COVID-19 Vaccine (ChAdOx1-S [recombinant])

RISK MANAGEMENT PLAN (RMP)

For a summary of the RMP, please refer to PART VI.

European Union Risk Management Plan	
Drug Substance	ChAdOx1-S (recombinant) (AZD1222)
Version Number	1
Succession number	5
Data lock point	04 November 2020
Date of final sign-off	See e-signature page

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR COVID-19 VACCINE ASTRAZENECA (ChAdOx1-S [RECOMBINANT])

The content of this RMP has been reviewed and approved by the QPPV

ADMINISTRATIVE INFORMATION

Rationale for submitting an updated RMP

Not applicable for initial marketing authorisation submission.

Summary of significant changes in this RMP

Not applicable – this is Version 1 of the RMP.

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PART VII. ANNEXES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	Definition/Explanation
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ARDS	acute respiratory distress syndrome
ATC	Anatomical Therapeutic Chemical
CCDS	Company Core Data Sheet
CMO	Contract Manufacturing Organization
CSP	Clinical Study Protocol
DME	Designated Medical Events
EAS	enhanced active surveillance
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
eRMR	electronic Reaction Monitoring Report
EU	European Union
EVDAS	EudraVigilance Data Analysis System
GD	gestational day
GLP	Good Laboratory Practice
GVP	Good Pharmacovigilance Practices
HCP	healthcare professional
HEK	human embryonic kidney
HLT	High-Level Term
hPRR	Hybrid Proportional Reporting Ratio
ICH	International Conference on Harmonisation
ICSR	individual case safety report
ICU	intensive care unit
IM	intramuscular
LMP	last menstrual period
MenACWY	meningococcal group a, c, w-135, and y conjugate vaccine
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
NOEL	no observed effect level

Abbreviation/ Special term	Definition/Explanation
O/E	observed versus expected
PASS	post-authorisation safety study(ies)
PCR	polymerase chain reaction
PL	package leaflet
PRR	Proportional Reporting Ratio
PSUR	Periodic Safety Update Report
PT	Preferred Term (MedDRA)
QPPV	Qualified Person Responsible for Pharmacovigilance
RoR	reporting odds ratio
RMP	Risk Management Plan
S	spike
SARS-CoV-2	severe acute respiratory syndrome-coronavirus 2
SD	standard dose
SmPC	Summary of Product Characteristics (EU)
SMQ	Standardised MedDRA Query(ies)
SOC	System Organ Class
UK	United Kingdom
US/USA	United States of America
VAED	vaccine-associated enhanced disease
VAERS	US Vaccine Adverse Event Reporting System
vp	viral particles
WHO	World Health Organization

I. PART I: PRODUCT OVERVIEW

Table I-1 Product Overview

Active substance	ChAdOx1-S [recombinant] (AZD1222[a]) (formerly ChAdOx1 nCoV-19)
Pharmacotherapeutic group(s) (ATC Code)	Covid-19 vaccines (J07BX03)
Marketing Authorisation Applicant	AstraZeneca AB, 15185 Södertälje, Gothenburg, Sweden
Medicinal products to which this RMP refers	One
Invented name in the EEA	COVID-19 Vaccine AstraZeneca
Marketing authorisation produced	Centralised
Brief description of the product	**Chemical class:** Recombinant replication-deficient viral vector vaccine
	Summary of mode of action: COVID-19 Vaccine AstraZeneca is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS-CoV-2. Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralizing antibody and cellular immune responses.
	Important information about its composition: AZD1222 is produced in genetically modified human embryonic kidney (HEK) 293 cells and by recombinant DNA technology. *List of excipients*: L-Histidine, L-Histidine hydrochloride monohydrate, magnesium chloride hexahydrate, polysorbate 80, ethanol, sucrose, sodium chloride, disodium edetate dihydrate, and water for injections.
Hyperlink to the product information	COVID-19 Vaccine AstraZeneca Summary of Product Characteristics
Indication in the EEA	**Proposed** COVID-19 Vaccine AstraZeneca is indicated for active immunisation to prevent COVID-19 caused by SARS CoV 2, in individuals 18 years of age and older.
Dosage in the EEA	**Proposed** The COVID-19 Vaccine AstraZeneca vaccination course consists of two separate doses of 0.5 mL each. The second dose should be administered between 4 and 12 weeks after the first dose.
Pharmaceutical form(s) and strengths	**Proposed** Suspension for injection. One dose (0.5 mL) contains Chimpanzee Adenovirus encoding the SARS CoV 2 Spike glycoprotein (ChAdOx1-S), not less than 2.5×10^8 infectious units.
Will the product be subject to additional monitoring in the EU?	Yes

[a] Note: COVID-19 Vaccine AstraZeneca will be referred to by its development number (AZD1222) throughout this RMP.

II. PART II: SAFETY SPECIFICATION

II.1 MODULE SI: EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

II.1.1 Prevention of COVID-19

Incidence

COVID-19 is a novel infectious disease, caused by a novel (or new) coronavirus that has not previously been seen in humans.

Prevalence

Since the first reports of COVID-19, infection has spread worldwide, prompting the World Health Organization (WHO) to declare a public health emergency in late January 2020 (WHO 2020a) and characterise the novel CoV a pandemic in March 2020 (WHO 2020b). As of 13 December 2020, over 70 million confirmed cases have been diagnosed globally with more than 1.6 million deaths (WHO 2020c).

Demographics of the population in the proposed indication (age, gender, racial and ethnic origin), and risk factors for the disease

Individuals of any age can acquire SARS-CoV-2 infection, although the risk of severe COVID-19 increases with age. Epidemiological studies suggest that acute COVID-19 occurs at a lower frequency in patients < 18 years old than in adults (CDC 2020a, Livingston and Bucher 2020, Wu and McGoogan 2020), with a smaller percentage of children with COVID-19 requiring hospitalisation or intensive care unit admission relative to adults (CDC 2020a, ECDC 2020). Patients with COVID-19 can experience a wide range of symptoms from mild to critical illness (CDC 2020b, ECDC 2020). Older adults and persons with medical conditions, including cardiovascular disease, chronic kidney disease, obesity, diabetes, pulmonary disease, immunosuppression, and sickle cell disease, are at increased risk of severe or critical disease (Gallo Marin et al 2020).

Increasing evidence of disaggregated data from China and Europe suggest that the number of confirmed COVID-19 cases is comparable among men and women; however, men may have more severe illness and higher mortality from COVID-19 than women (Gebhard et al 2020). In the United States of America (USA), non-Hispanic American Indian, Alaska Native, and Black and Hispanic persons have been disproportionally affected (Tian et al 2020, Williamson et al 2020, Zheng et al 2020).

The main existing treatment options

Pre-exposure and post-exposure prophylaxis

In December 2020, COVID-19 mRNA Vaccine BNT162b2 was granted temporary authorisation under Regulation 174 by the Medicines and Healthcare products Regulatory Agency (MHRA, United Kingdom [UK]) for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus in individuals ≥ 16 years of age.

