PASS Protocol	
Active substance	AZD1222
Study code	D8111R00003
Version number	1.0
Date	10 March 2021

A Phase IV Non-Interventional Enhanced Active Surveillance Study of Adults Vaccinated with AZD1222

Marketing Authorisation Holder

Marketing authorisation holder	AstraZeneca AB, 151 85 Södertälje, Sweden
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PASS INFORMATION

Title	A Phase IV Non-Interventional Enhanced Active Surveillance Study of Adults Vaccinated with AZD1222
Protocol version identifier	1.0
Date of last version of protocol	Not applicable
EU PAS register number	Study not yet registered
Active substance	AZD1222
Medicinal product	COVID-19 Vaccine AstraZeneca
Product reference	CCI
Procedure number	Not yet assigned
Marketing authorisation holder	AstraZeneca AB
Joint PASS	No
Research question and objectives	The purpose of this study is to assess the safety and tolerability of AZD1222 in adults vaccinated in real-world settings. **Primary objective:** • To estimate the incidence of SAEs, AESIs, and medically-attended AEFIs after at least one IM dose of AZD1222 for 3 months after vaccination. **Secondary objectives:** • To estimate the incidence of SAEs, AESIs, and medically-attended AEFIs after at least one IM dose of AZD1222 for up to 18 months after vaccination. • To estimate the incidence of SAEs, AESIs, and medically-attended AEFIs after at least one IM dose of AZD1222 in participants by age group. • To estimate the incidence of SAEs, AESIs, and medically-attended AEFIs after at least one IM dose of AZD1222 in participants with select comorbidities. • To estimate the frequency of select pregnancy outcomes in women vaccinated with AZD1222 during pregnancy or within 45 days of the estimated conception date. • To estimate the frequency of select outcomes at birth and up to 12 months of age in neonates/infants born to mothers vaccinated with AZD1222 during pregnancy or within 45 days of the estimated conception date.
Countries of study	Germany, France, Spain, and Sweden
Author	PPD PPD, AstraZeneca AB

AESI, adverse event of special interest; AEFI, adverse event following immunisation; EU, European Union; IM, intramuscular; PAS, post-authorisation studies; PASS, post-authorisation safety study; SAE, serious adverse event.

1. TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	adverse event
ADR	adverse drug reaction
AEFI	adverse event following immunisation
AESI	adverse event of special interest
AZD1222	COVID-19 Vaccine AstraZeneca
COVID-19	coronavirus disease 2019
CRO	contract research organisation
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GDPR	General Data Protection Regulation
GPP	Good Pharmacoepidemiology Practices
HCP	healthcare provider
CCI	CCI
IEC	Independent Ethics Committee
IM	intramuscular
MedDRA	Medical Dictionary for Regulatory Activities
PASS	post-authorisation safety studies
CCI	CCI
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
UK	United Kingdom
US	United States
VAED	vaccine-associated enhanced disease
VAERD	vaccine-associated enhanced respiratory disease
WHO	World Health Organization

2. RESPONSIBLE PARTIES

AstraZeneca Responsible Parties

Role	Name, title, qualifications
Scientific lead, epidemiology	PPD
Operational lead	PPD
Study physician	PPD
Statistician	PPD
Pharmacovigilance	PPD
Pharmacovigilance	PPD
Pharmacovigilance	PPD
Pharmacovigilance	PPD

PPD

Principal Investigator and Coordinating Investigators

The list of study investigators, qualifications, and contact information will be maintained as a standalone document and updated as needed throughout the study (Appendix A).

3. ABSTRACT

Title. A Phase IV Non-Interventional Enhanced Active Surveillance Study of Adults Vaccinated with AZD1222, version 1.0, 10 March 2021

Rationale and background. Safe, effective, and accessible vaccines are needed to prevent COVID-19. The COVID-19 Vaccine AstraZeneca (AZD1222) is a recombinant replication defective chimpanzee adenovirus expressing the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein. In Phase II and III clinical studies, AZD1222 helped to prevent COVID-19. Health authorities in some regions, including the European Union (EU) and United Kingdom (UK) have approved AZD1222, and AstraZeneca (the Sponsor) expects additional authorisations in 2021. In addition to ongoing Phase III studies and routine pharmacovigilance, the benefit-risk profile of AZD1222 will be assessed in regional post-authorisation studies. This Phase IV enhanced safety surveillance study will collect safety and tolerability data from adults vaccinated with AZD1222 in real-world

settings in the European Union (Germany, France, Spain, and Sweden). A similar study will be conducted in the UK, and, pending approval, in the United States.

Research question and objectives. The purpose of this study is to assess the safety and tolerability of AZD1222 in adults vaccinated in real-world settings.

The primary objective of the study is to estimate the incidence of serious adverse events (SAEs), adverse events of special interest (AESIs), and medically-attended adverse events following immunisation (AEFIs) after at least one intramuscular (IM) dose of AZD1222 for 3 months after vaccination.

The secondary objectives are:

- To estimate the incidence of SAEs, AESIs, and medically-attended AEFIs after at least one IM dose of AZD1222 for up to 18 months after vaccination.
- To estimate the incidence of SAEs, AESIs, and medically-attended AEFIs after at least one IM dose of AZD1222 in participants by age group.
- To estimate the incidence of SAEs, AESIs, and medically-attended AEFIs after at least one IM dose of AZD1222 in participants with select comorbidities.
- To estimate the frequency of select pregnancy outcomes in women vaccinated with AZD1222 during pregnancy or within 45 days of the estimated conception date.
- To estimate the frequency of select outcomes at birth and up to 12 months of age in neonates/infants born to mothers vaccinated with AZD1222 during pregnancy or within 45 days of the estimated conception date.

Study design: This is a Phase IV real-world, observational, non-interventional, prospective cohort study of adults vaccinated with AZD1222. The study will use an innovative digital platform (study app and web portal) as well as a traditional call centre to collect participant responses to a series of health and well-being questionnaires over an 18-month period. Investigators and study personnel will have real-time access to enrolment trends and reported adverse events (AEs) via an investigator dashboard within the digital platform.

Research coordinators at vaccination sites will invite vaccinated adults to join the study. Participants can enrol at the vaccination site with assistance from a research coordinator or can take home a study information brochure and enrol within 28 days after the first dose of AZD1222. Research coordinators and the study call centre will be available to assist with enrolment and informed consent, as needed. Electronic consent using the study app will be an option where permitted.

Participants using the digital platform will set up a secure account, complete the enrolment questionnaires, and provide details of their vaccination to confirm eligibility. Non-digital participants will complete the enrolment questionnaires and confirm eligibility at a

vaccination site or by a telephone call to the call centre. After enrolment, participants will be contacted to complete follow-up questionnaires at timed intervals over an 18-month period after their first AZD1222 dose. Digital participants will receive push notifications or emails and non-digital participants will receive phone calls. Participants can also submit unscheduled AE reports through the digital platform and call centre.

Adverse events reported by participants will be reviewed, followed-up, and assessed by study personnel. Participants will grant permission for study personnel to contact their healthcare providers and obtain medical records. All participant data will be coded and personal identifying information removed before the data is transferred to the Sponsor's safety database. Role-based permissions will ensure only authorised personnel can view data and records containing participant identities.

Population: Participants will be adults ≥ 18 years of age who receive the AZD1222 vaccine in Germany, France, Spain, or Sweden and are able and willing to consent to participate in the study. This study will enrol all eligible participants but, in particular, will seek to enrol older adults, with a target of 50% of participants being aged ≥ 65 years. Other subpopulations of interest include pregnant women, women who are breastfeeding, immunocompromised persons, persons with an autoimmune or inflammatory disorder, and frail persons with comorbidities. The study will also aim for an approximately equal enrolment of male and female participants.

Variables: The information to be collected at enrolment will include: AZD1222 vaccination details (date, batch/lot), exposure to any other vaccines, demographics, and relevant medical history (select comorbidities, smoking history, prior COVID-19 infection), pregnancy status, breastfeeding status, and CCI [redacted].

The primary and secondary objectives assessing the safety and tolerability of AZD1222 (up to 3 months, up to 18 months, by age group, and in participants with select comorbidities) will be measured by the incidence of SAEs, AESIs, and medically-attended AEFIs.
Medically-attended AEFIs are AEs after immunisation leading to consultation with a medical doctor, hospitalisation, or an emergency room visit. The additional secondary objectives (estimating the frequency of select pregnancy outcomes and neonatal/infant outcomes) will be measured by events within the AESI medical concept "Pregnancy outcome – Maternal" (including spontaneous abortions, stillbirths, and preterm births) and within the AESI medical concept "Pregnancy outcome – Neonates" (including major congenital malformations and infants small for gestational age).

