X	X	X	X	8.2.4
Serum sample for SARS-CoV-2 serology/nAb assessments	X [c]	-	X	-	X [c]	-	X	X [c]	-	X	X	X	8.5.2
Serum sample for additional immunogenicity assays	X [c]	-	X	-	X [c]	-	X	X [c]	-	X	X	X	8.5.2
[redacted]	[redacted]												[redacted]
[redacted]	[redacted]												[redacted]
Other Laboratory Assessments													
[redacted]	[redacted]												[redacted]

Table 2 Schedule of Activities: Vaccination/Follow-up Period for Immunocompromised Cohorts

Study procedure	Vaccination/Follow-up												For Details see Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8** [a]	**V9**	**V10**	**V11**	**V12** [b]	
Timeline (days)	**1**	**V1+7**	**V1+14**	**V1+21**	**V1+28**	**V5+7**	**V5+14**	**V5+28**	**V8+7**	**V8+28**	**V1+ 182**	**V1+ 364**	
Time window (days)	**-**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 14**	**± 30**	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Immunocompromised participants will receive a third dose of AZD1222 (i.e., cohorts 1 through 5). Participants in cohorts 1 through 5 that complete V8 prior to implementation of protocol amendment 3.0 will still be eligible to receive a third dose (primary series). In this case, a repeat V8 should be completed when the third dose is administered. V9 and V10 should be based on the date of the third dose visit (i.e., V9 is 7 days after V8, V10 is 28 days after V8). If, the third dose is administered more than 28 days after visit 5, and outside the visit window due to regulatory authority and/or ethics committee approval timelines, no protocol deviation will be issued.

[b] The last study visit will be the later of the following dates: Day 365 or 6 months after the administration of the 3rd dose (primary series). SAEs, MAAEs and AESIs will be collected up to the last study visit.

[c] These samples are collected pre-dose only.

[d] Participants who become symptomatic after vaccine administration (i.e., during follow-up through last study visit) should be assessed for COVID-19 infection as defined in Section 8.2.4.

[e] These samples are to be collected only for the first 15 participants in each cohort.

[f] Only the hematology/hemostasis assessments (i.e., complete blood count) will be performed at these visits (Section 8.2.3)

AE = adverse event; AESI = adverse event of special interest; [redacted]; MAAE = medically attended adverse events; nAb = neutralizing antibody; [redacted]; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 =severe acute respiratory syndrome-coronavirus-2; [redacted] WOCBP = women of childbearing potential

Table 3 Schedule of Activities: Vaccination/Follow-up Period for Immunocompetent Participants

Study procedure	Vaccination/Follow-up											For Details see Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9 [a]**	**V10**	**V11**	
Timeline (days)	**1**	**V1+7**	**V1+14**	**V1+21**	**V1+28**	**V5+7**	**V5+14**	**V5+28**	**V1+182**	**V9+28**	**V1+364**	
Time window (days)	**-**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 30**	
General Procedures												
Verify eligibility criteria	X	-	-	-	-	-	-	-	-	-	-	4.1.1, 5
Medical and surgical history	X	-	-	-	-	-	-	-	-	-	-	-
Urine pregnancy test (WOCBP only)	X [b]	-	-	-	X [b]	-	-	-	X [b]	-	-	8.2.3
Prior/concomitant medication(s)	X	X	X	X	X	X	X	X	X	X	X	6.5
Vaccine administration (after screening activities, the activities listed above, and the pre-doses sampling activities listed below are completed)	X	-	-	-	X	-	-	-	X	-	-	6
eDiary provided	X	-	-	-	X	-	-	-	-	-	-	8.3.6.1
eDiary with solicited AEs returned	-	X	-	-	-	X	-	-	-	-	-	8.3.6.1
Safety Assessments												
Vital signs	X	X	X	X	X	X	X	X	X	X	X	8.2.2

Table 3 Schedule of Activities: Vaccination/Follow-up Period for Immunocompetent Participants

Study procedure	**Vaccination/Follow-up**											**For Details see Section**
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9 [a]**	**V10**	**V11**	
Timeline (days)	**1**	**V1+7**	**V1+14**	**V1+21**	**V1+28**	**V5+7**	**V5+14**	**V5+28**	**V1+182**	**V9+28**	**V1+364**	
Time window (days)	**-**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 30**	
Targeted physical examination	X	X	X	X	X	X	X	X	X	X	X	8.2.1
Unsolicited AEs	X	X	X	X	X	X	X	X	X	X		8.3
SAEs, AESIs and MAAEs	X	X	X	X	X	X	X	X	X	X	X	8.3, Appendix B
Clinical safety laboratory assessments (local assessments)	X [b]	X	X [e]	X [e]	X [b]	X	X [e]	X [e]	-	-	-	8.2.3
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Symptomatic assessment of SARS-CoV-2 infection [c]	X	X	X	X	X	X	X	X	X	X	X	8.2.4
Serum sample for SARS-CoV-2 serology/nAb assessments	X [b]	-	X	-	X [b]	-	X	X	X [b]	X	X	8.5.2
Serum sample for additional immunogenicity assays	X [b]	-	X	-	X [b]	-	X	X	X [b]	X	X	8.5.2

Table 3 Schedule of Activities: Vaccination/Follow-up Period for Immunocompetent Participants

Study procedure	Vaccination/Follow-up											For Details see Section
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9 [a]**	**V10**	**V11**	
Timeline (days)	**1**	**V1+7**	**V1+14**	**V1+21**	**V1+28**	**V5+7**	**V5+14**	**V5+28**	**V1+182**	**V9+28**	**V1+364**	
Time window (days)	**-**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 30**	
[redacted]												
[redacted]												
Other Laboratory Assessments												
[redacted]												
[redacted]												
[redacted]												

[a] Immunocompetent participants (i.e., cohort 6) will be eligible to receive a third dose booster 6 months after dose 1.

[b] These samples are collected pre-dose only.

[c] Participants who become symptomatic after vaccine administration (i.e., during follow-up through Day 365) should be assessed for COVID-19 infection as defined in Section 8.2.4.

[d] These samples are to be collected only for the first 15 participants in each cohort.

[e] Only the hematology/hemostasis assessments (i.e., complete blood count) will be performed at these visits (Section 8.2.3)

AE = adverse event; AESI = adverse event of special interest; [redacted]; [redacted]; MAAE = medically attended adverse events; nAb = neutralizing antibody; [redacted]; [redacted]; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 =severe acute respiratory syndrome-coronavirus-2; [redacted]; WOCBP = women of childbearing potential

2 INTRODUCTION

2.1 Study Rationale

AZD1222 has been developed to address a public health need for vaccines that can prevent COVID-19. AZD1222 is a recombinant replication-defective chimpanzee adenovirus expressing the SARS-CoV-2 spike (S) surface glycoprotein driven by the human cytomegalovirus major immediate early promoter that includes intron A with a human tissue plasminogen activator leader sequence at the N terminus. Worldwide efforts to develop effective vaccines against SARS-CoV-2 are ongoing, with several vaccines approved and others currently in clinical development. Given the extent and continued rapid pace of infection, severity of the pandemic's medical and socioeconomic impact, and the supply challenges associated with a global vaccination program, multiple vaccines are needed that can be offered to individuals regardless of underlying conditions.

AZD1222 was granted temporary authorization for the active immunization of individuals aged ≥ 18 years for the prevention of COVID-19 in the UK on 29 December 2020 and in the EU on 29 January 2021. Currently, AZD1222 has been authorized under conditional marketing authorizations or emergency use provisions in more than 90 countries and is listed for emergency use by the World Health Organization. As of 31 March 2021, the cumulative global post-marketing patient exposure (by doses distributed) to AZD1222 has been estimated to be approximately 500,000,000 doses.

Clinical studies supporting the emergency use authorizations of AZD1222 have, to date, generally excluded participants with significantly compromised immune systems. While the WHO and CDC recommend vaccination of immunocompromised individuals (CDC 2021, WHO 2021), a recent preprint article investigating BNT162b2 (the Pfizer COVID-19 vaccine) in kidney transplant patients on immunosuppressive medication showed low rates of seroresponse and humoral response (Sattler et al 2021). In addition, during post-authorization use, very rare events of serious thrombosis in combination with thrombocytopenia (including fatal events), have been observed following vaccination with AZD1222 (Greinacher et al 2021, Schultz et al 2021).

The aim of this study is to assess the immunogenicity (including both humoral and cellular mediated immunogenicity) and safety of AZD1222 for prevention of COVID-19 as a 3-dose primary vaccination series in previously unvaccinated immunocompromised adult participants. Immunocompetent participants will be eligible to receive a third dose booster 6 months after dose 1. Data are urgently needed in immunocompromised individuals as effective COVID-19 prevention would have significant impact on mortality in these patients, who are often multi-morbid.

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). SARS-CoV-2 shares more than 79% of its sequence with SARS-CoV, and 50% with the coronavirus responsible for MERS-CoV, a member of the lineage C Betacoronavirus (Lu et al 2020). The disease these patients contracted was subsequently named Coronavirus Disease 2019 (COVID-19). COVID-19 is the infectious disease caused by SARS-CoV-2. 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 of 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 coronavirus 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 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 (i.e., 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).