Management of persons with COVID-19

Patients with SARS-CoV-2 infection can experience a range of clinical manifestations, from no symptoms to critical illness. Currently, there is no approved product for the treatment of COVID-19, but approximately 56 candidate vaccines are in clinical development and approximately 166 are in nonclinical investigation (WHO 2020d). Management of COVID-19 is based on best supportive care and emerging standard of care, with protective effects demonstrated in clinical studies for some drugs and interventions, including the antiviral remdesivir and the anti-inflammatory steroid dexamethasone in adult patients with severe disease. Remdesivir was granted conditional marketing authorisation in the European Union (EU) and may be administered for the treatment of COVID-19 in adults and adolescents with pneumonia requiring supplemental oxygen; however, the WHO has more recently updated its guidelines advising against the use of remdesivir in hospitalised patients with COVID-19 (regardless of disease severity) based on a recent meta-analysis. The European Medicines Agency (EMA) is currently assessing the evidence, in addition to other relevant data, to evaluate whether changes are needed to the marketing authorisation of Veklury (remdesivir) in the EU (EMA 2020a).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Estimated rates of asymptomatic SARS-CoV-2 infection are approximately 40% to 45%, with viral transmission possible from asymptomatic individuals (CDC 2020b, Lavezzo et al 2020, Oran and Topol 2020). Symptomatic patients can experience a range of symptoms from mild to critical illness. Based on the largest cohort study to date of > 44000 persons with confirmed COVID-19 from China, the majority of patients experienced mild to moderate illness (Wu and McGoogan 2020):

- Mild (mild symptoms up to mild pneumonia): 81%
- Severe (dyspnoea, hypoxia, or > 50% lung involvement on imaging): 14%
- Critical (respiratory failure, shock, or multiorgan system dysfunction): 5%

Overall, among patients who developed severe illness, the median time to dyspnoea ranged from 5 to 8 days, the median time to acute respiratory distress syndrome (ARDS) ranged from 8 to 12 days, and the median time to intensive care unit (ICU) admission ranged from 10 to 12 days (Huang et al 2020, Wang et al 2020, Yang et al 2020, Zhou et al 2020). Among all

hospitalised patients, a range of 26% to 32% of patients were admitted to the ICU. Among all patients, a range of 3% to 17% developed ARDS compared to a range of 20% to 42% for hospitalised patients and 67% to 85% for patients admitted to the ICU. Mortality among patients admitted to the ICU ranges from 39% to 72% depending on the study. The median length of hospitalisation among survivors was 10 to 13 days (Chen et al 2020, Guan et al 2020, Huang et al 2020, Wang et al 2020, Wu et al 2020a, Yang et al 2020).

Complications associated with COVID-19

- Acute respiratory distress syndrome is the major complication in patients with severe disease and can manifest shortly after the onset of dyspnoea. Approximately 12% to 24% of hospitalised patients have required mechanical ventilation (Petrilli et al 2020, Richardson et al 2020, Yang et al 2020).
- Arrhythmias, acute cardiac injury, cardiomyopathy, and shock (Arentz et al 2020, Cao et al 2020, Chen et al 2020, Wang et al 2020).
- Thromboembolic complications, including pulmonary embolism and acute stroke (Danzi et al 2020, Klok et al 2020, Mao et al 2020, Zhang et al 2020).
  - Large vessel thromboembolisms have also been reported in patients < 50 years of age without risk factors (Oxley et al 2020)
- Laboratory evidence of an increased levels of proinflammatory cytokines, similar to cytokine release syndrome, with persistent fevers, elevated inflammatory markers (eg, D-dimer, ferritin), and elevated proinflammatory cytokines have been associated with critical and fatal illnesses (Huang et al 2020, Mehta et al 2020).
- Central and peripheral nervous system complications including Guillain-Barré syndrome (Paterson et al 2020, Toscano et al 2020), encephalopathy (Helms et al 2020), meningo-encephalitis (Moriguchi et al 2020), acute disseminated encephalomyelitis (Paterson et al 2020), and acute necrotizing encephalopathy (Poyiadji et al 2020).
  - Neurologic complications, in particular encephalopathy manifesting with agitated delirium, was common in patients with critical illness.
  - Delirium/encephalopathy was reported in approximately two thirds of patients with COVID-19-related ARDS (Helms et al 2020).
- A multisystem inflammatory syndrome with clinical features similar to those of Kawasaki disease and toxic shock syndrome has been described in children with COVID-19 (Licciardi et al 2020).
- Secondary infections and bacterial or fungal coinfections were reported in 8% of patients (in 62 of 806); these included mainly respiratory infections and bacteraemia (Rawson et al 2020). Several reports of invasive pulmonary aspergillosis among immunocompetent patients with ARDS from COVID-19 have been described (Koehler et al 2020, Rutsaert et al 2020).

- Psychotic symptoms have been related to other CoV infections. Structured delusions mixed with confusional features were the most frequent psychiatric manifestations observed in the COVID-19 patients. Psychotic symptoms were seen in patients with no previous history of psychosis (Parra et al 2020, Rogers et al 2020, Varatharaj et al 2020).

According to the WHO, the average recovery time from COVID-19 is approximately 2 weeks for mild illness and 3 to 6 weeks for severe illness, with wide ranges dependent on risk factors and comorbidities (WHO 2020c).

Important comorbidities

There are no known expected co-morbidities co-existing within the target population that are deemed to be clinically relevant or have an impact on AZD1222 administration.

The risk for severe illness from COVID-19 increases with age, particularly in adults aged 70 years and older (Wu et al 2020b). In addition, proposed comorbidities associated with COVID-19 severity and mortality include: cardiovascular disease, chronic kidney disease, obesity, diabetes, pulmonary disease, immunosuppression, and sickle cell disease (ACEP 2020, Gallo Marin et al 2020). It is therefore anticipated that elderly individuals, and those with these underlying comorbidities will be prioritised for vaccination following AZD1222 marketing approval.

II.2 MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

II.2.1 Summary of Key Findings from Nonclinical Data

Key safety findings from non-clinical studies and their relevance to human usage are described below.

Toxicity

- ***Key issues identified from acute or repeat-dose toxicity studies:***

  A repeat-dose Good Laboratory Practice (GLP) toxicity study with AZD1222 in mice has been conducted, with preliminary findings (not including recovery data) indicating that there were no clinically relevant observations considered to be related to administration of AZD1222.

  Furthermore, as the ChAdOx1 platform technology utilised for AZD1222 is well characterised, non-clinical toxicology findings with the ChAdOx1 MERS-CoV vaccine expressing the full-length spike (S) protein in mice are also considered of direct relevance to the non-clinical safety profile of AZD1222. Additionally, results from toxicology studies on similar replication-defective ChAd vaccines (ChAdOx1 NP+M1 and AdCh63 MSP-1) are also considered to be of significance.