Participants will be contacted for safety outcomes at 1, 4, 8, and 14 weeks and 6, 9, 12, and 18 months after the first AZD1222 dose. Participants will be contacted to complete CCI [redacted] at 4.5 months and 15 months after the first dose.

Data sources: The main data sources for the study will be participants and their medical records. Vaccination details will be verified by a vaccination card, batch/lot number, and/or using a regional vaccination register. Participants will report all study outcomes using the study app, web portal, or call centre. Participants can also select a proxy to communicate on their behalf: a caregiver, family member, or other trusted individual. Participants will be asked for an emergency contact in case of death or incapacity.

Study size: Target enrolment is 15,000 participants.

Data analysis: This study is descriptive in nature. Distribution of participant characteristics at baseline will be described through point estimates (mean, median, rates or proportions) and the corresponding variability (interquartile range, 95% confidence intervals). The primary analysis will only include participants who enrolled within 7 days of vaccination with the first dose of AZD1222. For the primary and secondary analyses, the cumulative incidence of each outcome measure will be computed as the proportion of participants who reported an event among all AZD1222-vaccinated participants who completed each study-defined follow-up interval, as well as among all AZD1222-vaccinated participants regardless of completion status, in combination with corresponding patient-years. Where feasible, incidence rates will be calculated. Subgroup evaluations and sensitivity analyses will also be performed.

Milestones: The start of data collection (first participant enrolled) is planned for May 2021. Quarterly interim reports are planned, beginning at 1 month after the first enrolment and then every 3 months thereafter. The Sponsor expects to complete the final study report in 2024.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Table 1 Study Milestones

Milestone	Planned dates [a]
Start of data collection	May 2021
Interim report with data cut-off 1 month after first enrolment	Q3 2021
Interim report with data cut-off 3 months after first enrolment	Q3 2021
Interim reports every 3 months thereafter	TBD
Registration in the EU PAS register	TBD
End of data collection	Q4 2023
Final report of study results	Q2 2024

[a] Planned dates are the Sponsor's best estimates based on circumstances at the time of writing the protocol. As the COVID-19 pandemic is a dynamic situation, milestones and dates may be amended if recruitment forecasts change.

EU, European Union; PAS, post-authorisation studies; TBD, to be determined.

6. RATIONALE AND BACKGROUND

6.1 Rationale for the Study

Safe, effective, and accessible vaccines to prevent COVID-19 are needed to reduce the spread of the disease and mitigate the public health and socioeconomic crises that have resulted from the pandemic. The COVID-19 Vaccine AstraZeneca (AZD1222; formerly ChAdOx1 nCoV-19) helped prevent COVID-19 in Phase II and III clinical studies. Health authorities in some regions, including the European Union (EU) and United Kingdom (UK), have approved AZD1222, and AstraZeneca (the Sponsor) expects additional authorisations in 2021. In addition to ongoing Phase III studies, the Sponsor will continue to assess the benefit-risk profile of AZD1222 through post-authorisation safety studies and routine pharmacovigilance.

This Phase IV, non-interventional, enhanced active safety surveillance study will collect safety and tolerability data from 15,000 participants vaccinated with AZD1222 in real-world settings in 4 countries in the EU: Germany, France, Spain, and Sweden. A similar study will be conducted in the UK (10,000 participants), and, pending approval, a third similar study in the United States (US; 15,000 participants).

Germany, France, Spain, and Sweden have each developed a national vaccine deployment plan, including establishing priority groups (ECDC 2020a) In general, these plans prioritise elderly people, healthcare workers, and persons with certain comorbidities (ECDC 2020a). Until the vaccine supply is sufficient for universal vaccination, prioritisation recommendations will impact which populations are vaccinated in real-world settings (ECDC 2020b).

6.2 AZD1222 Background

Coronaviruses are enveloped viruses with positive-sense single-stranded RNA genomes. The spike glycoprotein is a coronavirus surface protein involved in receptor binding and mediating virus entry into host cells during infection (Li 2016). AZD1222 is a recombinant replication defective chimpanzee adenovirus expressing the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike glycoprotein. Development of AZD1222 was initiated by the University of Oxford with subsequent transfer of development activities to the Sponsor.

The University of Oxford is investigating the safety, immunogenicity, and efficacy of AZD1222 in 4 ongoing controlled (meningococcal vaccine or placebo) clinical studies. A pooled, interim analysis of the 4 ongoing studies found AZD1222 to have an acceptable safety profile in adults following vaccination (Voysey et al 2021). The incidence of serious adverse events (SAEs) and adverse events of special interest (AESIs) was similar between the analysis groups (participants receiving AZD1222 vs controls) and all 4 of the non-COVID-19 deaths (1 in an AZD1222 recipient and 3 in control recipients) were considered unrelated to the study product (Voysey et al 2021). Local and systemic reactogenicity of AZD1222 was tolerable and decreased in incidence and severity in older adults and after the second dose (Voysey et al

2021). Common local symptoms have included injection-site pain and tenderness and common systemic symptoms have included fatigue and headache (Folegatti et al 2020, Ramasamy et al 2021, Barrett et al 2020).

In addition to the Oxford studies, the Sponsor has 3 ongoing clinical studies, including a Phase III double-blind placebo-controlled study. All clinical studies to date have enrolled participants ≥ 18 years of age.

To date, there are no important identified risks for AZD1222. The important potential risks of AZD1222 are nervous system disorders (including immune-mediated neurological conditions), vaccine-associated enhanced disease (VAED) (including vaccine-associated enhanced respiratory disease [VAERD]), and anaphylaxis. Areas of missing information include use of AZD1222 during pregnancy and while breastfeeding, use in immunocompromised persons, use in frail persons with comorbidities, use in persons with autoimmune or inflammatory disorders, interactions with other vaccines, and long-term safety.

7. RESEARCH QUESTION AND OBJECTIVES

The purpose of this study is to assess the safety and tolerability of AZD1222 in adults vaccinated in real-world settings. Table 2 lists the study objectives and outcome measures.

Table 2 Study Objectives and Outcome Measures

Objective	Outcome measure(s)
Primary objective	
To estimate the incidence of SAEs, AESIs, and medically-attended AEFIs after at least one IM dose of AZD1222 for 3 months after vaccination.	• Serious adverse events • Adverse events of special interest • Medically-attended AEFIs
Secondary objectives	
To estimate the incidence of SAEs, AESIs, and medically-attended AEFIs after at least one IM dose of AZD1222 for up to 18 months after vaccination.	• Serious adverse events • Adverse events of special interest • Medically-attended AEFIs
To estimate the incidence of SAEs, AESIs, and medically-attended AEFIs after at least one IM dose of AZD1222 in participants by age group.	• Serious adverse events • Adverse events of special interest • Medically-attended AEFIs
To estimate the incidence of SAEs, AESIs, and medically-attended AEFIs after at least one IM dose of AZD1222 in participants with select comorbidities.	• Serious adverse events • Adverse events of special interest • Medically-attended AEFIs
To estimate the frequency of select pregnancy outcomes in women vaccinated with AZD1222 during pregnancy or within 45 days of the estimated conception date.	Events within the AESI medical concept "Pregnancy outcome – Maternal", including: • Spontaneous abortions • Stillbirths • Preterm births

Table 2 Study Objectives and Outcome Measures

Objective	Outcome measure(s)
To estimate the frequency of select outcomes at birth and up to 12 months of age in neonates/infants born to mothers vaccinated with AZD1222 during pregnancy or within 45 days of the estimated conception date.	Events within the AESI medical concept "Pregnancy outcome – Neonates", including: • Major congenital malformations • Small for gestational age
Exploratory objectives	
CCI	CCI
CCI	CCI
CCI	CCI

Serious adverse events, AESIs, and medically-attended AEFIs are defined in Section 10.1.
AE, adverse event; AEFI, adverse event following immunisation; AESI, adverse event of special interest; CCI ; CCI ; IM, intramuscular; CCI ; SAE, serious adverse event.

8. RESEARCH METHODS

8.1 Definitions

In this protocol, the following terms are used as defined here:

Participants: Individuals who have enrolled in the study.

Vaccination site: Any location where a participant was administered an AZD1222 vaccination (Section 8.5.1). Vaccination sites are not study investigators.

Research coordinators: Research coordinators will assist with study recruitment and enrolment at vaccination sites. Research coordinators will generally be employees or contractors of the vaccination site. Where this is not feasible, study personnel acting on behalf of the Sponsor will contract with the vaccination site to permit a research coordinator not otherwise associated with the site to be present at the site.

Healthcare provider: Healthcare providers (HCPs) are medically qualified individuals who treat participants for a health issue during the study. Healthcare providers are not study investigators. For some participants, their vaccination site could also be their HCP.