AZD1222 was developed for the prevention of COVID-19. AZD1222 is a recombinant replication-defective chimpanzee adenovirus expressing the SARS-CoV-2 S surface glycoprotein driven by the human cytomegalovirus major immediate early promoter that includes intron A with a human tissue plasminogen activator leader sequence at the N terminus. The clinical development program for intramuscular AZD1222 in adults currently includes 7 ongoing studies being conducted in: the UK (FIH COV001 [NCT04324606] and COV002 [NCT04400838]); Brazil (COV003 [ISRCTN89951424]); Kenya (COV004 [PACTR202005681895696]); South Africa (COV005 [NCT04444674]); the US and Latin America (D8110C00001); and Japan (D8111C00002). Primary pooled efficacy analysis data from each of these studies, except for the US and Latin America and the Kenya studies, have supported the approval of AZD1222 by several health authorities.

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

vaccines. Detail on the development and chemistry of AZD1222 is provided in the IB, Section 3.

Overall, the data from the clinical and nonclinical studies of AZD1222, and the acceptable safety and efficacy profile, support further exploration of AZD1222 in other populations. The purpose of this Phase IV, open-label, non-randomized, multi-cohort, multicenter study is to demonstrate the safety and immunogenicity of AZD1222 when administered as a 3-dose homologous primary vaccination series in previously unvaccinated immunocompromised adult participants. Immunocompetent participants will be eligible to receive a third dose booster 6 months after dose 1.

Immunocompromised patients, including cancer patients on chemotherapy, recipients of hematopoietic stem-cell transplantation, and patients with primary immunodeficiency, appear to have a higher risk of mortality due to COVID-19 complications than the general population (Kuderer et al 2020, Lee et al 2020, Robilotti et al 2020, Sharma et al 2021, Shields et al 2020). In addition, since immunosuppressed patients may be sources of prolonged viral shedding and development of variants (Aydillo et al 2020, McCarthy et al 2021), effective vaccination of these vulnerable patients may provide an additional societal benefit.

Clinical studies supporting emergency use authorizations of COVID-19 vaccines have, to date, generally excluded participants with significantly compromised immune systems. Antibody responses to vaccines are generally lower in immunocompromised patients, including those on chemotherapy, hematopoietic stem cell transplantation recipients, and patients with primary immunodeficiencies (Righi et al 2021). The timing of vaccination relative to immunosuppressive treatments, for example, may also play a role (Righi et al 2021).

Recently, an analysis was published of humoral and cellular responses in kidney transplant patients following vaccination with BNT162b2, with the abstract noting (Sattler et al 2021):

> "As opposed to all healthy vaccinees and the majority of hemodialysis patients, only 4/39 and 1/39 transplanted individuals showed IgA and IgG seroresponse at day 8 ± 1 after booster immunization with minor changes until day 23 ± 5, respectively. Although most transplanted patients mounted spike-specific T helper cell responses, frequencies were

> significantly reduced compared to controls and dialysis patients, accompanied by a broad impairment in effector cytokine production, memory differentiation and activation-related signatures. Spike-specific $CD8^+$ T cell responses were less abundant than their $CD4^+$ counterparts in healthy controls and hemodialysis patients and almost undetectable in transplant patients. Signs of alloreactivity promoted by BNT162b2 were not documented within the observation period. In summary, our data strongly suggest revised vaccination approaches in immunosuppressed patients, including individual immune monitoring for protection of this vulnerable group at risk to develop severe COVID-19."

Despite the lack of data on the effectiveness of COVID-19 vaccines in immunocompromised patients, treatment guidelines recommend COVID-19 vaccination in this population (Desai et al 2021, CDC 2021, MSK 2021). Results from the Cov-Boost trial demonstrated that a third dose booster of AZD1222 increased immunity after either mRNA or AZD1222 vaccine administration (Munro et al 2021). Additional data suggests that the efficacy after a third dose in immunocompromised participants ranges from 22 – 89% (Del Bello et al 2021, Kamar et al 2021, Karaba et al 2021). As well, certain medication may depress the immunoresponse further, as preliminary data from the OCTAVE study suggest that 72% of patients receiving rituximab fail to mount an antibody response to the spike protein (Kamar et al 2021, Karaba et al 2021, Kearns et al 2021). The common factors associated with the low seroresponse reported for some of the studies include degree of immunosuppression and age. Dosing intervals for these studies ranged from 4 – 28 weeks and the efficacy endpoints measurements varied according to the study.

These data add to the growing body of evidence that support the use of a third dose booster with AZD1222 as part of a homologous or heterologous schedule and confirm its acceptable safety profile. Accordingly, there is an unmet medical need to determine whether AZD1222 provides immunocompromised populations at high risk of COVID-19-related mortality with adequate protection against COVID-19.

There are a variety of conditions leading to, and immunosuppressive or immunomodulating therapies contributing to, an immunocompromised/immunosuppressed state. This study will include participants representing 5 cohorts of immunocompromised patients, as well as an immunocompetent cohort, to broadly reflect the range of underlying conditions and therapies. For further details on the rationales for the selections of these specific cohorts, see Section 4.2.1. Note that information on the risk of thromboembolic events in each cohort is included below due to the recent changes to the AZD1222 prescribing information in respect of thromboembolic events and thrombocytopenia.

The 5 cohorts included in this study are the following:

1. Solid Organ Transplant

Solid organ transplant patients often receive lifelong immunosuppression therapies such as calcineurin inhibitors, antiproliferative/antimetabolites and corticosteroids. Vaccine efficacy in such patients appears to be vaccine- and timing-specific (Duchini et al 2003). In a study of immunogenicity after the first dose of mRNA COVID-19 vaccines among solid organ transplant recipients, the majority of participants did not mount appreciable anti-spike antibody responses after a median of 20 days following the first dose (anti-S1 or anti–receptor-binding domain antibodies were detectable in 76 of 436 participants: 17%; 95% CI, 14%-21%) (Boyarsky et al 2021).

The risk of thromboembolic events is increased in solid organ transplant patients, most particularly in the period immediately following transplant (Alvarez-Alvarez et al 2015, Kainuma et al 2021, Kahan et al 2007).

Preliminary results from immunogenicity responses in kidney transplant recipients in the OCTAVE study show that Anti-S was detected in 61.8% patients. The results also showed that seroconversion in study participants was associated with vaccination occurring more than 1 year after transplantation, the use of calcineurin inhibitor treatment (i.e., monotherapy), and receiving BNT162b2 (Prendecki et al 2021).

2. Hematopoietic Stem Cell Transplant

A hematopoietic stem cell transplant results in immunosuppression because of the hematopoietic ablative therapy administered before the transplant, drugs used to prevent or treat graft-versus-host disease, and in some cases, from the underlying disease process necessitating transplantation (Tomblyn et al 2009). Inactivated vaccines are generally recommended to be administered at least 3 to 6 months (depending on the vaccine) after the transplant to improve antibody response (Ljungman et al 2009, AAP 2009, Desai et al 2021).

The risk of thromboembolic events is increased following hematopoietic stem-cell transplantation, most particularly in allogenic transplant patients, and the risk does not appear to decrease over time. Microangiopathic hemolytic anaemia is common in allogenic transplant patients in the weeks immediately after transplant (Munro et al 2021, Pihusch et al 2002, Zahid et al 2016).

3. Solid Organ Cancer Patients Receiving Cytotoxic Chemotherapy

Vaccination during cytotoxic chemotherapy is not recommended due to the suppressed immune system response. An exception is inactivated influenza vaccine. The recommended waiting period between cessation of therapy and administration of a vaccine is dependent on both the type of therapy and type of vaccine. For instance, the recommendation for patients on

chemotherapy with anti-B cell antibodies is 6 months or longer after cessation of therapy before being vaccinated with inactivated vaccines (Rubin et al 2014).

Cancer-associated thrombosis is a major cause of mortality in cancer patients. Cancer cells are capable of activating the coagulation cascade and other prothrombotic properties of host cells, and chemotherapy and immobilisation contribute to the increased risk (Abdol Razak et al 2018).

4. Chronic Inflammatory Disorders

Corticosteroids are commonly used in inflammatory disorders, including rheumatoid arthritis, inflammatory bowel disease, lupus, and asthma. Low to moderate chronic use of corticosteroids does not impact the efficacy of inactivated influenza vaccine (see Section 6.5). For high-dose corticosteroids and corticosteroid injection, which may reduce the immune response to vaccines, vaccination is recommended to occur 2 weeks before, or 1 week after, the injection/high-dose administration (CDC 1993).

The risk of thromboembolic events is increased in users of corticosteroids (Johannesdottir et al 2013, Lieber et al 2016) and in patients in inflammatory disorders, irrespective of treatment (Del Bello et al 2021, Desai et al 2017).

5. Primary Immunodeficiency

Primary immunodeficiencies include congenital immunodeficiency diseases such as X-linked agammaglobulinemia, severe combined immunodeficiency, and chronic granulomatous disease. The most common group of primary immunodeficiencies is primary antibody deficiencies. Antibody response to vaccination may be reduced or absent in patients with primary immunodeficiency (Sobh and Bonilla 2016).

Patients with primary immunodeficiencies (in particular those treated with immunoglobulins) are at increased risk of thrombotic events (Kamar et al 2021, Karaba et al 2021, Kearns et al 2021, Kimmig and Palevsky 2016, Ramirez et al 2014).

2.3 Benefit/Risk Assessment

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

2.3.1 Risk Assessment

The available safety profile of AZD1222 indicate that it is safe and well tolerated. A summary of safety events is presented below with additional information presented in AZD1222 IB section 5.1.

[redacted]

[redacted]

[redacted]

Table 4 Risk Assessment

[redacted]

Table 4 Risk Assessment

[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

2.3.2 Benefit Assessment

Clinical and real-world studies demonstrate that AZD1222 is efficacious in the general population and offers recipients protection from COVID-19. There is a high unmet need for a COVID-19 vaccine in immunocompromised individuals, as this population often has multiple morbidities and significant mortality risk from COVID-19. While a benefit is not guaranteed, as protection from COVID-19 may be reduced in immunocompromised recipients, individual participants may obtain protection from COVID-19. Further, information gained from this study could inform the use of AZD1222 or other COVID-19 vaccines in this population.