  Results from repeat-dose mouse toxicology studies with vaccines ChAdOx1 NP+M1 and AdCh63 MSP-1 were consistent with ChAdOx1 MERS, and demonstrated that these vaccines were well tolerated with no associated adverse effects. Toxicity data (and toxicity in the target organs) from the ChAdOx1- and ChAd63-based vaccines follow the same pattern, with findings consistent with a predicted response to vaccine administration (eg, observed changes in the intramuscular (IM) injection site and immune system response).

  Relevance to human use: None. Note changes in IM injection site are discussed under 'local tolerance' below.

- ***Reproductive/developmental toxicity:***

  In a preliminary GLP embryo-foetal development study, IM administration of AZD1222 to groups of CD-1 female mice on Day 1 (13 days prior to pairing for mating) and again on gestational day (GD) 6 at 2.59×10^{10} vp per occasion (embryofoetal development phase), or on GD 6 and GD 15 at 2.59×10^{10} vp per occasion (littering phase) was well tolerated. Anti-S glycoprotein antibody responses were raised in dams following administration of AZD1222 and these were maintained through the gestational and lactation periods. Seropositivity of foetuses and pups was confirmed and was indicative of placental and lactational anti-S glycoprotein antibody transfer, respectively. There were

no test item-related effects seen for dams in-life including at the injection site, for female reproduction, foetal or pup survival and no abnormal gross pathology findings in pups or in dams in either phase. There were no test item-related foetal visceral or skeletal findings.

Relevance to human use: Based on these preliminary findings no reproductive or developmental effects are anticipated with AZD1222; however as pregnant and breast-feeding participants were excluded from AZD1222 clinical studies, this is regarded as an area of missing information until such time further data can be obtained in the clinical setting. It is also noted that the main GLP embryo-foetal development study audited draft report is due end of January 2021.

- ***Genotoxicity:***

  Genotoxicity studies have not been performed with AZD1222. Consistent with WHO guidelines on the nonclinical evaluation of vaccines (WHO 2005), genotoxicity studies are normally not required for the final vaccine formulation and therefore have not been conducted.

  Relevance to human use: Not applicable.

- ***Carcinogenicity:***

  Carcinogenicity studies have not been performed with AZD1222. Consistent with WHO guidelines on the nonclinical evaluation of vaccines (WHO 2005), carcinogenicity studies are not required for vaccine antigens. AZD1222 is a replication deficient, non-integrating adenovirus vector so there is no risk of carcinogenicity.

  Relevance to human use: Not applicable. To date, there have been no clinical reports of chromosomal vector integration following adenovirus vector-mediated gene transfer.

Safety pharmacology

- ***Respiratory and cardiovascular:***

  A single AZD1222 safety pharmacology study has been performed to date, designed to investigate the potential effects of AZD1222 on respiratory parameters in conscious male mice for at least 4 hours following administration, in addition to assessment of arterial blood pressure, heart rate and body temperature for up to 24 hours post-dose. Single IM dose levels of zero (control), and 2.59×10^{10} vp (AZD1222) were administered, with an interval of 3 days between the 2 treatment sessions.

  There were no changes in arterial blood pressure, heart rate, body temperature or respiratory parameters considered to be AZD1222-related. The no observed effect level (NOEL) for cardiovascular and respiratory assessment was 2.59×10^{10} vp.

  Relevance to human use: None.

- ***Neurobehavioral assessment:***

  An Irwin Screen was included in a GLP repeat-dose toxicity study with AZD1222. There were no effects on body temperature, pupil size, or Irwin Screen observations considered to be AZD1222-related. The NOEL for the Modified Irwin Screen phase was 3.7×10^{10} vp.

  Relevance to human use: None.

Other toxicity-related information

- ***Local Tolerance:***

  Local tolerance with AZD1222 has been assessed in a GLP repeat-dose toxicity study in mice, from which preliminary findings indicated no erythema or oedema at the injection sites after administration of AZD1222 on any dosing occasion.

  Local tolerance was also evaluated as part of a repeat dose GLP toxicology study in mice with the related ChAdOx1 MERS vaccine. Changes related to treatment with ChAdOx1 MERS vaccine were seen in the tissues of the IM injection site, the right lumbar lymph node (draining lymph node) and the spleen of mice. The inflammatory cell infiltrate seen in the tissues of the IM injection sites (infiltrates of lymphocytic/mononuclear inflammatory cells) were caused by the IM injection of the vaccine with the increased germinal centre development of the right lumbar lymph node caused by immune stimulation of the lymphatic drainage from this area and were not considered adverse.

  Relevance to human use: Changes in the IM injection site have been observed as part of local tolerance testing in repeat-dose mouse toxicology studies with similar replication-defective ChAd vaccines. Injection site reactions are common adverse effects of vaccine administration, and were observed in patients receiving AZD1222 in the clinical development programme. Consequently, injection site reaction is considered to be an identified risk of AZD1222; however, as this risk is well characterised, and does not require any additional pharmacovigilance or risk minimisation activities, it is not considered important for inclusion in the list of safety concerns.

- ***Vaccine-related quality considerations:***

  There are no adjuvant, stabilisers or preservatives included in the AZD1222 formulation that are deemed to influence the safety profile of the final vaccine product.

  Host cell proteins may remain as a contaminant as a result of the manufacturing process; however, levels are controlled by biological product deviation (BPD) release criteria, and are therefore not of relevance.

  Relevance to human use: None.

II.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

A summary of exposure to AZD1222, based on pooled data from the ongoing University of Oxford-sponsored studies COV001, COV002, COV003, and COV005 as of a data cut-off date of 04 November 2020, is provided in Table II-1.

Across the 4 University of Oxford-sponsored studies, participants were randomised to receive a single dose or two doses of either AZD1222 (at doses ranging from 2.2 to 5.0 × 10^{10} vp) or control. Generally, 5 × 10^{10} vp or equivalent is designated as a standard dose (SD), and 2.2 × 10^{10} vp or 2.5 × 10^{10} vp are designated as a low dose.

A further breakdown of these data by age group and sex (Table II-2) and race (Table II-3) are also provided.

Table II-1 Exposure to AZD1222 (Pooled Clinical Studies - Safety Analysis Set)

AZD1222 treatment	Number of participants
Received at least 1 dose, regardless of dose level (Any dose)	12021
Received a standard dose as the first dose (Dose 1 SD)	10069

Table II-2 Exposure to AZD1222 by Age Group and Sex (Pooled Clinical Studies - Safety Analysis Set)

Parameter	Number of participants	
	Any dose [a] (N = 12021) n (%)	Dose 1 SD [b] (N = 10069) n (%)
Age group at screening (years)		
18 - 64	10852 (90.3)	9013 (89.5)
≥ 65	1169 (9.7)	1056 (10.5)
Sex		
Female	6711 (55.8)	5462 (54.2)
Male	5310 (44.2)	4607 (45.8)

[a] Any dose: Participant that received at least one dose of AZD1222, regardless of dose level.