Investigator(s): Investigators are responsible for the overall conduct of the study.

8.2 Study Design

This is a Phase IV real-world, observational, non-interventional, prospective cohort study of adults who receive the AZD1222 vaccine. Vaccine recipients ≥ 18 years old will be recruited

for the study at vaccination sites in Germany, France, Spain, and Sweden. Awareness of the study may be raised through social media and traditional media (television, print, and radio).

In this study, vaccination sites will not act as traditional study investigators and will not be responsible for participant screening or safety follow-up. Rather, participants will self-enrol in the study using the study app, web portal, or call centre and will submit answers to study questionnaires using those methods. Event follow-up and assessment, where needed, will also be performed remotely by study personnel. The digital platform will also include an investigator dashboard where investigators and selected study personnel can view and track, in real time, all adverse events (AEs) submitted. Role-based permissions will ensure only authorised personnel can view identifying confidential data like participant names.

Participants will enrol in the study after vaccination with AZD1222. Enrolment is permitted within 28 days of the first dose of AZD1222 and can be completed at the vaccination site or remotely. If a vaccine recipient chooses to enrol in the study at the vaccination site, a study research coordinator may be present and can assist by:

- Providing information about the study.
- Explaining the study participation options: study app, web portal, or telephone communication with the call centre.
- Assisting the participant with the informed consent process.
- Checking if participants meet the eligibility criteria and providing vaccination details.
- Recording contact information for the participant, the emergency contact (in case of apparent loss to follow-up), and the participant's proxy, if needed.
- Providing the proxy with instructions on how to assist the participant with reporting.

For vaccine recipients who would prefer to enrol remotely at a later date, up to 28 days after the first vaccine dose, a study information brochure will be available that includes instructions to remotely enrol (including electronic informed consent completion, where permitted) and their vaccination details (if a vaccination card was not already provided).

Study personnel will confirm each participant's receipt of AZD1222 using their vaccination card, reported batch/lot number of the vaccine dose, and/or regional vaccination register details. The batch/lot number of the vaccine dose will be recorded whenever possible. The enrolment questionnaires will also ask participants for demographic information, medical history, pregnancy status, breastfeeding status (Figure 1). CCI [redacted]

After enrolment, participants will receive study reminders and report outcomes using the app, web portal, or study call centre. Both digital and non-digital participants can select a proxy, ie, a caregiver, family member, or other trusted individual, who will have permission to complete

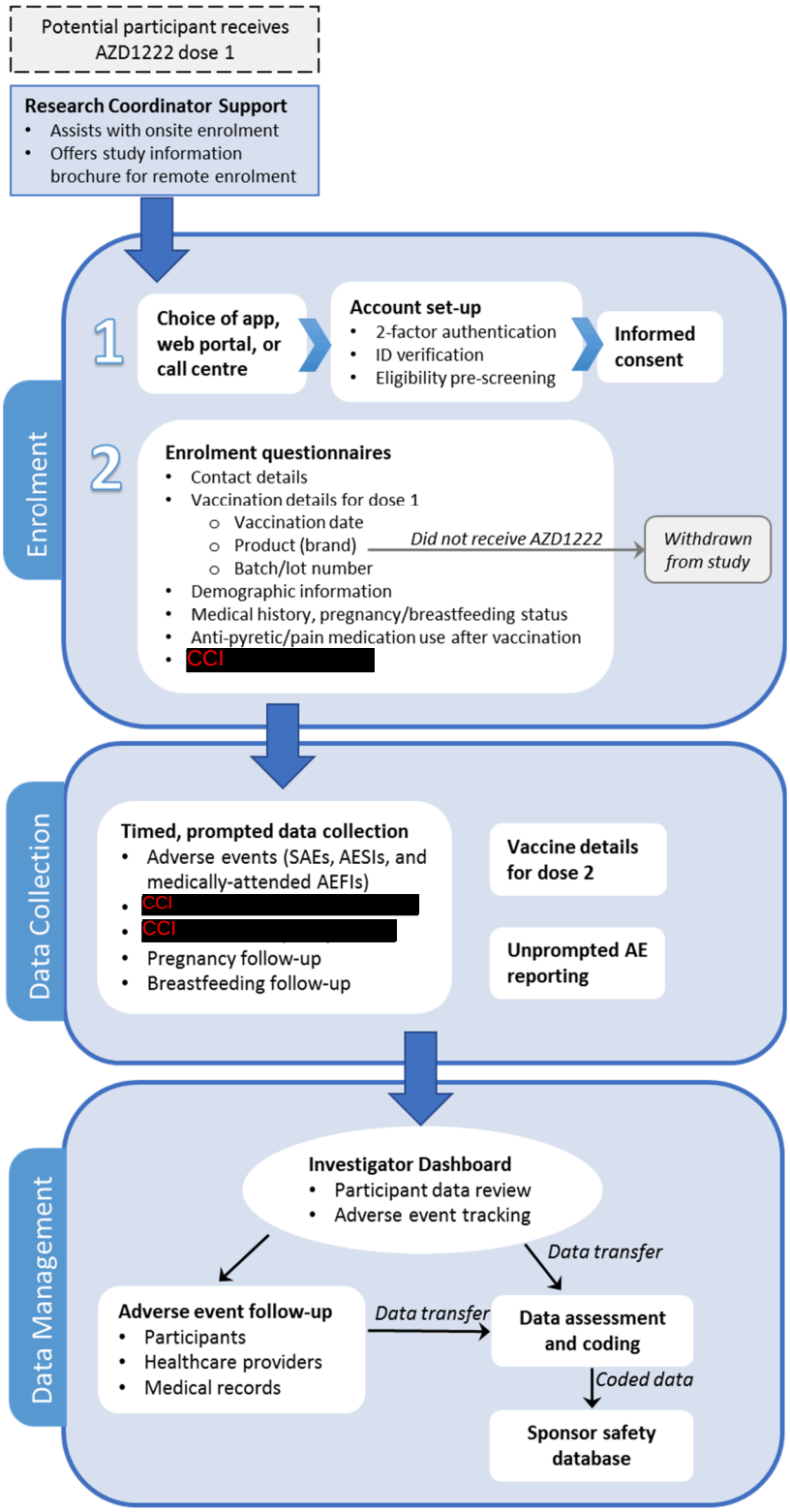
study questionnaires on behalf of the participant. Participants will receive study notifications at predefined time intervals for up to 18 months after the first AZD1222 dose. Study notifications will include prompts for safety outcomes at 1, 4, 8, and 14 weeks and 6, 9, 12, and 18 months following the first vaccine dose. Participants can also submit unscheduled, unprompted AE information, with focus on the AE types specified for this study: SAEs, AESIs, and medically-attended AEs following immunisation (AEFIs), including COVID-19 cases that were medically-attended. Should other AE types, however, be reported, these will also be collected and managed accordingly and presented in the study report.

CCI will be sent at 4.5 months and 15 months after the first vaccine dose.

When a participant reports an AE, study personnel will see a flag in the investigator dashboard and will perform event follow-up and assessment. Study personnel will request medical records from the participant's HCP and assess if the event is serious and/or an adverse drug reaction. For events without an HCP contact, study personnel will assess AEs based on details provided from the participants.

Participants who are pregnant at the time of vaccination or are vaccinated within 45 days prior to the estimated date of conception will be asked to provide additional information to assess pregnancy and neonatal/infant outcomes. Pregnant women will be asked for pregnancy outcomes 12 months after their last menstrual period and for infant outcomes up to 12 months of age or at 24 months post-first dose for the last participant enrolled in the study, whichever is first. Participants who are breastfeeding will also be asked for additional information.

Figure 1 Overview of the Study Design



If a participant is unable to directly provide requested information, a proxy can do so on the participant's behalf.
AE, adverse event; AESI, adverse event of special interest, AEFIs, adverse events following immunisation; CCI [redacted]; SAE, serious adverse event.

8.3 Setting

8.3.1 Vaccination Sites

Vaccination sites will include various site types such as general/primary care practices, hospitals, vaccination centres, mobile vaccination units, and long-term care facilities. The types of sites may differ over time and between countries, reflecting differences in local practices and vaccination policies. To boost enrolment of older adults (≥ 65 years of age), the choice of vaccination sites for the study will target locations likely to administer vaccines to older adults and geographical areas with higher populations of older adults. The study will initially include vaccination sites in Germany, France, Spain, and Sweden, but the study may be expanded to additional EU countries.