2.3.3 Overall Benefit: Risk Conclusion

For the safety of participants, this protocol incorporates various risk mitigation measures including appropriate inclusion and exclusion criteria, close monitoring of participants, and stopping criteria.

Taking these measures into account, the potential risks identified in association with AZD1222 are justified by the anticipated 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.

Table 5 Study Objectives and Endpoints

Primary Immunogenicity Objective	
• To characterize the immunogenicity of a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in SARS-CoV-2 naïve immunocompromised adults and immunocompetent adults ≥ 18 years. Estimand:	
Endpoints [a]	1) SARS-CoV-2 specific titres 2) Seroresponse of SARS-CoV-2 specific titres (≥ 4-fold rise in titres from baseline [b])
Serotype	Wuhan-Hu-1
Timepoints	28 days after Dose 1; 28 days after Dose 2
Population	Immunogenicity analysis set
Cohort	Each of 5 immunocompromised cohorts, pooled immunocompromised cohorts, and immunocompetent cohort
Secondary Safety Objective	
Objective	**Endpoints**
• To characterize the reactogenicity and safety of a 3-dose primary vaccination series with AZD1222 with a 4-week dosing interval in SARS-CoV-2 naïve immunocompromised adults ≥ 18 years.	• Reactogenicity: Incidence of local and systemic solicited AEs for 7 days after each dose of AZD1222 by eDiary. • Incidence of unsolicited AEs for 28 days post dose after each vaccination • Incidence of SAEs, MAAEs and AESIs from Day 1 post treatment to the last study visit. • Absolute and change from baseline [b] for safety laboratory measures.
Secondary Immunogenicity Objectives	

• To describe the immunogenicity of a 2-dose primary vaccination with AZD1222 in adults ≥ 18 years with a 4-week dosing interval between SARS-CoV-2 naïve participants with solid organ transplant compared to immunocompetent participants. Estimand:	
Endpoints [a]	1) Ratio of SARS-CoV-2 specific GMT titres 2) Difference in seroresponse rates of SARS-CoV-2 specific titres (≥ 4-fold rise in titres from baseline [b])
Serotype	Wuhan-Hu-1
Timepoint	28 days after Dose 2
Population	Immunogenicity analysis set
Comparator Cohort	Solid organ transplant
Reference Cohort	Immunocompetent
• To describe the immunogenicity of a 2-dose primary vaccination with AZD1222 in adults ≥ 18 years with a 4-week dosing interval between SARS-CoV-2 naïve participants with hematopoietic stem cell transplant compared to immunocompetent participants. Estimand:	
Endpoints [a]	1) Ratio of SARS-CoV-2 specific GMT titres 2) Difference in seroresponse rates of SARS-CoV-2 specific titres (≥ 4-fold rise in titres from baseline [b])
Serotype	Wuhan-Hu-1
Timepoint	28 days after Dose 2
Population	Immunogenicity analysis set
Comparator Cohort	Hematopoietic stem cell transplant
Reference Cohort	Immunocompetent
• To describe the immunogenicity of a 2-dose primary vaccination with AZD1222 in adults ≥ 18 years with a 4-week dosing interval between SARS-CoV-2 naïve participants with solid organ cancer patients receiving cytotoxic chemotherapy compared to immunocompetent participants. Estimand:	
Endpoints [a]	1) Ratio of SARS-CoV-2 specific GMT titres 2) Difference in seroresponse rates of SARS-CoV-2 specific titres (≥ 4-fold rise in titres from baseline [b])
Serotype	Wuhan-Hu-1
Timepoint	28 days after Dose 2
Population	Immunogenicity analysis set
Comparator Cohort	Solid organ cancer patients receiving cytotoxic chemotherapy
Reference Cohort	Immunocompetent
• To describe the immunogenicity of a 2-dose primary vaccination with AZD1222 in adults ≥ 18 years with a 4-week dosing interval between SARS-CoV-2 naïve participants with chronic inflammatory disorders compared to immunocompetent participants.	

Estimand:	
Endpoints [a]	1) Ratio of SARS-CoV-2 specific GMT titres 2) Difference in seroresponse rates of SARS-CoV-2 specific titres (≥ 4-fold rise in titres from baseline [b])
Serotype	Wuhan-Hu-1
Timepoint	28 days after Dose 2
Population	Immunogenicity analysis set
Comparator Cohort	Chronic inflammatory disorders
Reference Cohort	Immunocompetent
• To describe the immunogenicity of a 2-dose primary vaccination with AZD1222 in adults ≥ 18 years with a 4-week dosing interval between SARS-CoV-2 naïve participants with primary immunodeficiency compared to immunocompetent participants. Estimand:	
Endpoints [a]	1) Ratio of SARS-CoV-2 specific GMT titres 2) Difference in seroresponse rates of SARS-CoV-2 specific titres (≥ 4-fold rise in titres from baseline [b])
Serotype	Wuhan-Hu-1
Timepoint	28 days after Dose 2
Population	Immunogenicity analysis set
Comparator Cohort	Primary immunodeficiency
Reference Cohort	Immunocompetent
• To describe the immunogenicity of a 2-dose primary vaccination with AZD1222 in adults ≥ 18 years with a 4-week dosing interval between SARS-CoV-2 naïve participants with any immunocompromised condition compared to immunocompetent participants. Estimand:	
Endpoints [a]	1) Ratio of SARS-CoV-2 specific GMT titres 2) Difference in seroresponse rates of SARS-CoV-2 specific titres (≥ 4-fold rise in titres from baseline [b])
Serotype	Wuhan-Hu-1
Timepoint	28 days after Dose 2
Population	Immunogenicity analysis set
Comparator Cohort	Pooled immunocompromised
Reference Cohort	Immunocompetent
• To characterize the immunogenicity after a 3rd-dose in a 3 dose primary vaccination series with AZD1222 in immunocompromised adults ≥ 18 years. Estimand:	
Endpoints [a]	1) SARS-CoV-2 specific titres 2) Seroresponse of SARS-CoV-2 specific titres (≥ 4-fold rise in titres from baseline [b])

Serotype	Wuhan-Hu-1
Timepoint	28 days after the 3rd dose
Population	Immunogenicity analysis set
Cohort	Each of 5 immunocompromised cohorts and pooled immunocompromised cohorts
• To describe the immunogenicity after the 3rd dose in a 3-dose primary vaccination series with AZD1222 in adults ≥ 18 years between SARS-CoV-2 naïve immunocompromised participants compared to immunocompetent participants after a 2-dose primary vaccination. • Estimand:	
Endpoints [a]	1) Ratio of SARS-CoV-2 specific GMT titres 2) Difference in seroresponse rates of SARS-CoV-2 specific titres (≥ 4-fold rise in titres from baseline [b])
Serotype	Wuhan-Hu-1
Timepoint	28 days after Dose 3 (28 Days after Dose 2 for reference cohort)
Population	Immunogenicity analysis set
Comparator Cohort	Each of 5 immunocompromised cohorts and pooled immunocompromised cohorts
Reference Cohort	Immunocompetent
Exploratory Objectives	
Objective	**Endpoints**
• [redacted]	• [redacted]

	[redacted]
• To characterize the immunogenicity after a 3rd-dose booster vaccination of AZD1222, administered 6 months after dose 1 of a 2-dose primary vaccination with AZD1222, in immunocompetent adults ≥ 18 years. Estimand:	
Endpoints [a]	1) SARS-CoV-2 specific titres 2) Seroresponse of SARS-CoV-2 specific titres (≥ 4-fold rise in titres from baseline [b])
Serotype	Wuhan-Hu-1
Timepoint	6 months after the 3rd dose
Population	Immunogenicity analysis set
Cohort	Immunocompetent cohort

[a] Immunogenicity endpoints will be analyzed for both binding (anti-S) and pseudo-neutralization titres.
[b] Baseline is defined as the last collection prior to the first dose.

[redacted]

4 STUDY DESIGN

4.1 Overall Design

This study is a Phase IV, open-label, non-randomized, multi-cohort, multicenter study of the immunogenicity and safety of AZD1222 for the prevention of COVID-19 in previously unvaccinated immunocompromised adults ≥ 18 years. Immunocompromised participants will receive a primary vaccination series with 3 IM doses of AZD1222 separated by 4 weeks and will be followed to the end of the study. Immunocompetent participants will receive a third dose booster 6 months after dose 1 and will continue to be followed to the end of the study.

A total of approximately 360 SARS-CoV-2 nucleocapsid seronegative participants that have been screened and judged to be eligible for the study will be enrolled. The study will include adults ≥ 18 years with stable immunocompromising conditions or on stable doses of immunocompromising therapeutics, enrolled in 5 disease cohorts of approximately 60 participants each:

1. Solid organ transplant
2. Hematopoietic stem cell transplant

3. Solid organ cancer patients receiving cytotoxic chemotherapy
4. Chronic inflammatory disorders
5. Primary immunodeficiency

A sixth cohort of immunocompetent individuals will also be recruited. Participants will be allocated to the immunocompromised cohorts according to the underlying aetiology of their immunocompromised status (Section 5.1.2). The Sponsor will monitor recruitment status across all cohorts (including the immunocompetent cohort) on an ongoing basis in order to ensure balanced geographic and age representation.