[b] Dose 1 SD: Participants received a standard dose as the first dose.

Table II-3 Exposure to AZD1222 by Race (Pooled Clinical Studies – Safety Analysis Set)

Race	Number of participants	
	Any dose [a] (N = 12021) n (%)	**Dose 1 SD [b] (N = 10069) n (%)**
White	9081 (75.5)	7283 (72.3)
Asian	425 (3.5)	330 (3.3)
Black	1211 (10.1)	1185 (11.8)
Other	798 (6.6)	789 (7.8)
Mixed	489 (4.1)	465 (4.6)
Unknown	16 (0.1)	16 (0.2)
Missing	1 (< 0.1)	1 (< 0.1)

[a] Any dose: Participant that received at least one dose of AZD1222, regardless of dose level.

[b] Dose 1 SD: Participants received a standard dose as the first dose.

II.4 MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

II.4.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Important exclusion criteria in the ongoing University of Oxford-sponsored studies are described below:

- ***Pregnant and breastfeeding women***
  - Reason for exclusion: Women who were pregnant or breastfeeding were excluded from the clinical studies to avoid potential harm to the unborn foetus or breastfed infant.
  - Considered to be included as missing information: Yes
- ***Patients with severe immunodeficiency***
  - Reason for exclusion: Patients with severe immunodeficiency or requiring systemic immunosuppressive medication were excluded from the clinical studies. Patients with severe immunodeficiency were excluded in order to avoid factors that may confound a complete understanding of the safety and efficacy of AZD1222 and to ensure interpretability of data.
  - Considered to be included as missing information: Yes
- ***Patients with severe and/or uncontrolled underlying disease***
  - Reason for exclusion: Patients with severe and/or uncontrolled cardiovascular, respiratory, gastrointestinal, liver, renal, endocrine/metabolic disease, and neurological illness were excluded from the clinical studies in order to avoid factors that may confound a complete understanding of the safety and efficacy of AZD1222 and to ensure interpretability of data. Participants with mild/moderate well controlled comorbidities were allowed to participate in the clinical studies.
  - Considered to be included as missing information: Yes (included in the area of missing information of *'Use in frail patients with co-morbidities [eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders]*')
- ***Paediatric and adolescent patients < 18 years of age***
  - Reason for exclusion: This population was excluded from the majority of AZD1222 clinical studies based on the general principle that paediatric patients are not routinely exposed to an investigational product where the benefit-risk profile for the

intended adult population has not yet been established, rather than due to a specific safety concern.

- Considered to be included as missing information: No

- Rationale: Use of AZD1222 in children and adolescents < 18 years is not part of the proposed indication.

- ***History of allergy to any component of the vaccine***
  - Reason for exclusion: Patients with known allergy/hypersensitivity to the active ingredient or comparator were excluded from the clinical studies as these individuals may have a higher risk of hypersensitivity reactions, including anaphylaxis.

  - Considered to be included as missing information: No

  - Rationale: AZD1222 is contraindicated in patients with known hypersensitivity to active substance and excipients, therefore use in this patient population is not applicable for the approved indication.

- ***Patients with bleeding disorder or prior history of significant bleeding or bruising following IM injections or venepuncture***
  - Reason for exclusion: As AZD1222 is administered as an IM injection, patients with history of bleeding disorders were excluded from the clinical studies due to the potential for an increased risk of injection site haemorrhage or bruising.

  - Considered to be included as missing information: No

  - Rationale: Prevention and management of injection site bleeding and/or bruising after IM injection in patients with bleeding disorders or prior history of significant bleeding is fully integrated into standard immunisation practice. Use in this patient population does not require further characterisation and is therefore not considered as missing information. Precautions for individuals with thrombocytopenia and/or coagulation disorders are described in the Summary of Product Characteristics (SmPC) Section 4.4.

- ***Planned receipt of any vaccine (licensed or investigational; other than AZD1222), 30 days before and after each AZD1222 vaccination administration***
    - Reasons for exclusion: Patients who had undergone previous vaccination within 30 days of the first dose of AZD1222 were excluded from clinical studies in order to avoid factors that may confound a complete understanding of the safety and efficacy data of AZD1222 and ensure interpretability of data.
    - Considered to be included as missing information: Yes (included in the area of missing information of *'Interaction with other vaccines'*)

II.4.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare serious adverse events following immunisation (especially those with rates of occurrence of less than 1 per 100000 vaccinees), or adverse reactions with a long latency.

II.4.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table II-4 Exposure of Special Populations Included or not Included in the Clinical Development Programme

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	Not included in the clinical development programme.
Patients with hepatic impairment	Exposure data for this population are not available.
Patients with renal impairment	Exposure data for this population are not available.
Patient with controlled cardiovascular disease	1540 of 12021 participants (12.8%) reported a history of cardiovascular disease at baseline in the pooled safety dataset (any dose group)
Patient with controlled respiratory disease	1253 of 12021 participants (10.4%) reported a history of respiratory disease at baseline in the pooled safety dataset (any dose group)
Immunocompromised patients	Not included in the clinical development programme.
Subpopulations carrying relevant genetic polymorphisms	Data not collected in the clinical development programme.

II.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

Not applicable.

II.6 MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

AZD1222 is a vaccine and is non-habit forming, non-narcotic, and is unlikely to have any potential for abuse.

II.7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

II.7.1 Identification of Safety Concerns in the Initial RMP Submission

All safety data available from the AZD1222 clinical development programme have been evaluated in order to formulate a list of identified risks (adverse drug reactions [ADRs]), in addition to the important potential risks described within this Risk Management Plan (RMP). Risks that are not included in the list of safety concerns (including the supporting rationales) are presented in Section II.7.1.1, with safety concerns relevant for inclusion in this RMP and their justifications presented in Section II.7.1.2.

Further to these sections, a list of adverse events of special interest (AESI) for AZD1222 is presented in Section II.7.1.3. In addition, considerations specific to COVID-19 vaccine safety are discussed in Section II.7.1.4.

II.7.1.1 Risk Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

- *Known risks that do not impact the risk-benefit profile:*
  - **Local injections site reactions (including injection site tenderness, pain, warmth, erythema, pruritus, bruising, and swelling)**: Injection-site reactions are commonly observed following IM injections and have been reported in AZD1222 clinical studies as very common ADRs, which were generally mild or moderate in severity and self-limiting. Specific guidance on the administration of AZD1222 for HCPs is provided in the SmPC, and this is fully aligned with standard clinical practice for the management of injection site reactions following immunisation.
  - **Lymphadenopathy, Decreased appetite, Headache, Dizziness, Somnolence, Nausea, Vomiting, Diarrhoea, Hyperhidrosis, Pruritus, Rash, Myalgia, Arthralgia, Fatigue, Malaise, Feverishness, Fever, and Chills:** These risks are frequently reported class effects for vaccines, all of which tend to be of low-grade severity, and self-limiting. These risks are all considered to be ADRs for AZD1222, and are listed in the AZD1222 SmPC. These risks are considered non-serious and have limited clinical impact.
- *Other reasons for considering risks not important:*
  - **HLA sensitisation in transplant candidates and recipients**: There is a theoretical concern related to the potential presence of soluble HLA or cell fragments from the human embryonic kidney (HEK) 293 cell line in AZD1222 leading to HLA sensitisation in transplant candidates and recipients. However, analytical investigations showed no evidence for the presence of HLA proteins in AZD1222 Process 4 Drug Substance and serum sample testing from AZD1222 vaccinated-

individuals showed no de-novo occurrence of anti-HLA antibodies following vaccination.