8.3.2 Study Population

8.3.2.1 Eligibility Criteria

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

- Aged 18 or older at the time of vaccination.
- Received AZD1222 as the first dose of COVID-19 vaccination in the prior 28 days.
- The participant has provided sufficient details to validate the vaccination (vaccination card, batch/lot number, and/or regional vaccination register details).
- Provided informed consent to participate in the study, either personally or through a legal representative.
- Able and willing to provide responses to study notifications using the mobile device app, web portal, or call centre or have a proxy (a caregiver, family member, or other trusted individual) who can do so on their behalf.
- Able and willing to grant, personally or through a legal representative, permission to contact the participant's healthcare providers and to access the participant's medical records at the time of vaccination and during the post-vaccination follow-up period.

8.3.2.2 Key Subpopulations

This real-world, non-interventional study will enrol all eligible participants but, in particular, will seek to enrol older adults, with a target of 50% of participants aged ≥ 65 years. The study will also aim to have equal enrolment of male and female participants. Additional subpopulations of interest in this study include:

- Pregnant women, breastfeeding women
- Immunocompromised participants
- Participants with autoimmune or inflammatory disorders
- Frail participants with comorbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)

8.3.3 Participant Withdrawal and Lost to Follow-up

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. 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. Participants who choose to withdraw will be asked for the reason they are leaving the study.

A participant will be considered lost to follow-up if he or she fails to respond to the study notifications and does not respond to subsequent follow-up attempts. At least 2 follow-up attempts will be made, at least one week apart.

For participants who are apparently lost to follow-up, study personnel will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants enrolled. Participant's emergency contact, provided at enrolment, will be contacted and asked for the status of the participant, and, if appropriate, the reason the participant has not responded to study notifications. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8.4 Variables

8.4.1 Study Variables to be Collected

Table 3 summarises the data collection plan.

Table 3 Data Collection Plan for Key Variables and Information

Procedure or variable	Enrolment (post-vaccine dose 1) [b]	Post-vaccination follow-up with participants via app, email, or phone call (months, weeks after first vaccine dose)										Data source(s)	Data capture format
		1 wk	4 wk	8 wk	14 wk	4.5 m 20 wk	6 m 26 wk	9 m 39 wk	12 m 52 wk	15 m 65 wk	18 m 78 wk		
Consent and Contact Details													
Informed consent [a]	X											Participant	ICF form
Choice of digital or non-digital participation	X											Participant	Profile questionnaire
Personal contact information, including emergency contact	X												
Primary HCP and contact information	X												
Name and contact information for proxy, if needed	X											Participant	App or web portal interface
Vaccination Details													
Vaccine product (brand)	X		Starting at Week 4, participants can complete a post-vaccination questionnaire for their second dose. Second doses are expected between Week 4 and Week 14 based on recommended schedules.									Vaccination site, RC, participant	Vaccination details questionnaire
Vaccination date	X												
Vaccine batch/lot number	X												
Type of vaccination site	X												
Photo of vaccination card [c]	X											Participant	Vaccine card photo
Any antipyretic/pain-reliever within 5 days of vaccination		X										Participant	Antipyretic/ pain-reliever questionnaire
Participant Background Information													
Age	X											Participant	Background questionnaire
Sex/gender	X												
Height/weight	X												
Race/ethnicity [d]	X												
Country of birth/residence	X												
Employment status	X												
Smoking status/history	X												

Table 3 Data Collection Plan for Key Variables and Information

Procedure or variable	Enrolment (post-vaccine dose 1) [b]	Post-vaccination follow-up with participants via app, email, or phone call (months, weeks after first vaccine dose)										Data source(s)	Data capture format
		1 wk	4 wk	8 wk	14 wk	4.5 m 20 wk	6 m 26 wk	9 m 39 wk	12 m 52 wk	15 m 65 wk	18 m 78 wk		
Medical History													
Prior infection with SARS-CoV2 or prior COVID-19 disease, including symptoms	X											Participant, medical records	Medical history questionnaire
Recent non-AZD1222 vaccination	X	X	X	X	X		X	X	X		X		
Select comorbidities and medications [e]	X												
Safety Outcomes													
SAEs, AESIs, and medically attended AEFIs [f] • Symptoms • Diagnosis • Onset date/duration • Intensity • Resolution • Treatment • Seriousness [g] • Causality [g]		X	X	X	X		X	X	X		X	Participant, HCP, medical records	Health status questionnaire, AESI form (when applicable)
CCI [redacted]		X	X	X	X		X	X	X		X	Participant, medical records	CCI [redacted]
Death												Emergency contact, proxy, HCP, medical records	Safety database

Table 3 Data Collection Plan for Key Variables and Information

Procedure or variable	Enrolment (post-vaccine dose 1) [b]	Post-vaccination follow-up with participants via app, email, or phone call (months, weeks after first vaccine dose)										Data source(s)	Data capture format
		1 wk	4 wk	8 wk	14 wk	4.5 m 20 wk	6 m 26 wk	9 m 39 wk	12 m 52 wk	15 m 65 wk	18 m 78 wk		
Pregnancy Status and Outcomes (Pregnant and Breastfeeding Women Only)													
Pregnancy status, including maternal medical and obstetric history	X	X	X	X	X		X	X	X		X	Participant, medical records	Pregnancy status questionnaire
Pregnancy/infant outcomes, pregnant participants		Participants who report pregnancy at the time of vaccination will be followed-up at 12 months after their estimated last menstrual period and, for those reporting live-birth, at infant age up to 12 months to assess pregnancy/infant outcomes.[j]										Participant, medical records	Pregnancy follow-up questionnaire
Breastfeeding status, including infant outcomes	X	X	X	X	X		X	X	X			Participant, medical records	Breastfeeding status questionnaire
Parent/caregiver informed consent [i]	X											Participant	Parent/caregiver ICF
Patient-reported Quality of Life Outcomes													
CCI	X [k]					X [k]				X [k]		Participant	CCI
CCI						X [k]				X [k]		Participant	CCI

[a] Informed consent will include consent to participate in the study as well as to contact HCPs and for the release of medical records relevant to the study.

[b] Participants can enrol up to 28 days after their first vaccine dose.

[c] For digital participants only. For non-digital participants, vaccination details will be validated by the call centre.

[d] Will be collected in countries where permitted.

[e] Selected medical conditions: neuroimmune condition, other neurological condition, bleeding disorder, asthma, chronic obstructive pulmonary disease, diabetes, cerebrovascular conditions, heart disease, other cardiovascular disease, chronic kidney disease cancer, autoimmune disease, solid organ transplant recipient, other condition affecting immune system, liver disease, history of allergic conditions, depression/anxiety, viral/bacterial infection leading to hospital admission, and other chronic condition or conditions for which participant received treatment or medication in last month. If a participant indicates having any of these conditions, the participant will be asked if they are currently taking any medication or being treated for it. Specific medication will not be asked unless the participant indicates they are taking an immunosuppressant.

[f] Adverse event reports can be scheduled (timed follow-ups) or unscheduled. At the scheduled timepoints, participants will be asked if they've had any new or worsening health issue resulting in consultation with a medical doctor, an emergency room visit or hospitalisation, or a significant or long-term disability or incapacitation. When a participant responds "yes", the participant will be asked for more details. For reported COVID-19 cases, this will include patient-reported symptoms.

[g] Healthcare providers will provide input and study personnel will assess the seriousness and causality of AEs.

[h] CCI

[i] Participants vaccinated with AZD1222 during pregnancy or up to 45 days before the estimated date of conception will be asked to follow outcomes in their child for up to 12 months after birth. Breastfeeding participants will also be asked to follow-up on their child's health. Before any request for a child's medical records, the participant will be asked for additional informed consent. The child's other parent may also be asked for consent, depending on local requirements.

[j] Outcomes in infants will be requested up to 12 months of age. However, follow-up of pregnancy and infant outcomes will not be continued past 24 months post-first dose for the last participant enrolled in the study.

[k] CCI [redacted]

As a data source, participant means either the participant directly or the participant's designated proxy.

For the safety outcome follow-ups at Weeks 1, 4, 8, 14, and Month 6, 9, 12, and 18, depending on the interval between scheduled contacts, participants will receive reminders for 2 to 8 weeks after the initial notification to complete the questionnaire.

AE, adverse event; AEFI, adverse event following immunisation; AESI, adverse event of special interest; CSP, clinical study protocol; HCP, healthcare provider, CCI [redacted]; ICF, informed consent form; m, month; NA, not applicable; CCI [redacted]; CCI [redacted]; RC research coordinator; SAE serious adverse event; wk, week.

8.4.2 Variables for Identifying Subpopulations

8.4.2.1 Adults Aged ≥ 65 Years and Other Age Groups

Participants will record their age at enrolment and will be categorised accordingly.