All participants will receive 2 intramuscular doses of AZD1222 (5×10^{10} viral particles), separated by 4 weeks, on Day 1 and Day 29, and followed for to the last study visit (see Table 2 and Table 3). Immunocompromised participants will receive a third dose (primary vaccination series) 4 weeks or more after dose 2 with AZD1222 and will continue to be followed to the end of the study. Immunocompetent participants will be eligible to receive a third dose booster 6 months after dose 1 and will continue to be followed to the end of the study. All participants who have received at least one dose of AZD1222 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. There will be no follow-up on participants who have not received AZD1222, regardless of reason.

Immunogenicity [redacted] will be assessed in serum samples collected pre-dose on the day of each vaccination (baseline levels before vaccination), 14 days after doses 1 and 2, 28 days after dose 3, and as per the Schedule of Activities (see Section 1.3).

All participants will be given a thermometer, tape measure, and a proprietary eDiary application designed for use with a smart device with instructions for use. Follow-up visits will take place as per the Schedule of Activities (Section 1.3). All participants will be assessed for local and systemic AEs, physical examination, review of eDiaries, and use of concomitant medications according to the time points as detailed in the Schedule of Activities (Section 1.3). Blood will also be taken for safety and immunological assessments.

Safety will be assessed for the duration of the study. Immunocompromised participants will be asked to report on solicited AE signs and symptoms for 7 days following each vaccination. Immunocompetent participants will be asked to report on solicited AE signs and symptoms for 7 days following the first and second dose of study vaccine administration. An eDiary will be used to collect information on the timing and severity of the solicited signs and symptoms.

Unsolicited AEs will be recorded for 28 days post dose after each vaccination. SAEs, MAAEs, and AESIs will be recorded through to the final study visit. Occurrence of COVID-19 in the trial will be reported as a safety event, including monitoring of the potential risk of vaccine-induced enhanced disease as an AE of special interest (see Appendix F). Detailed information will be collected in a standard way and reported on a specific case report form. COVID-19 will be diagnosed and treated as per standard medical practice. Experimental treatments for COVID-19 are permitted. Symptomatic participants may be regularly contacted over the phone for safety monitoring until symptom resolution.

4.1.1 Screening Visit

All potential participants will be screened, which may take place up to 7 days prior to Day 1 (see Section 1.3). Screening activities can occur on the same day as vaccination only if laboratory results for HIV, urine pregnancy test, complete blood count, and SARS-CoV-2 assessments are obtained. Vaccine administration cannot occur until screening safety lab results are available.

Informed consent will be obtained before screening/enrollment. If written consent is obtained, the procedures specified in the Schedule of Activities (see Section 1.3) will be undertaken including a medical history, physical examination, height and weight, and concomitant medications, and clinical safety laboratory assessments (biochemistry and hematology).

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 pregnancy 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 screening visit and again when all results from the screening visit have been received. Decisions to exclude the participant from enrollment or to withdraw a participant from the study will be at the discretion of the Investigator.

4.1.2 Vaccination Visit

Participants will be considered enrolled upon administration of the investigational product. 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 urine pregnancy test will need to be obtained from WOCBP before vaccination. Baseline blood samples will be obtained before the first vaccination.

Participants will receive one dose of AZD1222 with 5×10^{10} viral particles (nominal)[1] administered by intramuscular injection on 3 occasions (see Section 6.2.1 for details on administration).

All participants will be given an axillary thermometer, tape measure, and a proprietary eDiary application with instructions for use to report on solicited signs and symptoms for 7 days following vaccination. Immunocompromised participants are not required to report solicited AEs following the third dose booster (see Table 3).

4.1.3 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 eDiary and blood tests at these time points as detailed in the Schedule of Activities (Section 1.3). Blood will also be taken for 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 method until the last study visit in order to collect information on any SAEs/MAAEs/AESIs and event of SARS-CoV-2 infection, which includes: 1) hospital admissions associated with COVID-19; 2) intensive care unit admissions associated with COVID-19; and 3) deaths associated with COVID-19.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Study Design and Participant Population

The participant population includes adults ≥ 18 years that are immunocompromised. Participants are allowed to be on stable immunosuppressive or immunomodulating medications in order to provide real-world evidence in this group.

There are a variety of conditions leading to, and immunosuppressive or immunomodulating therapies contributing to, an immunocompromised/immunosuppressed state. Due to possible variation in the immune response to AZD1222 and safety considerations relevant to specific conditions/therapies, participants representing 5 cohorts of immunocompromised patients, as well as a sixth cohort of immunocompetent individuals, were chosen for this study. Patients with HIV are not included in this study as they were included in prior studies of AZD1222 and other COVID-19 vaccines. To date there are preliminary data available on immune responses in these cohorts.

[1] Corresponding to not less than 2.5×10^8 infectious units

The 5 immunosuppressed cohorts are described in Section 5.1.2. The solid cancer on cytotoxic chemotherapy, hemopoietic stem-cell transplantation, and solid organ transplant cohorts were chosen to provide results applicable to large real-world populations. The mixed cohort of patients with chronic inflammatory conditions was chosen to reflect the variation in treatments that can lead to an immunocompromised state. For this cohort, enrollment of a proportion of participants that are receiving biological immunosuppressing medications is planned. The fifth cohort of participants are those with primary immune deficiency. Primary immune deficiency diseases, while rare, are increasing in incidence and are an understudied population.

The sixth cohort includes immunocompetent individuals. Consistent with the study populations included in the US and Latin America (D8110C00001) study and the University of Oxford sponsored COV studies, participants included in this cohort cannot be immunosuppressed/immunodeficient or have severe/uncontrolled comorbidities (mild/moderate well-controlled comorbidities are allowed). To reflect the real world and improve feasibility, no upper age limit was applied to any of the cohorts.

For the primary and secondary objectives, those enrolled in the study must test negative for SARS-CoV-2 nucleocapsid protein antibody during screening. Pregnant/breastfeeding women will be excluded from participation in the study. Persons who have previously received any other investigational product for the prevention of COVID-19 will be excluded from participation in this study.

4.2.2 Rationale for Study Endpoints

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

The primary analysis will occur when all participants within a cohort have completed visit 8 (i.e., 28 days after the second dose; see Table 2 and Table 3). Secondary analyses of third dose (primary series) will occur when all participants within an immunocompromised cohort have completed visit 10 (i.e., 28 days after the third dose; see Table 2). The final analysis will occur when data from all vaccinated participants are available through completion of the last study visit (see Table 2 and Table 3).

For the primary objective, without a prespecified directional hypothesis, 2-sided 95% confidence intervals will be calculated as descriptive measures for each immunogenicity endpoint.

The primary immunogenicity endpoints in this study are analogous to those used for evaluating the immunogenicity of AZD1222 in a pivotal Phase 3 efficacy study. Given that an immunological correlate of protection has yet to be defined, the assessment of humoral immunogenicity through (1) binding antibodies to SARS-CoV-2 (spike, receptor binding

domain), and (2) neutralizing antibodies (pseudo-neutralization assay) are considered the best predictors of immune response to vaccination.

The primary immunogenicity endpoints of interest in this study are:

- Antibody titre
- Seroresponse, defined as ≥ 4-fold increase in the antibody titre from baseline (pre-dose 1)

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. Geometric mean fold rise over baseline values (GMFR) will be reported along with all GMT analyses.

Additionally, cell mediated immunogenicity assessments including intracellular cytokine staining to investigate the induction of cluster of differentiation 4 and 8 (CD4/CD8) cells specific to the S protein (and T helper 1 and 2 [T_h1/T_h2] balance of these cells) will be measured. To understand if immunocompromising conditions can affect the B cell receptor and T cell receptor repertoire (a measurement of the breadth and depth of the cellular immune response), immunosequencing will be conducted in an exploratory endpoint.

The secondary safety endpoints include:

- Incidence of local and systemic solicited AEs for 7 days after each dose of AZD1222 by eDiary
- Incidence of unsolicited AEs for 28 days post dose after each vaccination
- Incidence of SAEs, MAAEs and AESIs from Day 1 post treatment to last study visit (see Table 2 and Table 3)

Solicited AEs will be collected for 7 days after each dose of AZD1222 for the immunocompromised participants, a period that has proven adequate to describe reactogenicity events in previous vaccine studies. Other safety endpoints to be collected include unsolicited AEs, SAEs, MAAEs, AESIs and clinical safety laboratory assessments. AESIs were selected to include terms identified by the Brighton Collaboration involving events associated with vaccination in general (SPEAC 2020).

The study is not powered to demonstrate differences in SARS-CoV-2 infections and COVID-19 between cohorts.

Assessment of AZD1222 immunogenicity and safety will begin immediately after Dose 1. To align with other studies in the development plan, immunogenicity will be assessed ≥ 15 days

after the second dose of study intervention (as this time period is still considered necessary for the vaccine to induce protective immune responses in this population).

4.3 Justification of Dose

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

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 protocol waivers or exemptions, are 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 at the time of signing the informed consent.

Type of Participant

2. Able to understand and comply with study requirements/procedures based on the assessment of the investigator.

3. Signed informed consent obtained before conducting any study-related procedures.

Reproduction

4. 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 Day 1
   - Use one highly effective form of birth control for at least 28 days prior to Day 1 and agree to continue using one highly effective form of birth control through 60 days following administration of the last dose of AZD1222. 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
   - Postmenopausal:
     - For women aged < 50 years, postmenopausal is defined as having both:
       - A history of ≥ 12 months amenorrhea prior to first dosing, 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, postmenopausal is defined as having a history of ≥ 12 months amenorrhea prior to first dosing, 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]	Combined (oestrogen- and progestogen-containing hormonal contraception)

Barrier Methods	Hormonal Methods
Bilateral tubal occlusion Vasectomized partner [b] Sexual abstinence [c]	Oral (combined pill) Intravaginal Transdermal (patch) Progestogen-only hormonal contraception a) Oral b) Injectable c) 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

Informed Consent

5. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form and in the protocol.