II.7.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important identified risks

There are no important identified risks for AZD1222.

Important potential risk

The following topics are classified as important potential risks for AZD1222:

- **Nervous system disorders, including immune-mediated neurological conditions**
  - *Risk benefit impact:* There is a theoretical concern that vaccination could be associated with immune-mediated neurological conditions. Very rare events of demyelinating disorders were reported in the AZD1222 clinical development programme; however, there is no evidence suggesting a causal relationship between AZD1222 and demyelinating disorders. Severe neurological conditions may result in persistent or significant disability or incapacity and require early detection, careful monitoring, and timely medical intervention.
- **Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)**
  - *Risk benefit impact*: There is a theoretical concern that vaccination against SARS-CoV-2 may be associated with enhanced severity of COVID-19 episodes which would manifest as VAED. Vaccine-associated enhanced respiratory (VAERD) refers to the predominantly lower respiratory tract presentation of VAED. Although available data have not identified VAED/VAERD as a concern for AZD1222, the risk of VAED/VAERD cannot be ruled out. VAED/VAERD may be potentially serious or life-threatening, and require early detection, careful monitoring, and timely medical intervention.
- **Anaphylaxis**
  - *Risk benefit impact:* Anaphylaxis is an acute serious allergic reaction with multi-organ-system involvement that can present or rapidly progress to a severe life-threatening reaction requiring immediate medical attention. Risk of anaphylaxis after all vaccines is estimated to be 1.31 per million vaccine doses (McNeil et al 2018). The risk of anaphylaxis is idiosyncratic in nature, and no serious or acute events of anaphylaxis were reported in AZD1222 clinical trials. Nevertheless, anaphylaxis is a topic of particular relevance for pandemic vaccines due to the large number of individuals who will undergo vaccination.

Missing Information

The following topics are classified as missing information for AZD1222:

- **Use during pregnancy and while breastfeeding**
  - *Risk benefit impact*: There is a limited amount of data from the use of AZD1222 in pregnant and/or lactating women, or from women who became pregnant after receiving AZD1222. Whilst preliminary non-clinical safety studies have not indicated any concern to date, the effect of AZD1222 on the foetus and breastfed infant is unknown, as data are currently insufficient to inform on any vaccine-associated risk. As AZD1222 is intended for use in mass vaccination campaigns in a large proportion of the global population, the collection of pregnancy and infant outcomes data with the aim of characterising the safety profile in this population, is considered necessary.
- **Use in immunocompromised patients**
  - *Risk benefit impact*: Immunocompromised individuals are at greater risk of morbidity and mortality from vaccine-preventable disease. In addition, vaccines may be less effective in severely immunocompromised subjects, as the vaccinees weakened immune system may not mount a sufficient response. Although there is no evidence that the safety profile of this population receiving AZD1222 will be different to that of the general population, given the paucity of data, the possibility cannot be excluded. As immunodeficient subjects have been identified as a priority group for initial vaccination in several jurisdictions following vaccine availability, proactive data collection in this population receiving AZD1222 is important.
- **Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)**
  - *Risk benefit impact:* This population is potentially at risk of developing a more severe manifestation of COVID-19. Although there is no evidence that the safety profile of this population receiving AZD1222 will be different to that of the general population, given the paucity of data, the possibility cannot be excluded. As this population has been identified as a priority group for initial vaccination in several jurisdictions following vaccine availability, proactive data collection in this population receiving AZD1222 is important.
- **Use in patients with autoimmune or inflammatory disorders**
  - *Risk benefit impact:* This population is potentially at risk of developing a more severe manifestation of COVID-19. Although there is no evidence that the safety profile of this population receiving AZD1222 will be different to that of the general population, given the paucity of data, the possibility cannot be excluded. As this population has been identified as a priority group for initial vaccination in several jurisdictions following vaccine availability, proactive data collection in this population receiving AZD1222 is important.

- **Interactions with other vaccines**

  Risk benefit impact: The safety, immunogenicity, and efficacy of AZD1222 when co-administered with other vaccines (eg.,with seasonal illness vaccines [such as the influenza and pneumococcal vaccines]) has not been evaluated. Therefore, whilst there is currently no evidence to suggest the safety profile of the subjects receiving AZD1222 when co-administered with other vaccines would be impacted, given the paucity of data, the possibility cannot be excluded.

- **Long-term safety**
  - *Risk benefit Impact:* Given the expedited nature of the AZD1222 clinical development programme, understanding of the long-term safety profile of AZD1222 is currently limited. Whilst there is currently no evidence to suspect an adverse long-term safety profile, given the paucity of data, the possibility cannot be excluded.

II.7.1.3 Adverse Events of Special Interest

Adverse events of special interest in the context of this RMP are defined as adverse events that may be of interest in the context of a mass COVID-19 vaccine administration campaign, which may represent potential signals requiring timely investigation or regulatory action, that could lead to a change in the benefit-risk balance of AZD1222, or that could require prompt communication to the public by regulatory or public health authorities.

The list of AESIs applicable to AZD1222 is presented in Table II-5. This list is informed by global regulatory guidance, global vaccine safety research networks, and data obtained from the ongoing AZD1222 clinical development programme. The inclusion of these AESIs may be based on theoretical considerations and/or be based on past associations, whether causal or not, with different vaccines, or are conditions that are expected to occur naturally with COVID-19 in the absence of vaccination. This AESI list will be reviewed on an ongoing basis, and will be updated as necessary. Consequently, should an update to the AESI list be required, any impact on the ongoing/planned PASS will be assessed at that time.

Medical Dictionary for Regulatory Activities (MedDRA) search term lists (at the Preferred Term [PT] level) used for AESIs are included in Annex 7.

Table II-5 List of AZD1222 AESIs

Body System/Classification	AESI
Other system	Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)
	Multisystem inflammatory syndrome in children
	Sudden Death
Immunological	Autoimmune thyroiditis
	Anaphylaxis

Table II-5 List of AZD1222 AESIs

Body System/Classification	AESI
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	Thrombocytopenia
	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/ME/PVFS
Pregnancy /Foetal /Neonatal	Pregnancy outcome – Maternal
	Pregnancy outcome – Neonates
Skin	Erythema multiforme

II.7.1.4 Further Considerations for COVID-19 Vaccines

Further considerations for RMP Module SVII in specific relation to COVID-19 vaccine development are also described in the EMA guidance document 'Consideration on core requirements for RMPs of COVID-19 vaccines' (EMA/544966/20200) (EMA 2020b). These considerations are therefore discussed below for completeness:

- ***Reactogenicity***

  Solicited local and systemic adverse events (AEs) were reported by 74.7% and 73.0% of evaluated participants, respectively, within the first 7 days following any dose of AZD1222. In the control group (MenACWY vaccine active control or saline placebo),

solicited local and systemic AEs were reported by 50.4% and 59.6% of participants, respectively. The reduced reactogenicity in the control group of the overall pooled safety population is expected given that participants in this group could have received either the MenACWY active control or saline placebo compared to the AZD1222 group, in which all participants received active treatment.