8.4.2.2 Pregnant Women

At enrolment, females aged < 50 years will be asked the date of their last menstrual period and if they are currently pregnant. Those who have not reported pregnancy, will be prompted for this information at each safety follow-up. Women who report pregnancy will be asked for their expected due date. Their estimated date of conception will be calculated, and those vaccinated (either first or second dose) between 45 days prior to the estimated date of conception and, any other point during pregnancy, will be included in the pregnant women subpopulation.

8.4.2.3 Breastfeeding Women

At enrolment and at all safety follow-ups (except at 18 months), females aged < 50 years will be asked if they are currently breastfeeding. Participants who report they are breastfeeding when they receive either vaccine dose (first or second) will be included in the subpopulation.

8.4.2.4 Immunocompromised Participants and Participants with Autoimmune or Inflammatory Disorders

At enrolment, participants will be asked if they have ever been diagnosed with certain medical conditions and if they are currently taking an immunosuppressant medication. Study personnel will confirm medical conditions and immunosuppressant medications with medical records. Confirmed medical conditions and medications will be used to categorise participants as immunocompromised and/or as having an autoimmune or inflammatory disorder.

The subpopulation of immunocompromised participants will include participants taking an immunosuppressant (eg, tracrolimus, cyclosporine, corticosteroids, and methotrexate), participants with a diagnosis of an autoimmune disease, neuroimmune condition, or another condition affecting the immune system, and participants currently taking medication for cancer or being treated for cancer.

The subpopulation of participants with an autoimmune or inflammatory disorder will include participants diagnosed with an autoimmune disease or neuroimmune condition.

8.4.2.5 Frail Participants with Comorbidities

The EMA's reflection paper on physical frailty has defined the concept of frailty "as a state of increased vulnerability resulting from aging and often disease associated decline … leading to increased risk of adverse health outcomes…" (EMA 2015).

For this study, physical frailty will be identified at baseline using participant answers to the enrolment questionnaire as well as to the CCI

CCI . Comorbidities will be reported by participants at enrolment and then confirmed by study personnel through medical record reviews.

Only participants with physical frailty and comorbidities at baseline will be included in this subpopulation.

8.4.3 Outcome Measures

8.4.3.1 Adverse Events

The collection and analysis of AEs will focus on 3 categories of events:

- Serious adverse events
- Adverse events of special interest
- Medically-attended AEFIs

The following variables will be recorded for all collected AEs:

- Onset date of the health issue or start of the worsening of the issue
- Intensity (mild, moderate, severe)
- Duration of the issue (estimated number of days)
- Outcome (resolved, unresolved, fatal, unknown)
- CCI
- Treatment received for the issue
- Seriousness (SAE, non-SAE)
- Causality
- Adverse event of special interest details (if relevant)

If the participant indicates an AE may be related to COVID-19 or if they received a diagnosis for COVID-19, they will be asked about any COVID-19 testing and results.

For additional details on AE definitions, management, and reporting, refer to Section 10.

8.4.3.2 Pregnancy Outcomes

Data will be collected for pregnancy outcomes and infant outcomes. For pregnancy outcomes, events within the AESI medical concept "Pregnancy outcome – Maternal" will be collected, including spontaneous abortions, still births, and preterm births. For infant outcomes, events within the AESI medical concept "Pregnancy outcome – Neonates" will be collected, including major congenital malformations and small for gestational age.

8.4.3.3 CCI

CCI

[redacted]

8.4.3.4 CCI

CCI

[redacted] as per the data collection schedule described in Table 3.

CCI

[redacted]

CCI

[redacted]

8.5 Data Sources

8.5.1 Vaccination Sites

Vaccination sites will provide participants with a vaccination card/record that includes the participant's name, the vaccine dose date, and the batch/lot number.

8.5.2 Participants: Study App, Web Portal, and Call Centre

Participants will record their baseline characteristics and will report post-vaccination outcomes using the study app, web portal, or call centre. Generally, participant inputs will be responses to the timed study questionnaires but can also include documentation like a photo of their vaccination card. A proxy may assist with any enrolment, reporting, or follow-up actions on behalf of the participant (Section 8.5.3). Participants can switch data reporting methods during the study but will be encouraged to use a consistent method for answering the health-related quality of life questionnaires.

The study app can be downloaded by participants to their mobile device. At vaccination sites with a study research coordinator present, the coordinator may assist participants with downloading and using the app. In mobile units where a study research coordinator might not be present, or when a participant decides to enrol later remotely, vaccine study cards will be available that will provide similar instructions.

The web portal will be accessible from any internet-connected computer and will allow users to securely login to a website and perform study-related activities.

The call centre will be toll-free. In some locations, it will be available 24 hours/day and 7 days/week. In locations where the call centre is not 24/7, it will be available weekdays during business hours and have an out of hours voicemail with call-back support. For participants that choose to communicate by telephone call, the call centre team will enter their responses into the digital platform. Accordingly, all patient-reported data will be integrated in the digital platform, regardless of the reporting method.

8.5.3 Emergency Contacts and Proxies

At enrolment, all participants will be asked to provide information for an emergency contact. In the case of non-response from a participant, the emergency contact would be contacted to confirm if the participant is unavailable due to incapacity or death.

If a participant is unable to directly provide any requested information, a proxy can do so on the participant's behalf. Participant proxies may include a caregiver, family member, or other trusted individual. The proxy will enter the participant's data into the app or web portal on the participant's behalf.

A proxy may act on the participant's behalf throughout the study or may step in if needed due to the participant's illness or incapacity. If a proxy is needed at the onset of the study, the participant can identify the proxy during enrolment. Instructions for the proxy on how to report outcomes on behalf of the participant will be available from a research coordinator or study information brochure.

Participants will be asked to only nominate a single proxy and will be asked for the appropriate permission for the proxy to handle their medical data for the limited purpose of assisting with data collection for this study, in accordance with local rules.

8.5.4 Medical Records

Medical records (paper or electronic) will be used to confirm comorbidities and medications at baseline and to follow up AEs reported during the study. Medical records will also be used to confirm pregnancy, birth, and infant outcomes. For all SAEs, AESIs, and medically-attended AEFIs, medical records will be requested from the participant's HCP.

8.5.5 External Data

External data from published studies or other publicly available sources such as registry databases will be identified. These additional data sources may be utilised to provide supporting data and context, and, if feasible, background event rates for risk assessment analyses (ACCESS 2020).

8.6 Study Size

This study plans to enrol 15,000 participants in at least 4 countries in the EU (Germany, France, Spain, and Sweden). The Sponsor will aim for at least 50% of participants to be 65 years of age or older and approximately equal proportions of male and female participants.

As the COVID-19 pandemic is a dynamic situation, the enrolment target may be amended if recruitment forecasts change.

8.7 Data Management

Data management will be performed by a contract research organisation (CRO) according to the Data Management Plan.

8.7.1 Digital Platform Data

All data entered into the study app or web portal will be integrated in the digital platform and will be tracked by reporting method (app or web portal), who reported it (participant, proxy, or emergency contact), and who entered it (participant, proxy, or call centre). The digital platform will also include an investigator dashboard where investigators and selected study personnel can view and track, in real time, all AEs submitted. Role-based permissions will ensure only authorised personnel can view identifying confidential data like participant names.

The study app and web portal will be validated and compliant with good practice guidelines and regulations and the EU General Data Protection Regulation (GDPR). The app will support

iOS and Android operating systems. The app and web portal will be approved by local IECs and translated into local languages.

8.7.2 Study Call Centre

The call centre will be available to assist participants throughout the study, including during the informed consent and enrolment process. The call centre will operate in local languages. The call centre team will enter data into the digital platform on the participant's behalf. For consistency, the call centre will be provided with instructions on how to collect and enter data in a standardised way.

8.7.3 Record Retention

The study archive, including all source data, will be maintained for at least 5 years after the final report or first publication of study results, whichever comes later, in accordance with the International Society for Pharmacoepidemiology Guidelines on Good Pharmacoepidemiology Practices (GPP). Study records and data must be retained for longer than 5 years if required by applicable local regulations.

The Sponsor will comply with all the requirements of GPP and regional legislation related to archiving of study documentation. Records containing participant sensitive data will not be archived by the Sponsor, but must be kept with a CRO, investigators, and/or patient and according to local regulations pertaining to personal data protection.

Participant medical records must be kept for the maximum period permitted. Investigators and CRO personnel involved with handling participant medical records must agree to archive the documentation pertaining to the study after completion or discontinuation of the study, if not otherwise notified. They should not destroy any documents without prior permission from the Sponsor.

8.8 Data Analysis

This study is descriptive in nature. Proposed data analysis methods are summarised here. Detailed methodologies will be documented in a separate statistical analysis plan.