5.1.2 Cohort-Specific Inclusion Criteria

If a participant meets the inclusion criteria for more than one cohort then the Sponsor should be contacted to determine enrollment as soon as possible.

Solid organ transplant

– Participants with heart, lung, kidney, or liver transplant, and are stable on immunosuppressants (defined as no change in dose in the previous 4 weeks). Transplant of more than one organ is acceptable.

Hematopoietic stem cell transplant

– Participants with autologous (up to 6 months after transplantation) or allogeneic stem cell transplant who are immunosuppressed, with no evidence of active graft-versus-host disease, at least one month after the procedure.

Cancer patients on chemotherapy

– Participants with solid tumors (except breast cancer), histologically diagnosed, who were undergoing intravenous cytotoxic chemotherapy within the last 6 months, who received at least 1 cycle prior to cytotoxic chemotherapy, and have a life expectancy of longer than 3 months.

Chronic inflammatory conditions

– Participants with chronic inflammatory conditions, including those on immunosuppressant medications, can be recruited such as the following: rheumatoid arthritis, systemic sclerosis, mixed connective tissue disorder, systemic lupus erythematosus, or inflammatory bowel disease. The following conditions are specifically excluded: multiple sclerosis and peripheral demyelinating disease.

Primary immune deficiency

– Examples include combined granulomatous disorder, SCID, common variable immunodeficiency.

Immunocompetent:

– No confirmed or suspected immunosuppressive or immunodeficient state.

– No use of immunosuppressant medication within the past 1 month (≥ 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 AZD1222). The following exceptions are permitted: topical/inhaled steroids or short-term oral steroids (course lasting ≤ 14 days).

– No receipt of immunoglobulins and/or any blood products within 3 months prior to administration of AZD1222 or expected receipt during the period of study follow up.

– No severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder, and neurological illness, as judged by the Investigator (mild/moderate well-controlled comorbidities are allowed such as diabetes mellitus, hypertension, asthma, and chronic obstructive pulmonary disease).

The Sponsor reserves the right to reposition the primary cohort group of any participant, in discussion with the Investigator.

5.2 Exclusion Criteria

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

Medical Conditions

1. History of allergic disease or reactions likely to be exacerbated by any component of AZD1222.
   c) Active infection with SARS-CoV-2 as confirmed locally by nucleic acid amplification test (e.g., RT-PCR).
   d) Known current or past laboratory-confirmed SARS-CoV-2 infection.

e) Significant infection or other acute illness, including fever (temperature > 37.8°C) on the day prior to or day of first dosing.

f) Thrombocytopenia with platelet count ≤ 75,000 x 10^9/microliter based on complete blood count test at screening visit.

g) HIV-positive participants based on a positive ELISA test performed at screening visit.

h) Apart from participants in cohort 2, 3 below (cancer patients), history of primary malignancy except for:

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

   a. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease

   b. Adequately treated uterine cervical carcinoma in situ without evidence of disease

   c. Localized prostate cancer

i) Clinically significant bleeding disorder (e.g., factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following intramuscular injections or venipuncture, according to Investigator's judgement.

j) History of cerebral venous sinus thrombosis (CVST).

k) History of Guillain-Barré syndrome, any demyelinating disease, or any other neuroimmunological disease.

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

Prior Concomitant Therapy

m) Receipt of, or planned receipt of, licensed or unlicensed SARS-CoV-2 or COVID-19 vaccine, or investigational product. Note: For participants in the study who become hospitalized with COVID-19, receipt of licensed treatment options and/or participation in investigational treatment studies is permitted.

n) Receipt of any vaccine (licensed or investigational) within 30 days prior to and after administration of AZD1222. Thirty (30) days after the last vaccination, other routine vaccinations are permitted as clinically indicated.

Other Exclusions

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

p) 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.

q) 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.

r) Previous enrollment in the present study.

s) 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

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

5.3 Lifestyle Considerations

Participants must follow the contraception requirements outlined in Section 5.1.

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Only 2 rescreenings are 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

6.1 Study Intervention Administered

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

6.1.1 Investigational Product

The investigational product is described in Table 7.

Table 7 Investigational Product

Intervention Name	AZD1222
Type	Vaccine
Dose formulation	[redacted]
Unit dose strength(s)	[redacted]
Dosage level(s)	[redacted]
Route of administration	Intramuscular
Use	Experimental
IMP and NIMP	IMP
Sourcing	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
Current/Former name or alias	Previous clinical documentation: ChAdOx1 nCoV-19 Current trade name: Vaxzevria

IMP = Investigational medical product; NIMP = non-investigational medical product; w/v = weight/volume

AZD1222 will be supplied by the Sponsor as a vial solution for injection. It is a sterile, clear to slightly opaque solution, practically free from visible particles, with a label-claim volume of 5 mL and can provide up to ten 0.5mL doses.

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

6.1.2 Dosing Instructions

Each participant will receive 3 doses of AZD1222 with the first dose administered on Day 1, the second dose administered 28 days after dose 1, and the third dose administered 28 days after dose 2 for the immunocompromised participants (see Table 2). Immunocompetent participants will receive a third dose booster 6 months after dose 1 (see Table 3).

It is recommended that AZD1222 is administered as an IM injection into the deltoid of the nondominant arm. Other injection sites may be used if necessary.

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

6.2 Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., 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 AZD1222 must be prepared by the Investigator's or site's designated investigational product manager using aseptic technique. Each dose is prepared by withdrawing 0.5 mL from a vial of AZD1222 in a sterile syringe.

AZD1222 does not contain preservatives. Each vial must be assigned a beyond-use-date of 6 hours at 2-25°C (36-77°F) from first needle puncture of the AZD1222 vial, after which any unused portion must be discarded.

Once an AZD1222 dose is drawn into a syringe for administration, the dose must be administered within the 6-hour beyond-use-date of the vial, otherwise a new dose must be prepared from a new vial.

6.3 Measures to Minimize Bias: Randomization and Blinding

Not applicable

6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date, and time if applicable, of dose

administered in the clinic 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(s) or vaccines taken from signed informed consent through post-study follow-up (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 (see Section 1.3) must be recorded in the eCRF along with the information listed below. All non-study COVID vaccinations received should be recorded. Study drug, vitamins and/or herbal supplements should not 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 COVID19 after receiving AZD1222 should be treated with licensed medications and interventions according to standard of care. This should be recorded as an AE/SAE (Section 8.3). All routine vaccinations are permitted beginning > 30 days after last dose of AZD1222. Non-study vaccines are to be recorded in eCRF.

Given the study population, the following medications are expected to be prescribed in some cohorts:

- Glucocorticoids at any dose
- Other systemically administered drugs with significant immunosuppressive activity, including, but not limited to: azathioprine, tacrolimus, cyclosporine, methotrexate, sulfasalazine, rituximab or cytotoxic chemotherapy
- Immunoglobulins and/or any blood product
- Anticoagulants

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 necessarily require withdrawal from the study, but may determine a participant's eligibility to receive a second or third dose or evaluability in the per-protocol analysis set.

- Investigational products indicated for the treatment of SARS-CoV-2 or COVID-19

  Note: For participants who become hospitalized with COVID-19, receipt of licensed treatment options and/or participation in investigational treatment studies is permitted.
- Experimental vaccinations, other than 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 in the study to be followed for safety reporting and all assessments. Non-study vaccines are to be recorded in eCRF
- Receipt of any vaccine (licensed or investigational) within 30 days prior to and after administration of AZD1222 (e.g., Dose 1, Dose 2, Dose 3). Thirty (30) days after the third vaccination, other routine vaccinations are permitted as clinically indicated.

If a participant receives a prohibited concomitant medication, the Investigator should, in consultation with the Sponsor, evaluate any potential impact on receipt of AZD1222 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.

6.6 Dose Modification

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

6.7 Interventional 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 Investigational Product

Participants will receive 3 doses of open-label AZD1222 in this study. A participant must not receive the first, second or third dose of AZD1222 if any of the following has occurred:

- Withdrawal of consent after signing informed consent
- Participant meets one or more of the exclusion criteria or fails to meet all inclusion criteria for study participation
- Laboratory-confirmed SARS-CoV-2 infection or HIV infection
- Participant is pregnant or nursing
- Any allergic reaction including anaphylaxis that is assessed as related to AZD1222
- Any SAE assessed as related to AZD1222
- Any AE that, in the judgment of the site investigator, is related to AZD1222 and may jeopardize the safety of the study participant (e.g., a thrombotic event after Dose 1).
- Receipt of a prohibited concomitant medication that may jeopardize the safety of the study participant or interpretation of the data

Each participant who has received at least one dose of AZD1222 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 AZD1222, regardless of reason, will not be followed.

In the event that a study participant receives a licensed and/or authorized COVID-19 vaccine, the Sponsor 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 Study Suspension or Termination

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

Any death, SAE, or other safety finding assessed as related to AZD1222 that in the opinion of the Sponsor may preclude further administration of AZD1222.

Inability to recruit for the study if insufficient participants are able to be enrolled.

7.3 Participant Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons.

A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (e.g., 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-specified analysis is complete.

7.4 Lost to Follow-up

A participant will be considered lost to follow-up if he/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 described in Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Schedule of Activities (Section 1.3). Protocol 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 (e.g., 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 and, e.g., signs of thrombosis or thrombocytopaenia. Each clinically significant abnormal finding following vaccination will be recorded as an AE.