With respect to the reactogenicity profile of AZD1222 by age group, solicited local and systemic AEs were milder and reported less frequently in older adults (≥ 65 years) compared to younger adults (18 to 64 years). Solicited AEs were milder and reported less frequently after the second dose than after the first dose in both age groups. Furthermore, no imbalances in the nature and severity of reactogenicity events was noted in participants with comorbidities.

The reactogenicity events associated with AZD1222 occurring in close temporal association to vaccination were generally mild to moderate in severity, of short duration, and generally did not require medical intervention; and were thereby of limited clinical impact. Further characterisation of solicited local and systemic reactogenicity events is therefore not warranted.

- ***Formulation and preparation aspects of the vaccine***

  AZD1222 can only form infectious particles in E1-complemented producer cells, which are in factories. In contrast, AZD1222 does not form infectious particles in vaccinated individuals. Shedding from vaccinated individuals to unvaccinated close contacts does not occur, because the vaccine is injected via IM route. As AZD1222 is replication-deficient, it does not replicate in vaccinated individuals, so transmission does not occur.

  In animals and humans, ChAdOX1 reversion to virulence has not been detected. The biological material used in the manufacturing process are not known to be pathogenic to humans, and are thus not known to have potential for infection in humans. Contaminations introduced by the manufacturing process do not have a potential for transmission of infectious agents.

- ***Risk of vaccine drop out***

  Data pertaining to the reason for drop out (ie, discontinuation from treatment) following each dose of AZD1222 were not collected in pivotal studies. However, the overall discontinuation rate in the pooled safety dataset (any dose group; N = 12021) indicates that early discontinuation for any reason was very low in the AZD1222 arm (n = 65 participants [0.5%]).

- ***Relevance of the long-term follow-up***

  Given the expedited nature of the AZD1222 clinical development programme in response to the global COVID-19 pandemic, understanding of the long-term safety profile of AZD1222 is currently limited. Consequently, whilst there is no scientific evidence to suspect an adverse long-term safety profile, it is recognised that further follow-up for all vaccines developed in response to the COVID-19 pandemic is required. This topic is therefore included as an area of missing information (see Section II.7.3.2).

  For AZD1222, long-term safety will be evaluated in 2 ways: through the planned post-authorisation safety study (PASS) activities (see Section III.2.1), and through follow-up in ongoing pivotal clinical studies in the AZD1222 clinical development programme (see Section III.2.2).

  The 4 planned PASS activities will follow participants for varying lengths of time to allow meaningful data collection for the evaluation of long-term safety and effectiveness: participants in the enhanced active surveillance (EAS) studies and pregnancy registry will be followed up for 1 year, and participants in the post-marketing observational study using existing secondary health data sources will be followed up for 2 years. The design of the post-marketing effectiveness study remains under consultation with external collaborators.

  In the ongoing pivotal clinical studies, it is planned to follow-up all participants contributing to safety pool for up to 1-year either post-last vaccination (in studies COV001, COV002, COV003) or from enrolment (Study COV005). However, it is recognised that with the increasing availability of alternative authorised COVID-19 vaccines, individuals may seek to receive confirmation of their vaccination status, thereby requesting to be unblinded and thus limiting the ability to collect long-term follow-up data for the entire study population in an unbiased fashion. In order to manage this potential issue, AstraZeneca (in collaboration with the Sponsor of the ongoing pivotal clinical studies) has proactively developed a set of options available to all study participants with regards to their continuation in the study, as follows:

  A) Remain blinded in the trial per the Clinical Study Protocol (CSP).

  B) Request to be unblinded, allowing a discussion with the investigator to take place on the best course of action based on risk to the individual participant. Unblinding options include:

     1) If a participant has received active treatment with AZD1222:

        - If the participant has received only 1 dose of AZD1222 the investigator may encourage the study participant to remain in the study. Such

participant will either receive a locally authorised vaccine, or receive the second dose of AZD1222 as local regulatory/guidance dictates.

- If the participant has received 2 doses of AZD1222 the investigator will recommend that they continue in the study.

2) If a participant has received control: choose to receive another vaccine; however, participants will be encouraged to have a withdrawal visit whereby final safety and immunology data will be collected. The choice of authorised vaccine for the study participant will be dependent on the timing of the unblinding relative to the availability of locally authorised vaccines.

Any participant who requests to be unblinded will have this decision captured in the study database for transparency.

AstraZeneca anticipate that a significant number of participants may be unblinded during the follow-up period of the pivotal studies. Consequently, AstraZeneca is currently assessing with global experts, health authorities and other sponsors, the most appropriate and robust way to evaluate long term safety data generated within the context of the pandemic whereby new vaccines are being introduced during the conduct of these randomised trials.

- ***Risks of vaccination errors in a context of mass vaccination campaigns***

  As AZD1222 will initially be administered in large scale vaccination programmes, there is a potential to introduce the risk of vaccination errors. Vaccination errors may relate to administration, vaccination scheme, storage conditions, or errors associated with multi-dose vials. These potential vaccination errors will be mitigated through a number of strategies:

  - SmPC Section 6.6 contains instructions on administration and storage conditions for AZD1222. Instructions on vaccination scheme are provided in SmPC Section 4.2.
  - HCP and the public guides have been prepared, which include specific sections on AZD1222 administration and storage.
  - Medical information call centres are available for the public and HCPs to respond to questions about AZD1222.
  - Traceability and Vaccination reminder cards will be provided by AstraZeneca, where applicable (see Section III.1.6).

Furthermore, as other COVID-19 vaccines are also available, there is the potential for confusion or interchangeability with other COVID-19 vaccines. The above tools will facilitate the education of HCPs on the avoidance of this situation.

II.7.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

II.7.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

II.7.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Potential Risk: Nervous system disorders, including immune-mediated neurological conditions

Potential mechanisms

Several hypothetical biologic mechanisms have been proposed to explain the pathophysiology of neurologic adverse reactions following immunisation; most involve the concept of autoimmunity and the possibility that the immunostimulatory effect of the vaccine results in an aberrant immunologic response (Stratton et al 1994).