Sample Size. The planned sample size of this study is approximately 15,000 participants. For this study, the sample size reflects the Sponsor's best estimation of the enrolment potential in Germany, France, Spain, and Sweden, as well as the Sponsor's broader target to enrol between 30,000 to 40,000 participants across multiple studies. As described in the Vaccine COVID-19 Monitoring Readiness (ACCESS) protocol, a sample size of 30,000 with a mean follow-up of 12 months will be sufficient to rule out rare AEFIs with a frequency of more than 1:10,000 per person-year at an alpha of 5% (Meurs and Kant 2020). A sample size of 15,000 with 12 months follow-up would permit the frequency per year of common AEFIs to be estimated with a maximal confidence interval of ± 0.8% using the binomial distribution. An

estimate of 12 months follow-up is used, rather than the full 18 months, to account for possible loss-to-follow-up.

Demographic and Baseline Characteristics. Distribution of participant characteristics at baseline will be described through point estimates (mean, median, rates, or proportions) and the corresponding variability (interquartile range, 95% confidence intervals). For a summary of participant demographics and characteristics to be collected at enrolment, refer to Table 3 in Section 8.4.1. Demographics and baseline characteristics collected in the participant enrolment questionnaire will also be used to categorise participants into subpopulations of interest (see Section 8.4.2) and to perform the subgroup analyses (described below).

Disposition. Participant dispositions will be tabulated, including study completion, study withdrawal, participants lost-to-follow-up, and deaths.

Primary and secondary analyses. The primary analysis will only include participants who enrolled within 7 days of vaccination with the first dose of AZD1222. All AEs collected, regardless of seriousness, will be tabulated. The cumulative incidence of SAEs, AESIs, and medically-attended AEFIs will be computed as the proportion of participants who reported an event among all AZD1222 vaccinated participants who completed each study-defined follow-up interval as well as among all AZD1222-vaccinated participants regardless of completion status, in combination with corresponding patient-years.

Where feasible, incidence rates will be calculated (in person-years), both by dividing by number of person-years, as well as by taking into account death as a competing event and withdrawal from the study/loss-to-follow-up as a censoring event (using cumulative incidence). Kaplan-Meier curves will be used for this analysis where appropriate.

Summaries of SAEs, AESIs, and medically-attended AEFIs by intensity, seriousness, and relatedness will also be presented.

In the pregnancy sub-cohort, the prevalence of pregnancies that resulted in live births, spontaneous abortions, and stillbirths will be summarised along with any other pregnancy outcomes reported within the AESI medical concept of Pregnancy Outcomes - Maternal. Infant outcome measures will also by summarised by the prevalence of events in the AESI medical concept of Pregnancy Outcomes – Neonates, including small for gestational age and major congenital malformations.

Additional Supportive Analysis. To support safety signal evaluation, a risk assessment will be conducted for AESIs using background event rates established through the ACCESS project or another source (Meurs and Kant 2020, ACCESS 2020). To further enhance background rate identification, additional literature review will be conducted if ACCESS data is insufficient or unavailable. Appropriate risk windows will be estimated for these analyses

and counts of AESIs that occurred within the prespecified risk window will be compared against expected values using sequential testing. Where appropriate, analyses will be stratified by sex and age. To assess whether larger risks can be found based on bias, the background rates based on the external sources will be evaluated as they are and with additional scenarios.

Subgroup Analyses. Incidence rates and potential differences in the risk and pattern of participants experiencing AEs within different subgroups will be explored, including categories that are considered missing information at the start of the study. The subgroup analyses will include:

- Age at vaccination (18 to 34, 35 to 49, 50 to 64, 65 to 79, and ≥ 80 years)
- Sex (male, female)
- Race/ethnicity
- Country (Germany, France, Spain, Sweden)
- Previous COVID-19 infection
- Pregnant/breastfeeding women
- Participants with immunodeficiency
- Participants with autoimmune or inflammatory disorders
- Frail participants with comorbidities (chronic obstructive pulmonary disease, diabetes, chronic neurological disease, or cardiovascular disorders)
- Participants who receive other vaccines in addition to AZD1222 (within 1 month)
- Number of AZD1222 doses received (1 dose, 2 doses)

Handling of Missing Data. No restrictions on the percentage of missingness will be made, but the baseline characteristics of the participants lost-to-follow-up will be tabulated. The differences between the baseline characteristics for the total group and the group lost-to-follow-up will be related to the subgroup analyses to assess for a possible impact on AE risk. Adjustment for missingness will be further specified in the statistical analysis plan but may include multiple imputation, joint modelling, and inverse probability weighting.

To deal with missingness due to death, death will be interpreted as a competing risk in the above analyses.

Mitigation of Potential Bias and Confounding. Strategies include:

- To account for possible sampling bias due to the recruitment of vulnerable populations first (residual confounding), in the risk assessment analyses, in addition to the expected background event rate, the rates will be multiplied by 1.2, 1.5, and 2.0 times, for example.
- Subgroup analyses within risk assessment analyses will also be performed, if feasible. When characteristics are found that both are related to differences in AE risk and to differences between study participants and the overall vaccinated population, weighting will be added.
- Additional sensitivity analyses will include:
  - As participants can enrol in the study within 28 days of their initial vaccination, it will also be evaluated whether the AE risk for participants enrolling in the days and weeks after vaccination differs from the risk for participants enrolling immediately after vaccination. A sensitivity analysis will be performed that excludes subjects enrolled more than 2 days after the date of vaccination.
  - Participants who report pregnancy at the time of vaccination or an estimated date of conception within 45 days of vaccination will be included in the analyses for pregnant women. Sensitivity analyses will consider time windows less than 45 days.
  - Sensitivity analyses will evaluate the relationship between sex and loss-to-follow-up and the relationship between age and loss-to-follow-up.

Exploratory analyses: CCI [redacted]

8.9 Quality Control

Quality Control Guidelines and Procedures

This study will follow all applicable international and local quality regulations, including GPP. AstraZeneca standard operating procedures will also be used to ensure the quality of the data and study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality control procedures for study monitoring, standards for writing a statistical analysis plan, and requirements for senior scientific review.

Data Quality Assurance

- Vaccination sites and study personnel must maintain accurate documentation and must permit study-related monitoring, audits, IEC review, and regulatory agency inspections, and provide direct access to study documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques, are provided in the Site Monitoring Plan.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- In-person monitoring of vaccination sites will only be performed if a specific cause requires investigation.
- Records and documents, including signed informed consent forms, pertaining to the conduct of this study must be retained by the Sponsor or designee for 5 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.

Audits and Inspections

The Sponsor or designee may conduct a quality assurance assessment and/or audit of study records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

8.10 Limitations of the Research Methods

Limitations of the research methods and how they are addressed by the study design are summarised in Table 4.

Table 4 Study Limitations and Mitigations

Potential limitation	Reason for potential limitation	Rationale or mitigation
Study population limitations		
Uncertain enrolment	The status of the COVID-19 pandemic, availability of other vaccines, and the social and political environment at each location will impact recruitment and follow-up of vaccinated volunteers. The uncertainty of the situation and the highly dynamic environment can hinder enrolment forecasts.	Will evaluate enrolment on an ongoing basis and expand study to additional countries if needed.
Sampling bias	Some subgroups (ie, vulnerable persons and the elderly) may be over-represented in the study population, as compared to the general population who will receive the vaccine in the future.	As this study aims for at least 50% of participants ≥ 65 years, potential bias towards older persons is a benefit. However, the ability to enrol sufficient participants ≥ 75 years or ≥ 80 years will depend on how many elderly individuals are still waiting to receive a vaccine or have chosen not to vaccinate yet due to vaccine hesitancy or local guidance when the study begins.
Selection bias	Self-enrolment of participants in the study after vaccination.	To reduce selection bias, the study includes digital and non-digital participation options, an option to use a proxy, and a range of vaccination site types where recruitment will take place.
Overall study design limitations		
Unknown confounders	Sources of unmeasured and residual confounding could include socioeconomic factors, lifestyle factors (including exercise, diet, etc), and healthcare-seeking behaviour.	In this non-interventional surveillance study, the benefit of additional personal information needed to be weighed against the burden on participants' time and privacy.
Lack of internal comparator	While an internal comparison (ie, a cohort unexposed to any COVID-19 vaccine) is preferable, it was deemed not feasible.	An internal comparator was not feasible because: • Unethical to include volunteers that could be discouraged from vaccination • Selection bias of volunteers who opt out of vaccination could result in different risk of outcomes • An additional cohort would prolong study delivery
Recall bias	This study will permit enrolment remotely up to 28 days after the first vaccine dose and will only periodically remind participants to report outcomes, introducing the possibility of recall bias.	The following study elements address recall bias: • The primary analysis will be limited to participants who enrolled within 7 days of their first vaccine dose. • Participants must complete the scheduled questionnaires within certain time windows.
Misclassification of events	Participants could self-report events inaccurately.	Study personnel will follow up to confirm as many event details as possible using medical records, as described in Section 10.2.