All physical examinations will be performed by a licensed healthcare provider (e.g., 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.

Situations in which vital sign results should be reported as AEs are described in Section 8.3.

8.2.3 Clinical Safety Laboratory Assessments

Blood samples for determination of clinical chemistry and hematology 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. See Appendix D, and Section 8.3.8.1for information on decrease in platelets from baseline.

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

The laboratory safety variables in Table 8 will be assessed.

Table 8 Local Laboratory Safety Variables

Hematology/Hemostasis (blood)	**Clinical Chemistry (serum/plasma)**
Hemoglobin	Creatinine
Leukocyte count	Bilirubin, total
Leukocyte differential count (absolute count)	Alkaline phosphatase (ALP)
Platelet count	Aspartate aminotransferase (AST)
	Alanine aminotransferase (ALT)
Clotting (serum/plasma)	
Activated partial thromboplastin time	
Prothrombin time	
Fibrinogen	
D-dimer	

For women participants of childbearing potential, a urine sample for pregnancy testing will be collected and a urine pregnancy test will be performed at screening, and a negative test result must be confirmed, before each vaccination. Urine pregnancy tests for β-human chorionic gonadotropin may be performed at the site using a licensed test (dipstick).

See Appendix D for additional investigations to be performed if a venous thromboembolic and thrombocytopenia event occurs.

8.2.4 COVID-19 Assessments

Participants should be tested for SARS-CoV-2 infection at the screening visit using a nucleic acid amplification test (e.g., RT-PCR). After vaccine administration, participants who become symptomatic with at least one of the qualifying symptoms listed below (Table 9) during follow-up (i.e., through the last study visit; see Table 2 and Table 3) will be instructed to call the trial staff who will then advise on how to proceed with clinical testing for COVID-19. When participants are suspected of being infected with SARS-CoV-2, based on their symptoms and a positive nucleic acid amplification test (e.g., RT-PCR), they will be advised to contact hospitals/clinics designated for treatment of COVID-19 as per local guidance.

Table 9 COVID-19 Qualifying Symptoms

Participant must present with at least one of the following symptoms to qualify for clinical COVID-19 testing	
Duration	**Symptom**
No minimum duration	Fever
	Shortness of breath
	Difficulty breathing
Must be present for ≥ 2 consecutive days	Chills
	Cough
	Fatigue
	Muscle aches
	Body aches
	Headache
	New loss of taste
	New loss of smell
	Sore throat
	Congestion
	Runny nose
	Nausea
	Vomiting
	Diarrhoea

Adapted from (CDC 2020)

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 an eDiary (Section 8.3.6) 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 eDiary 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 authorised representative).

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

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

Solicited AEs will be recorded for 7 days after each study vaccination for the immunocompromised participants (see Table 2). Solicited AEs will be recorded for 7 days after the first and second dose of study vaccine in the immunocompetent participants (see Table 3). Immunocompromised participants are not required to report solicited AEs following the third dose booster (see Table 3).

If a solicited AE is not resolved within the eDiary 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.

Unsolicited AEs will be recorded for 28 days after each study vaccination (see Table 2 and Table 3).

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.

All participants will be followed up after the administration of the first dose of study vaccine.

SAEs, MAAEs and AESIs will be collected up to the last study visit. 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 IP 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 IP (yes or no)
- Action taken with regard to IP
- 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 used for all unsolicited events with an assigned severity grading including Grade 5.

8.3.3 Causality Collection

The investigator should assess causal relationship between IP 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

Results from Clinical Study Protocol-mandated vital signs and laboratory safety assessments will be summarised in the Clinical Study Report.

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

If deterioration in a vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an SAE or MAAE, and the associated vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical rather than the laboratory term (e.g., anaemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.3.6 [redacted]

[redacted]

Table 10 List of Predefined Solicited Adverse Events for Reactogenicity Assessment

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

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

[b] Swelling and redness must be ≥ 0.25 inches (≥ 0.6 centimetres) in diameter.

8.3.6.1 Solicited AE eDiary

On Day 1, participants (or, if applicable, their caregiver, surrogate, or legally authorized representative) will be given an oral thermometer, tape measure, and access to the Solicited AE eDiary, 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 AZD1222, the timing and severity of local and systemic solicited AEs, if applicable, and whether medication was taken to relieve the symptoms.

8.3.6.2 Severity Assessment of Solicited AEs

Severity will be assessed for solicited AEs by the participant (or, if applicable, their caregiver, surrogate, or legally authorised representative) according to toxicity grading scales modified and abridged from the US FDA guidance (FDA 2007) as defined in Appendix E. Because solicited AEs are expected to occur after vaccination, they will not be assessed for relationship to AZD1222.

8.3.7 Medically Attended Adverse Events

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

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

8.3.8 Adverse Events of Special Interest

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

AESIs are events of scientific and medical interest specific to the further understanding of the AZD1222 safety profile and require close monitoring and rapid communication by the investigators to the sponsor. AESIs for AZD1222 are based on Brighton Collaboration case definitions (SPEAC 2020), clinical experience, and scientific interest. A list of events is provided in (Appendix F)

An AESI can be serious or nonserious. All AESIs will be recorded in the eCRF. If any AESI occurs in the course of the study, investigators or other site personnel will inform the appropriate Sponsor representatives within one day (i.e., immediately but **no later than 24 hours)** of when he or she becomes aware of it.

[redacted]

[redacted]

8.3.8.3 [redacted]

8.3.9 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation. This evaluation will be conducted at the local laboratory.

Hy's Law criteria: AST or ALT ≥ 3 × ULN together with total bilirubin ≥ 2 × ULN, where no other reason, other than the study intervention, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevation in transaminases must precede or be coincident with (i.e., on the same day) the elevation in total bilirubin, but there is no specified timeframe within which the elevations in transaminases and total bilirubin must occur.

Any occurrences of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 × 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 and confirmed as Hy's Law should be reported to the Sponsor as an SAE within 1 day with a serious criteria of 'Important medical event'.

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.

8.3.10 COVID-19 Assessment

This study will describe the incidence of COVID-19 adverse events reported from Day 1 to last study visit (see Table 2 and Table 3).

COVID-19 is defined as a positive symptomatic illness that is confirmed by a nucleic acid amplification test (e.g., RT-PCR). 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 diagnosis 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 (see Section 8.2.4). Events will be reported as AEs/SAEs.

If a participant presents at clinic visit with COVID symptoms, diagnosis will be confirmed as described in Section 8.2.4.

8.3.11 COVID-19 Severity

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

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 breaths per minute, heart rate ≥ 125 beats per minute, oxygen saturation ≤ 93% on room air at sea level, or partial pressure of oxygen to fraction of inspired oxygen ratio < 300 mm Hg)
- Respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation)
- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction
- Admission to an intensive care unit
- Death

8.3.12 Reporting of Serious Adverse Events

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

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

Once the investigators or other site personnel indicate an AE is serious in the Electronic Data Capture system, an automated email alert is sent to the designated 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 a SAE, see Appendix B.

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

8.3.13 Pregnancy

All pregnancies and outcomes of pregnancy with conception dates following administration of study intervention should be reported to the Sponsor except for:

- If the pregnancy is discovered before the study participant has received any study intervention
- Pregnancies in the partner of male participants

8.3.13.1 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 (Section 5.2). Pregnancy itself is not regarded as an AE unless there is a suspicion that AZD1222 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 (**i.e., 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 Sponsor Patient Safety data entry site **within 1 or 5 calendar days** for SAEs (Section 8.3.12) and **within 30 days** for all other pregnancies that are not associated with 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.

8.3.14 Medication Error

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate Sponsor representatives within **1 day (**i.e., 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 (Section 8.3.12) and **within 30 days** for all other medication errors.

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

8.4 Overdose

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

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

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

If an overdose occurs in the course of the study, the investigator or other site personnel inform appropriate Sponsor representatives immediately, but **no later than 24 hours** 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 one or 5 calendar days** for overdoses associated with an SAE (Section 8.3.12) and **within 30 days** for all other overdoses.

8.5 Human Biological Samples

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

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

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 (e.g., exploratory immunology), such as systems serology and profiling of B- and T-cell repertoire. The results from further analysis may be reported in an appendix of 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 Clinical Study Report.

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). [redacted]

[redacted]

8.5.2.2 SARS-CoV-2 Neutralizing Antibody Assessments

Serum samples to measure SARS-CoV-2 neutralizing antibody levels will be collected from participants according to the timepoints specified in the Schedule of Activities (Section 1.3). Authorized laboratories will measure neutralizing antibodies to SARS-CoV-2 using validated wild-type neutralization assay and/or pseudo-neutralization assays. Neutralizing antibody assessments to emerging variants may also be investigated.

8.5.2.3

[redacted]

8.5.2.4 Monitoring for Asymptomatic Infection

Blood samples will be collected according to the Schedule of Activities (Section 1.3) for SARS-CoV-2 serology testing to determine if participants have had an asymptomatic infection.

8.5.2.5

[redacted]

8.5.3 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6 Human Biological Sample Biomarkers

8.6.1 Collection of Mandatory Samples for Biomarker Analysis

Samples for biomarker research are required and will be collected from all participants. Details for sample collection, processing, and testing will be provided in the Laboratory Manual.

8.6.1.1 Blood Sample for Targeted Sequencing Analyses

A blood sample for targeted sequencing analyses will be collected on Day 1 in accordance with the Schedule of Activities (Section 1.3) and will be tested to investigate predictive markers of safety per Appendix D. If, for any reason, the blood sample is not drawn on Day 1, it may be taken at any time up until the last study visit.