Evidence source(s) and strength of evidence

The association between vaccines and acute demyelinating events has been assessed in a range of studies and expert reviews, including a population-based analysis of nearly 64 million vaccine doses in the US, which concluded that if there is an association between transverse myelitis and vaccines, it is < 2 per million doses of live-zoster and live-attenuated influenza vaccines, and < 1 per million doses for other vaccines (Baxter et al 2016). Moreover, demyelinating diseases occur more frequently with infections than with vaccination (Miravalle et al 2010). Taken together, the evidence is inconclusive regarding a causal relation between contemporary vaccines and acute demyelinating events (Principi and Esposito 2020, Mouchet et al 2018, Phillips et al 2018).

Characterisation of the risk

A review of the events in the pooled safety dataset in the MedDRA SOC of Nervous System Disorders in AZD1222-treated participants (any dose group) demonstrated that reactogenicity events (ADRs) comprised the majority of events in this SOC. No imbalance (between the AZD1222 group and the control group) in the incidence of events in the Nervous System Disorders SOC was noted when reactogenicity ADRs were removed.

Overall, there were no clinically meaningful imbalances in the incidence of neurological AESIs between the AZD1222 group (n = 64 participants [0.5%]) and the control group (n = 79 participants [0.7%]) in the pooled safety dataset (any dose group).

Nonserious AEs of facial paralysis occurred in 3 participants in the AZD1222 group and 3 participants in the control group.

There were 3 SAEs of demyelinating events: 2 cases in the AZD1222 group (1 case of transverse myelitis, and 1 case of multiple sclerosis in a participant with pre-existing, but previously unrecognised, multiple sclerosis), and 1 case of myelitis in the control group.

Risk factors and risk groups

There are no known risk factors for the development of nervous system disorders, including immune-mediated neurological conditions, following vaccination.

Preventability

Prevention of nervous system disorders, including immune-mediated neurological conditions, in the context of SARS-COV-2 vaccination is unknown.

Impact on the risk-benefit balance of the product

Severe neurological conditions, if not recognised or managed appropriately, may result in persistent or significant disability or incapacity.

Public health impact

Severe neurological disorders are very rare, and as such the public health benefit of vaccination is considered to outweigh the very rare potential occurrences of such events.

Important Potential Risk: Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)

Potential mechanisms

The pathogenesis of VAED in the context of SARS-CoV-2 is unclear, and there are no consistent mechanisms or immune markers of disease enhancement from nonclinical studies (Haynes et al 2020). VAERD refers to the predominantly lower respiratory tract presentation of VAED. The mechanism of the pathogenesis of VAERD may be specific to the lower respiratory tract, or may be part of a systemic process.

Evidence source(s) and strength of evidence

There is a theoretical concern that vaccination against SARS-CoV-2 may be associated with enhanced severity of COVID-19 episodes which would manifest as VAED/VAERD. Vaccine-associated enhanced disease was observed in children given formalin-inactivated whole-virus

vaccines against respiratory syncytial virus and measles virus (Haynes et al 2020), and findings from experimental models of SARS-CoV and MERS-CoV infection suggest that VAED/VAERD may be possible in certain conditions (FDA 2020).

Characterisation of the risk

No events of VAED/VAERD have been reported in the current AZD1222 clinical development programme.

Risk factors and risk groups

There are no known risk factors identified for VAED/VAERD.

Preventability

Prevention of VAED/VAERD in the context of SARS-COV-2 is currently unknown.

Impact on the risk-benefit balance of the product

Vaccine-associated enhanced disease (including VAERD) may present as severe disease or modified/unusual clinical manifestations of a known disease presentation and may involve one or multiple organ systems. Subjects with VAED/VAERD may experience rapid clinical deterioration and will likely require non-invasive or invasive mechanical ventilation; and patients diagnosed with ARDS have poorer prognosis and potentially higher mortality rate.

Public health impact

As this safety concern is currently theoretical in relation to AZD1222 administration, there is no public health impact noted at this time.

Important Potential Risk: Anaphylaxis

Potential mechanisms

Anaphylaxis is an acute reaction mediated by an immunological mechanism which results from the sudden release of mast cells and basophil mediators in response to the introduction of a foreign substance to the body.

Evidence source(s) and strength of evidence

The risk of anaphylaxis is idiosyncratic in nature, with anaphylaxis risk after all vaccines estimated to be 1.31 (95% CI, 0.90-1.84) per million vaccine doses (McNeil et al 2018). No serious or acute events of anaphylaxis were reported in AZD1222 clinical trials, and therefore the risk of anaphylaxis is a theoretical concern based on data from other vaccines (as a class of medications).

Characterisation of the risk

There were no serious reports of anaphylaxis, and no reported acute allergic reactions in the AZD1222 clinical development programme.

Risk factors and risk groups

Almost all components of a vaccine (including excipients) may be considered as potential triggers of an allergic reaction, and therefore known hypersensitivity to any component of AZD1222 and/or a history of allergic reactions are considered to be risk factors for the development of anaphylaxis.

Preventability

Individuals with known hypersensitivity to any component of AZD1222 (as listed in SmPC Section 6.1) should not undergo vaccination (as described in SmPC Section 4.3).

In individuals with no known hypersensitivity to any component of AZD1222, prevention of anaphylaxis may not be possible; and therefore appropriate supervision and treatment should always be available at the time of vaccination (as described in SmPC Section 4.4). A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of AZD1222.

Impact on the risk-benefit balance of the product

Anaphylaxis is a life-threatening reaction which involves multiple organ systems and can progress rapidly. Anaphylaxis requires immediate medical intervention.

Public health impact

As this safety concern is currently theoretical in relation to AZD1222 administration, there is no public health impact noted at this time.

II.7.3.2 Presentation of Missing Information

Missing Information: Use during pregnancy and while breastfeeding

Evidence source

There is a limited amount of data from the use of AZD1222 in pregnant and/or lactating women, or from women who became pregnant after receiving AZD1222. Whilst preliminary non-clinical safety studies have not indicated any concern to date, the effect of AZD1222 on the foetus and breastfed infant is unknown, as data are currently insufficient to inform on any vaccine-associated risk.

As AZD1222 is intended for use in mass vaccination campaigns in a large proportion of the global population, the collection of pregnancy and infant outcomes data in with the aim of characterising the safety profile in this population, is considered necessary.

Population in need of further characterisation

Use of AZD1222 in pregnant and breastfeeding women will be investigated in the planned PASS activities (EAS, a post-marketing observational study using existing secondary health data sources, and a pregnancy registry; see Sections III.2.1.1, III.2.1.3 and III.2.1.2, respectively, for further details).

Missing Information: Use in immunocompromised patients

Evidence source

Vaccines may be less effective in severely immunocompromised subjects, as the vaccinees weakened immune system may not mount a sufficient response; however, immunocompromised individuals may also be at greater risk of morbidity and mortality from vaccine-preventable disease, and consequently this population have been identified as a priority group for initial vaccination in several jurisdictions following vaccine availability. Although there is no evidence that the safety profile of this population receiving AZD1222 will be different to that of the general population, given the paucity of data, the possibility cannot be excluded.