Table 4 Study Limitations and Mitigations

Potential limitation	Reason for potential limitation	Rationale or mitigation
Failure to report events due to incapacity	Primary method of reporting outcomes is self-reporting	All participants will be asked to provide an emergency contact when they enrol. As described in Section 8.3.3, if a participant seems lost-to-follow-up, study personnel will reach out to the emergency contact and/or perform a search for vital status information.
Data analysis limitations		
Generalisability	Point estimates and confidence intervals resulting from the analyses should only be interpreted as indications and not as reflective of a 'true' underlying estimand because of the limitations of conducting a study during an ongoing pandemic. This may impact the interpretation of the results as well as the ability to generalise the results to post-pandemic circumstances.	Will be considered for final analysis.
Missing data	Loss of participants in follow-up and/or missing data are limitations inherent in all primary data collection observational studies. In this non-interventional, observational study, participants may not respond to all prompts and may not complete the full 18-month follow-up period.	See Section 8.8 for planned handling of missing values in the analyses.
Risk assessment analyses	It is unclear how efficient risk assessment analyses will be during the COVID-19 pandemic given the impact of COVID-19 on general healthcare seeking behaviour. This may change over time as COVID-19 activity decreases. Paradoxically, increased outcomes may then be observed as vaccination coverage increases and COVID-19 decreases. Trends may be challenging to interpret in this changing healthcare-use environment, confounded by vaccine and other treatment/prevention measures.	Will be considered for final analysis.
Detection of rare events	Some rare events may not be detected in a sample size of 15,000.	Data from this study may be used in a pooled analysis or meta-analysis combining data from similar studies in different regions, for an overall enrolment of at least 30,000 across the studies.

AESI, adverse event of special interest.

8.11 Other Aspects

Study Governance and Committees

A Scientific Committee will be set up to support and oversee the study and will be governed by a charter detailing responsibilities and processes.

Other teams and committees will be established as needed.

9. PROTECTION OF HUMAN SUBJECTS

9.1 Ethical Conduct

Independent Ethics Committee approval will be obtained in accordance with applicable national and local regulations.

This study will be conducted in accordance with International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices (ISPE 2015) and applicable regulatory requirements including the European Medicines Agency Guideline on Good Pharmacovigilance Practices: Module VIII – Post-Authorisation Safety Studies (EMA 2017).

The Sponsor will also adhere to the general principles of transparency and independence in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct (ENCePP 2018). The ENCePP Checklist for Study Protocols is located in Appendix B.

9.2 Informed Consent

A signed and dated electronic or written informed consent will be obtained before any participant data is collected for the study. Electronic consent will be an option where permitted.

For vaccine recipients who choose to enrol in-person at a study site, if a study coordinator is present, the coordinator will ensure they are given full and adequate information about the nature and purpose of the study. They will be given the opportunity to ask questions and allowed time to consider the information provided. For vaccine recipients who choose to enrol remotely, similar information will be available electronically and the call centre will be available to answer questions.

All participants will need to consent to requests for their medical records (paper and electronic) to further evaluate safety events.

Participants vaccinated with AZD1222 during pregnancy or up to 45 days before estimated date of conception will be asked to follow outcomes in their child for up to 12 months after birth. Breastfeeding participants will also be asked to follow-up on the health of their child. If

any follow-up requires access to a child's medical records, consent will be requested from the participant and may be requested from the child's other parent/caregiver, depending on local requirements.

9.3 Participant Data Protection

Data privacy and confidentiality practices will abide by local rules and will be subject to review by local IECs prior to the start of the study.

Participants will be assigned a unique identifier code by the digital platform. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only. No information that could make the participant identifiable will be transferred to the Sponsor.

Participants will be informed that their 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 will be explained to participants in the informed consent. The participants will be informed that their medical records may be examined by authorised personnel appointed by the Sponsor, by appropriate IEC members, and by inspectors from regulatory authorities.

As part of the study onboarding steps, participants will need to choose if they are planning to use a proxy to act on their behalf in the study and provide their contact information. Participant proxies who use the study digital solutions will create a separate account that will be linked to the participant's account.

9.4 Registration of Study on Public Websites

The study will be registered in the ENCePP EU Register of Post-Authorisation Studies after protocol approval and before the study implementation commences.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

10.1 Definitions

10.1.1 Adverse Events

An AE is the development of any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not 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.

10.1.2 Serious Adverse Events

An SAE is an AE that fulfils one or more of the following criteria: results in death, is immediately life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital

abnormality or birth defect, or is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

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

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

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

10.1.3 Medically-attended Adverse Events Following Immunisation

A medically-attended AEFI is a new or worsening health problem or symptom following immunisation, resulting in a consultation with a medical doctor, an emergency room visit, or hospitalisation. A consultation with a medical doctor can be remote (by phone or video) or can be an in-person visit.

10.1.4 Adverse Events of Special Interest

Adverse events of special interest are events of scientific and medical interest specific to the further understanding of the safety profile of a product and require close monitoring. An AESI can be serious or non-serious. A list of AESIs for AZD1222 was developed for the AZD1222 Risk Management Plan and will be followed for this study.

Table 5 lists the AESIs for AZD1222. The AESI list will be reviewed on an ongoing basis and the EU Risk Management Plan and the list for this study will be updated accordingly.

Table 5 Adverse Events of Special Interest for AZD1222

Body System/Classification	AESI or AESI Medical Concept
Other system	Vaccine-associated enhanced disease (VAED), including vaccine associated enhanced respiratory disease (VAERD) [a]
	Multisystem inflammatory syndrome in children
	Sudden death
Immunological	Autoimmune thyroiditis
	Anaphylaxis
Respiratory	Acute respiratory distress syndrome (ARDS)
Neurologic	Guillain-Barré syndrome
	Peripheral neuropathy and polyneuropathy
	Multiple sclerosis, transverse myelitis, and other demyelinating disorders
	Optic neuritis / neuromyelitis optica spectrum disorder
	Non-infectious encephalitis (inc. acute disseminated encephalomyelitis) / non-infectious encephalopathy
	Myasthenia gravis
	Bell's palsy
	Seizure disorders (inc. febrile)
	Narcolepsy
Cardiovascular system	Myocarditis/pericarditis
	Myocardial infarction
	Postural orthostatic tachycardia syndrome
Circulatory system/Haematological	Thrombocytopaenia
	Stroke and other cerebrovascular events, venous thromboembolism
Renal	Acute kidney injury
Gastrointestinal	Acute liver injury
	Acute pancreatitis
Musculoskeletal system	Acute aseptic arthritis
	Fibromyalgia
	Rhabdomyolysis
General	Chronic Fatigue Syndrome/myalgic encephalomyelitis/postviral fatigue syndrome
Pregnancy/Foetal/Neonatal	Pregnancy outcome – Maternal [b]
	Pregnancy outcome – Neonates [b]
Skin	Erythema multiforme

[a] The case definition for VAED, including VAERD will follow the Brighton Collaboration Case Definition (Munoz et al 2021).

[b] Additional information about the case definitions and preferred terms for these AESI medical concepts is provided in the EU Risk Management Plan and/or will be included in the Statistical Analysis Plan or other study documentation.

AESI, adverse event of special interest, EU, European Union.

10.1.5 Adverse Drug Reaction

An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility. An ADR, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

In this study, causality information will be requested from the HCP for all SAEs, AESIs, and medically-attended AEFIs. Study personnel will make a causality assessment for those events, considering the input from the HCP. For events without an HCP contact, study personnel will assess the events based on details provided from the participants.

10.1.6 COVID-19 Diagnosis and Lack of Efficacy

A COVID-19 diagnosis is defined as virologically-confirmed SARS-CoV-2 (eg, reverse transcription polymerase chain reaction [RT-PCR]) and:

- At least 1 symptom of COVID-19 disease (eg, objective fever [defined as ≥ 37.8 °C], cough, shortness of breath, anosmia, or ageusia) or
- COVID-19 diagnosis stated/provided by the physician.

In this study, lack of efficacy is defined as the occurrence of COVID-19 caused by SARS-CoV-2 in a person who is appropriately and fully vaccinated following an incubation period of ≥ 15 days following the second dose of the vaccine.

10.2 Collection and Assessment Process for Adverse Events

Adverse events will be collected from the time of informed consent through 18 months post-first dose for participants. However, among pregnant women, follow-up will continue for 12 months after the birth of the child or until 24 months post-first dose of the last participant enrolled, whichever happens first.