8.6.1.2 Blood Samples for Other Biomarker Analyses

[redacted]

8.6.2 [redacted]

[redacted]

8.7 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable in this study.

8.8 Health Economics

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

There is no formal statistical hypothesis testing planned for this study. Descriptive analyses will support evaluation of safety and immunogenicity and qualitative comparison between groups.

9.2 Sample Size Determination

[redacted]

Table 11 indicates the probability of observing one 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 cohort. With the sample size of 60 participants per cohort, at least 1 participant with an AE of incidence rate of 1% can be detected with probability of about 45%.

Table 11 Probability of Detecting One or More Safety Events in AZD1222

Event Frequency	Probability (> 1 event)	
	N=60	N=300
≥ 10% (Very Common)	> 99%	> 99%
≥ 1% (Common)	45.3%	95.1%
≥ 0.1% (Uncommon)	5.8%	25.9%
≥ 0.01% (Rare)	0.6%	3.0%

The primary objective of this study is to characterize anti-SARS-CoV-2 antibody (specific binding (anti-S) and pseudo-neutralization) levels in serum following 2 IM doses of AZD1222 administered 28 days apart in immunocompromised individuals.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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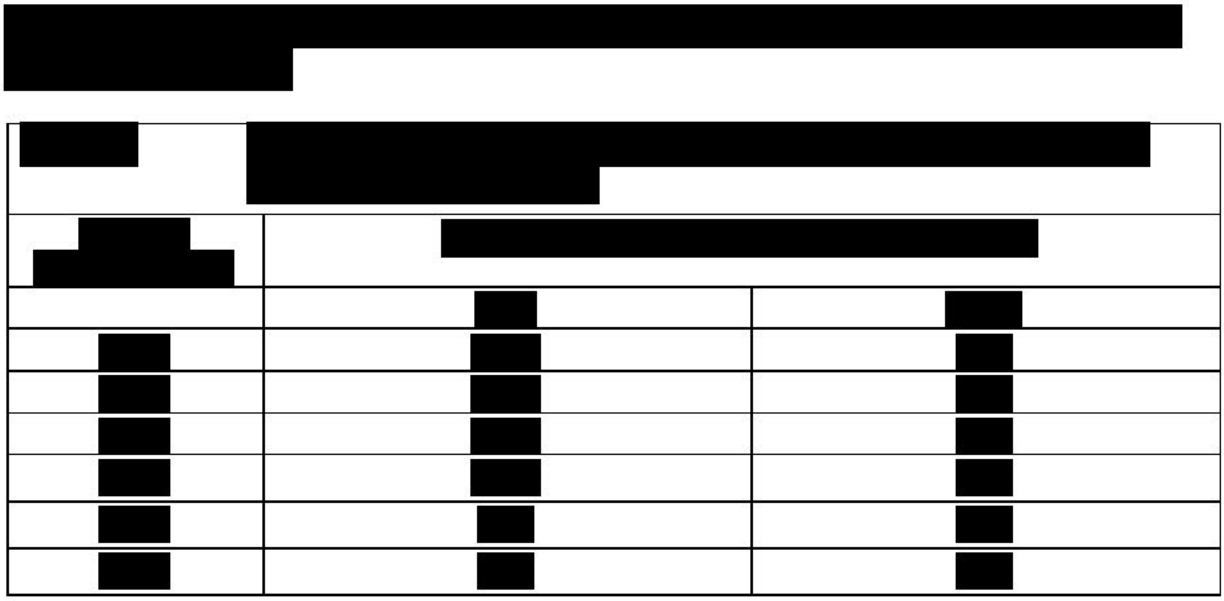

9.3 Populations for Analyses

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 enrolled participants, i.e., those participants who meet screening eligibility criteria. 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 who have received at least one dose of AZD1222. 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.
Immunogenicity analysis set	The immunogenicity analysis set will include all participants in the safety analysis set who have no protocol deviations judged to have the potential to interfere with the generation or interpretation of an immune response. Examples of such protocol violations will be documented in the Statistical Analysis Plan. This will be the primary analysis set for all immunogenicity analyses.

9.4 Statistical Analyses

9.4.1 General Considerations

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 any primary analyses.

The primary analysis will occur when all participants within a cohort have completed visit 8 (i.e., 28 days after the second dose; see Table 2 and Table 3). Analyses of pooled immunocompromised cohorts will be performed only after all immunocompromised cohorts have completed visit 8 (i.e., 28 days after the second dose; see Table 2) for this analysis.

Secondary analyses of third dose (primary series) will occur when all participants within an immunocompromised cohort have completed visit 10 (i.e., 28 days after the third dose; see Table 2). Analyses of pooled immunocompromised cohorts will be performed only after all immunocompromised cohorts have completed their visit 10 (i.e., 28 days after the third dose; see Table 2) for this analysis.

The final analysis will occur when data from all vaccinated participants are available through completion of the last study visit (see Table 2 and Table 3).

[redacted]

9.4.2 Immunogenicity

The immunogenicity endpoints of interest in this study are:

- Antibody titre

- Seroresponse, defined as ≥ 4-fold increase in the antibody titre from baseline (pre-dose 1)

For the primary objective (to characterize the immunogenicity of a 2-dose primary vaccination series with AZD1222), without a prespecified directional hypothesis, 2-sided 95% CIs will be calculated as descriptive measures for each immunogenicity endpoint.

The geometric mean titre and seroresponse rate will be summarised descriptively by cohort, timepoint and antibody for the immunogenicity population (Table 16). GMFR will be reported along with all GMT analyses.

Table 16 Primary Immunogenicity Summaries to be Completed (by Cohort, Timepoint, Antibody, and Endpoint)

Cohort	Day	Antibody	Endpoint	Index
Organ Transplant	28 post 1st dose[a]	Pseudo	GMT	1
			Seroresponse	2
		Anti-S	GMT	3
			Seroresponse	4
	28 post 2nd dose[a]	Pseudo	GMT	5
			Seroresponse	6
		Anti-S	GMT	7
			Seroresponse	8
Hemopoietic Stem Cell Transplantation	28 post 1st dose[a]	Pseudo	GMT	9
			Seroresponse	10
		Anti-S	GMT	11
			Seroresponse	12
	28 post 2nd dose[a]	Pseudo	GMT	13
			Seroresponse	14
		Anti-S	GMT	15
			Seroresponse	16
Solid organ cancer on chemotherapy	28 post 1st dose[a]	Pseudo	GMT	17
			Seroresponse	18
		Anti-S	GMT	19
			Seroresponse	20
	28 post 2nd dose[a]	Pseudo	GMT	21
			Seroresponse	22
		Anti-S	GMT	23
			Seroresponse	24

Table 16 Primary Immunogenicity Summaries to be Completed (by Cohort, Timepoint, Antibody, and Endpoint)

Cohort	Day	Antibody	Endpoint	Index
Inflammatory	28 post 1st dose[a]	Pseudo	GMT	25
			Seroresponse	26
		Anti-S	GMT	27
			Seroresponse	28
	28 post 2nd dose[a]	Pseudo	GMT	29
			Seroresponse	30
		Anti-S	GMT	31
			Seroresponse	32
Primary Immunodeficiency	28 post 1st dose[a]	Pseudo	GMT	33
			Seroresponse	34
		Anti-S	GMT	35
			Seroresponse	36
	28 post 2nd dose[a]	Pseudo	GMT	37
			Seroresponse	38
		Anti-S	GMT	39
			Seroresponse	40
Pooled Immunocompromised	28 post 1st dose[a]	Pseudo	GMT	41
			Seroresponse	42
		Anti-S	GMT	43
			Seroresponse	44
	28 post 2nd dose[a]	Pseudo	GMT	45
			Seroresponse	46
		Anti-S	GMT	47
			Seroresponse	48
Healthy (Immunocompetent)	28 post 1st dose[a]	Pseudo	GMT	49
			Seroresponse	50
		Anti-S	GMT	51
			Seroresponse	52
	28 post 2nd dose[a]	Pseudo	GMT	53
			Seroresponse	54
		Anti-S	GMT	55
			Seroresponse	56

[a] Samples collected for the Day 28 post 1st dose must be collected on or before the date of 2nd dose to be included in analyses. Similarly, samples collected for the Day 28 post 2nd dose must be collected on or before the date of 3rd dose to be included in analyses.

Secondary immunogenicity antibody responses will be performed similarly to the primary immunogenicity analyses at 28 days post 3rd dose (Table 17).

Table 17 Secondary Immunogenicity Summaries to be Completed (by Cohort, Timepoint, Antibody, and Endpoint)

Cohort	Day	Antibody	Endpoint	Index
Organ Transplant	28 post 3rd dose	Pseudo	GMT	1
			Seroresponse	2
		Anti-S	GMT	3
			Seroresponse	4
Hemopoietic Stem Cell Transplantation	28 post 3rd dose	Pseudo	GMT	5
			Seroresponse	6
		Anti-S	GMT	7
			Seroresponse	8
Solid organ cancer on chemotherapy	28 post 3rd dose	Pseudo	GMT	9
			Seroresponse	10
		Anti-S	GMT	11
			Seroresponse	12
Inflammatory	28 post 3rd dose	Pseudo	GMT	13
			Seroresponse	14
		Anti-S	GMT	15
			Seroresponse	16
Primary Immunodeficiency	28 post 3rd dose	Pseudo	GMT	17
			Seroresponse	18
		Anti-S	GMT	19
			Seroresponse	20
Pooled Immunocompromised	28 post 3rd dose	Pseudo	GMT	21
			Seroresponse	22
		Anti-S	GMT	23
			Seroresponse	24
Healthy (Immunocompetent) [a]	28 post 3rd dose	Pseudo	GMT	25
			Seroresponse	26
		Anti-S	GMT	27
			Seroresponse	28

[redacted]

[redacted]

[redacted]

[redacted]

For secondary analyses to be completed at the time of primary analysis, immunocompromised groups will be compared to the immunocompetent group at 28 days post 2nd dose using both geometric mean titre ratios and seroresponse rate differences, with corresponding 2-sided 95% CIs (Table 19).