Participants will receive timed notifications via push notification, email, or phone call asking for any new or worsening health issues that have resulted in consultation with a medical doctor, an emergency room visit or hospitalisation, or a significant or long-term disability or incapacitation.

Participants can also submit unprompted AE information at any time though the app, web portal, or call centre. All AEs collected during this study will be considered solicited AEs, regardless if they were prompted or unprompted.

If a participant indicates a new or worsened health problem, the participant will be asked additional questions about the issue, intensity, treatment, and outcome. Adverse events collected for this study, both prompted and unprompted, will focus on the events of interest for the study assessments and analyses: SAEs, AESIs, and medically-attended AEFIs, including COVID-19 infections. Should other AE types, however, be reported, these will also be collected and managed accordingly and presented in the study report.

All collected events will be immediately available to study personnel in the investigator dashboard, where new events will be flagged. Study personnel will then validate the cases, request medical records, and assess seriousness and causality with input from HCPs and the medical records (Figure 2).

Study personnel will confirm all collected AEs with the participant, the proxy, the emergency contact, and/or through the review of medical records. If the participant received care from an HCP aside from their primary care physician, study personnel will follow up to obtain contact information for that HCP to permit a medical record request. Follow-up for AESIs with the HCP will include the completion of a targeted safety questionnaire. The adjudication committee can be consulted for advice on whether any reported non-serious symptoms or events may be a suspected AESI and will also adjudicate select AESIs (Section 10.6).

Certain situations require collection and reporting to the Sponsor, regardless of whether the situation was related to an AE: exposure to the product during pregnancy, exposure to the product while breastfeeding, overdose, medication error, off-label use issue, drug abuse, drug misuse, occupational exposure, product quality complaints/issues, and lack of efficacy. For lack of efficacy definition, refer to Section 10.1.6.

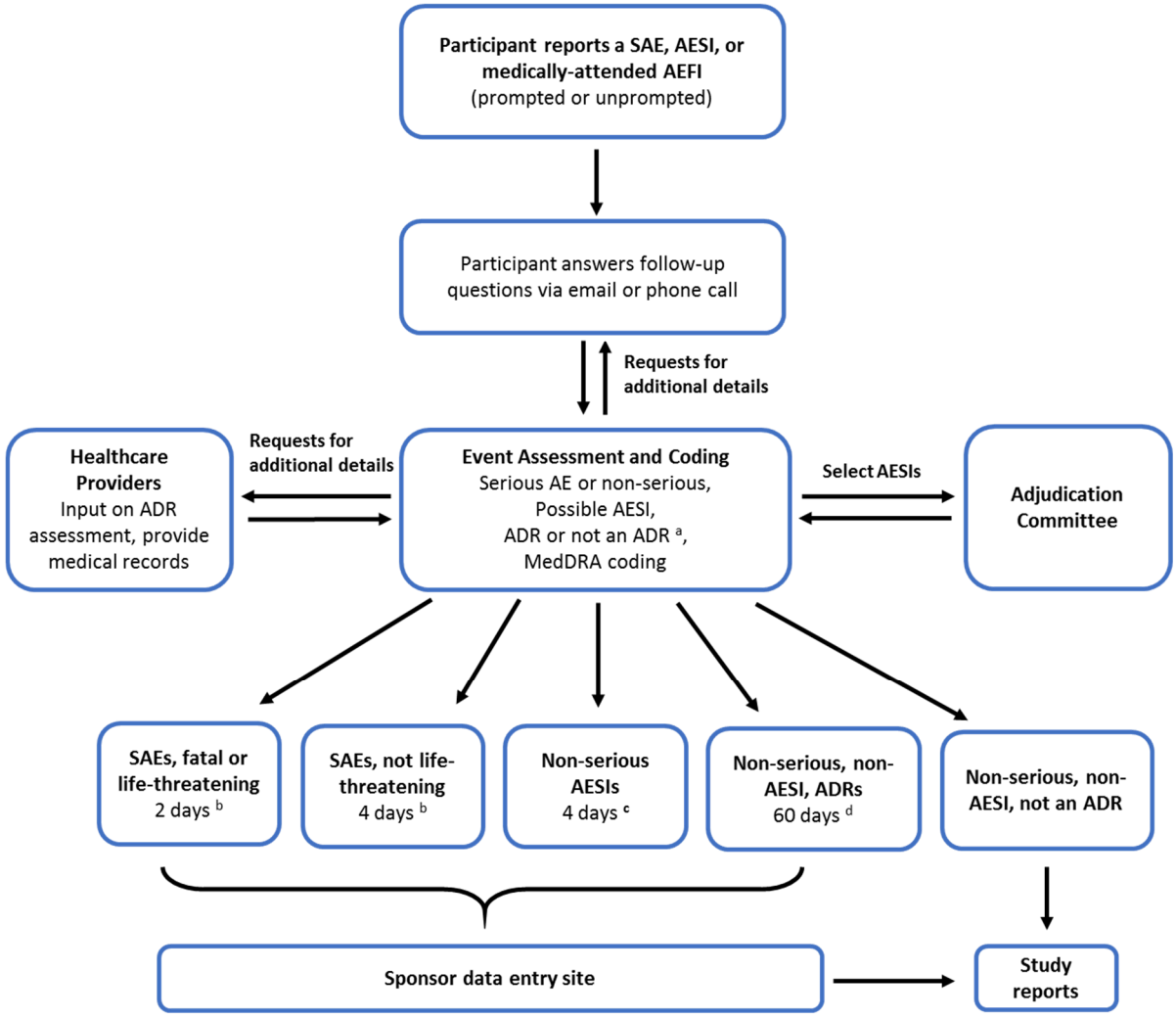
10.3 Adverse Event Reporting

Serious adverse events and AESIs require expedited reporting from non-Sponsor study personnel (CRO) to the Sponsor. Any fatal or life-threatening event must be reported within 2 calendar days and other SAEs and non-serious AESIs within 4 calendar days (Figure 2). Related, non-serious, non-AESI adverse events will be reported to the Sponsor within 60 days.

The Sponsor will report ADRs to the EudraVigilance database within the appropriate timeframe (15 days for serious ADRs and 90 days for non-serious ADRs) and will comply with all other health authority reporting requirements in the EU and elsewhere.

Additional details will be included in a Safety Handling Plan.

Figure 2 Adverse Event Data Collection and Reporting



[a] The primary source for causality information is the participant's HCP. Study personnel will utilise that information to determine if an event was an ADR.

[b] Fatal or life-threatening SAEs must be reported to the Sponsor within 2 calendar days. All other SAEs must be reported to the Sponsor within 4 calendar days.

[c] Non-serious AESIs should be reported to the Sponsor with 4 calendar days.

[d] For events that are not SAEs and not AESIs but are ADRs, the event should be reported to the Sponsor within 60 days.

AE, adverse event; ADR, adverse drug reaction; AEFI, adverse event following immunisation; AESI, adverse events of special interest; HCP, healthcare provider; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.

10.4 Adverse Event Coding

Adverse events and medical history will be classified according to the terminology of the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the World Health Organization (WHO) Drug Dictionary. A CRO will perform all coding.

10.5 Pregnancies and Outcomes

Pregnancy outcomes and outcomes in neonates/infants will be recorded in separate follow-up questionnaires.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the product may have interfered with the effectiveness of a contraceptive medication.

10.6 Independent Adjudication Committee

One or more Independent Adjudication Committees will be in place with the following mandate:

1 Provide advice, where needed, to study personnel on reported symptoms/events as to whether they should be treated as AESIs.
2 For select AESIs, the committee will independently review and adjudicate events, determining in a standardised, unbiased manner if the event meets the case definition criteria. AESIs considered for adjudication will include immune-mediated neurological conditions, and VAED, including VAERD.

Additional details will be included in the committee charter(s). The committee charter will be reviewed at least quarterly following the review of the AESI list for the Risk Management Plan and updates to the list of AESIs selected for adjudication will be considered contemporaneously.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The Sponsor plans to prepare quarterly interim reports, as detailed in Section 5. A final report describing the study results will be prepared at the end of study, when the last participant completes the follow-up period or discontinues from the study. An additional combined study report, jointly describing results from this study and the closely related US and UK studies, may also be prepared after the completion of all 3 studies. The Sponsor will provide all interim and final study reports to the relevant regulatory authorities. The Sponsor may also submit interim and/or final results for publication in peer-reviewed journals.

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Appendix A List of Stand-alone Documents

Table 6 List of Stand-alone Documents

Number	Date	Title
1	Not yet available	List of investigators and contact information

Appendix B ENCePP Checklist for Study Protocols

Appendix C Participant Questionniares

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

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