Table 19 Secondary Immunogenicity Comparisons to be Completed at the time of the Primary Analysis (by Cohorts Compared, Timepoint, Antibody, and Endpoint)

Comparator Cohort	Reference Cohort	Day	Antibody	Endpoint	Index
Organ Transplant	Healthy (Immunocompetent)	28 post 2nd dose	Pseudo	GMT Ratio	1
				Difference in Seroresponse	2
			Anti-S	GMT Ratio	3
				Difference in Seroresponse	4

Comparator Cohort	Reference Cohort	Day	Antibody	Endpoint	Index
Hemopoietic Stem Cell Transplantation	Healthy (Immunocompetent)	28 post 2nd dose	Pseudo	GMT Ratio	5
				Difference in Seroresponse	6
			Anti-S	GMT Ratio	7
				Difference in Seroresponse	8
Solid organ cancer on chemotherapy	Healthy (Immunocompetent)	28 post 2nd dose	Pseudo	GMT Ratio	9
				Difference in Seroresponse	10
			Anti-S	GMT Ratio	11
				Difference in Seroresponse	12
Inflammatory	Healthy (Immunocompetent)	28 post 2nd dose	Pseudo	GMT Ratio	13
				Difference in Seroresponse	14
			Anti-S	GMT Ratio	15
				Difference in Seroresponse	16
Primary Immunodeficiency	Healthy (Immunocompetent)	28 post 2nd dose	Pseudo	GMT Ratio	17
				Difference in Seroresponse	18
			Anti-S	GMT Ratio	19
				Difference in Seroresponse	20
Pooled Immunocompromised	Healthy (Immunocompetent)	28 post 2nd dose	Pseudo	GMT Ratio	21
				Difference in Seroresponse	22
			Anti-S	GMT Ratio	23
				Difference in Seroresponse	24

For secondary analyses to be completed at the time of the secondary analysis, immunogenicity responses at 28 days post 3rd dose in immunocompromised groups will be compared to the immunogenicity responses at 28 days post 2nd dose in the immunocompetent group using both geometric mean titre ratios and seroresponse rate differences, with corresponding 2-sided 95% CIs (Table 20).

Table 20 Secondary Immunogenicity Comparisons to be Completed at the time of the Secondary Analysis (by Cohorts Compared, Timepoint, Antibody, and Endpoint)

Comparator Cohort	Reference Cohort	Day	Antibody	Endpoint	Index
Organ Transplant	Healthy (Immunocompetent)	Comparator: 28 post 3rd dose Reference: 28 post 2nd dose	Pseudo	GMT Ratio	1
				Difference in Seroresponse	2
			Anti-S	GMT Ratio	3
				Difference in Seroresponse	4
Hemopoietic Stem Cell Transplantation	Healthy (Immunocompetent)	Comparator: 28 post 3rd dose Reference: 28 post 2nd dose	Pseudo	GMT Ratio	5
				Difference in Seroresponse	6
			Anti-S	GMT Ratio	7
				Difference in Seroresponse	8
Solid organ cancer on chemotherapy	Healthy (Immunocompetent)	Comparator: 28 post 3rd dose Reference: 28 post 2nd dose	Pseudo	GMT Ratio	9
				Difference in Seroresponse	10
			Anti-S	GMT Ratio	11
				Difference in Seroresponse	12
Inflammatory	Healthy (Immunocompetent)	Comparator: 28 post 3rd dose Reference: 28 post 2nd dose	Pseudo	GMT Ratio	13
				Difference in Seroresponse	14
			Anti-S	GMT Ratio	15
				Difference in Seroresponse	16
Primary Immunodeficiency	Healthy (Immunocompetent)	Comparator: 28 post 3rd dose Reference: 28 post 2nd dose	Pseudo	GMT Ratio	17
				Difference in Seroresponse	18
			Anti-S	GMT Ratio	19
				Difference in Seroresponse	20
Pooled Immunocompromised	Healthy (Immunocompetent)	Comparator: 28 post 3rd dose Reference: 28 post 2nd dose	Pseudo	GMT Ratio	21
				Difference in Seroresponse	22
			Anti-S	GMT Ratio	23
				Difference in Seroresponse	24

[redacted]

9.4.3 Safety

The safety of AZD1222 will primarily be assessed by:

- Incidence of unsolicited AEs for 28 days after each dose of AZD1222
- Incidence of SAEs from Day 1 post treatment through the last study visit
- Incidence of AESIs from Day 1 post-treatment through the last study visit
- Incidence of MAAEs from Day 1 post-treatment through the last study visit
- Incidence of local and systemic solicited AEs for 7 days after each dose of AZD1222
- Description of safety laboratory assessments, including coagulation and platelet assay results

AE severity will be graded according to a revised toxicity grading scale from the US FDA guidance (FDA 2007) see Appendix F and coded using the most recent version of the Medical Dictionary for Regulatory Activities. AEs will be presented for each cohort 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. Summaries will present the relationship to IP as assessed by the investigator, maximum intensity, seriousness, and death.

A listing will cover details for each AE.

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

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 clinical study protocol (CSP) and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Sponsor will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with the Sponsor.

The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), 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 a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the [Investigator's Brochure or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial Disclosure

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

A 3 Informed Consent Process

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

Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.

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

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 authorised 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 authorised 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.

An independent Neurology Expert Committee for AESIs will be available to review and provide advice on request about their diagnosis and causality assessment of selected neurological AESIs occurring in the AZD1222 clinical development program. Details on the composition and operation of this committee are described in the Neurology Expert Committee for AESIs Charter.

An independent Hematology Expert Panel will be available to review and provide advice on requests about their diagnosis and causality assessment of selected thrombosis with thrombocytopenia AESIs occurring in the AZD1222 clinical development program. Details on the composition and operation of this committee are described in the Hematology Expert Panel 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 (e.g., 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 (e.g., 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 (e.g., 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 GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

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

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

A 10 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before

submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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

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

B 1 Definition of Adverse Events

An adverse event 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 (e.g., an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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

B 2 Definition of Serious Adverse Events

A serious adverse event is an AE occurring during any study phase (i.e., 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 jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse Events (AEs) for **malignant tumours** reported during a study should generally be assessed as **Serious AEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious AE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require 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 product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., 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 jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

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

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- 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 4.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for

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

B 3 A Guide to Interpreting the Causality Question

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

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

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

Is this a recognised feature of overdose of the drug?
Is there a known mechanism?

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

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

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

B 4 Medication Error

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

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

Medication error includes situations where an error.

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

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

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

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

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

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

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

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

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

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

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 outlined in the informed consent.

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, the samples are disposed of or repatriated as appropriate, 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, e.g., 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, e.g., 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

[redacted]

[redacted]

Appendix E Toxicity Grading Scales for Solicited Adverse Events

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

Table 21: Clinical Abnormalities, Local Reactions to Injectable Product

Table 22: Clinical Abnormalities, Vital Signs

Table 23: Clinical Abnormalities, Systemic (General or Illness)

Table 21 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 eDiary.

ER: emergency room.

Table 22 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 23 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 F [redacted]

[redacted]

Table 24 [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
	[redacted]
	[redacted]
	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
	[redacted]
	[redacted]

	[redacted]
	[redacted]

Table 25 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
Neuroinflammatory disorders	Acute disseminated encephalomyelitis, including site specific variants (e.g., non-infectious encephalitis, encephalomyelitis, myelitis, radiculomyelitis)
	Cranial nerve disorders, including paralyses/paresis (e.g., 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
Other	Antiphospholipid syndrome
	Autoimmune hemolytic 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 G Abbreviations

Abbreviation or special term	Explanation
AEs	Adverse events
AESIs	Adverse events of special interest
[redacted]	[redacted]
ChAdOx1 nCoV-19	AZD1222 when initially developed by the University of Oxford
COVID-19	Coronavirus disease 2019
CSP	Clinical Study Protocol
CVST	Cerebral venous sinus thrombosis
DIC	Disseminated intravascular coagulation
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titre
HSCT	Hematopoietic stem-cell transplantation
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH/GCP	International Council of Harmonisation/Good Clinical Practice
IM	Intramuscular
I(M)P	Investigational (Medical) Product
IRB/IEC	Institutional Review Board/ Independent Ethics Committee
ISTH	International Society on Thrombosis and Haemostasis
MAAEs	Medically attended adverse event
MERS	Middle East respiratory syndrome
MSD	Meso Scale Discovery
nAb	Neutralizing antibody
[redacted]	[redacted]
RBD	Receptor binding domain
RT-PCR	Reverse transcriptase-polymerase chain reaction
S	Spike protein
SAEs	Serious adverse events
SARS-CoV-2	Severe acute respiratory syndrome-coronavirus-2
SCID	Severe combined immunodeficiency
[redacted]	[redacted]
VAED	Vaccine-associated enhanced disease
VAERD	Vaccine-associated enhanced respiratory disease

Abbreviation or special term	Explanation
WOCBP	Women of childbearing potential

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