Population in need of further characterisation

Use in immunocompromised patients will be investigated in the planned PASS activities (EAS, a post-marketing observational study using existing secondary health data sources, a post-marketing safety study in patients receiving immunosuppressant medication or with primary immunodeficiency, and an interventional study in immunocompromised subjects; see Sections III.2.1.1 and III.2.1.3 for further details).

Missing Information: Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)

Evidence source

Frail subjects with co-morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) are potentially at risk of developing a more severe manifestation of COVID-19, and as a consequence have been included as a priority group for initial vaccination in several jurisdictions following vaccine availability. Although there is no evidence that the safety profile of this population receiving AZD1222 will be different to that of the general population, given the paucity of data, the possibility cannot be excluded.

Population in need of further characterisation

Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) will be investigated in the planned PASS activities (EAS and a post-marketing observational study using existing secondary health data sources; see Sections III.2.1.1 and III.2.1.3, respectively, for further details).

Missing Information: Use in patients with autoimmune or inflammatory disorders

Evidence source

Subjects with autoimmune or inflammatory disorders are potentially at risk of developing a more severe manifestation of COVID-19, and as a consequence have been included as a priority group for initial vaccination in several jurisdictions following vaccine availability. There is no evidence form AZD1222 clinical studies to date that the safety profile of this population differs with that of the general population. However, given the paucity of data, the possibility cannot be excluded.

Population in need of further characterisation

Use in patients with autoimmune or inflammatory disorders will be investigated in the planned PASS activities (EAS and a post-marketing observational study using existing secondary health data sources; see Sections III.2.1.1 and III.2.1.3, respectively, for further details).

Missing Information: Interactions with other vaccines

Evidence source

The safety, immunogenicity, and efficacy of AZD1222 when co-administered with other vaccines (eg, seasonal illness vaccines [such as the influenza and pneumococcal vaccines]) has not been evaluated. Therefore, whilst there is currently no evidence to suggest the safety profile of the subjects receiving AZD1222 when co-administered with other vaccines would be impacted, given the paucity of data, the possibility cannot be excluded.

Population in need of further characterisation

The co-administration of AZD1222 with other vaccines (either together, or 30 days before or after administration) will be investigated in the planned PASS activities (EAS studies and a post-marketing observational study using existing secondary health data sources; see Sections III.2.1.1 and III.2.1.3, respectively, for further details). Vaccines to be evaluated include the influenza and pneumococcal vaccines.

Missing Information: Long-term safety

Evidence source

Given the expedited nature of the AZD1222 clinical development programme, understanding of the long-term safety profile of AZD1222 is currently limited. However, there are no known risks with a potentially delayed onset, with the exception of the theoretical concern of VAED/VAERD. Whilst there is currently no evidence to suspect an adverse long-term safety profile, given the paucity of data, the possibility cannot be excluded.

Population in need of further characterisation

Long-term safety will be evaluated in 2 ways: through the planned PASS activities (EAS studies and a post-marketing observational study using existing secondary health data sources; see Sections III.2.1.1 and III.2.1.3, respectively, for further details) and through follow-up in ongoing clinical studies in the AZD1222 clinical development programme (see Section III.2.2).

II.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

A summary of safety concerns for AZD1222 is presented in Table II-6.

Table II-6 Summary of Safety Concerns

Important identified risks	None
Important potential risks	• Nervous system disorders, including immune-mediated neurological conditions • Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) • Anaphylaxis
Missing information	• Use during pregnancy and while breastfeeding • Use in immunocompromised patients • Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) • Use in patients with autoimmune or inflammatory disorders • Interactions with other vaccines • Long-term safety

III. PART III: PHARMACOVIGILANCE PLAN

III.1 Routine Pharmacovigilance Activities

AstraZeneca undertakes routine pharmacovigilance activities consistent with the International Conference on Harmonisation (ICH) E2E Pharmacovigilance Planning Guideline.

Routine pharmacovigilance activities (as defined by standard operating procedures and guidelines) are designed to rapidly assess the ongoing safety profile of AZD1222 throughout clinical development and in the post-authorisation period in order to characterise and communicate pertinent safety data appropriately. A comprehensive description of all aspects of the pharmacovigilance system is provided in the Pharmacovigilance System Master File, which is available upon request.

In addition to ICH requirements, AstraZeneca's routine pharmacovigilance activities in relation to AZD1222 are also aligned with the measures described in GVP PI, GVP IX for vaccine surveillance, and recent regulatory guidance specific vaccine risk management in the context of the COVID-19 pandemic (EMA 2020b, MHRA 2020). Routine surveillance activities to specifically address the challenges in the context of the pandemic are described in the sections below.

III.1.1 Signal Detection

Given the specific requirements of vaccines and the need to rapidly identify potential safety issues during the pandemic, routine signal detection activities will be supplemented as described below.

Data sources that will be used for signal detection and the frequency of their review are listed in Table III-1.

Table III-1 Data sources for signal detection and frequency of review

Data Source	Frequency of review
AstraZeneca global safety database (SAPPHIRE), which includes Clinical Trial SAEs and all Post Marketing case reports received by AstraZeneca and License Partners (including special situation reports and case reports from the MHRA and EU [EudraVigilance])	Weekly
EudraVigilance Data Analysis System (EVDAS) Electronic Reaction Monitoring Report (eRMR)	Bi-Weekly
US Vaccine Adverse Event Reporting System (VAERS)	Weekly
Literature (Embase and Insight Meme)	Weekly
All Clinical Trial AEs from AZ and non-AZ sponsored studies	Bi-Weekly
Batch distribution data	Monthly

Due to the unique nature in which safety data will be obtained for AZD1222 (both in methods

of data collection and in volume on data), multiple methods for the evaluation of data retrieved from the above data sources will be utilised for signal detection. These data sources will be interrogated via a number of internal systems using a combination of quantitative and qualitative methodology. Further detail on both methodologies is provided below.

Quantitative methodology

- *Disproportionality analysis using a targeted database*: Due to the limited volume of vaccine cases within AstraZeneca's safety database, an external database (the US Vaccine Adverse Event Reporting System [VAERS]) was chosen for application of disproportionality analysis due to its large and varied vaccine profile. Two proportionality reporting ratio scores from this analysis are produced: a hybrid ratio score, and a standard proportionality score. The difference between these scores is described below:
  - Disproportionality analysis score using a Hybrid Proportional Reporting Ratio (hPRR) – AZD1222 safety data in AstraZeneca's safety database compared to all VAERS data
  - Disproportionality analysis score (Proportional Reporting Ratio [PRR]) using VAERS data alone - comparison of AZD1222 vaccine reports in VAERS to all VAERS data.

  A ratio score of ≥ 1.8 will be applied for events that require evaluation for both methods. A filter of 3 case minimum is applied and a Yates corrected chi-square ≥ 4 is also applied for both hPRR and PRR.

- *Disproportionality analysis using EudraVigilance*: EudraVigilance data is downloaded and integrated into the AstraZeneca Global Safety Database on daily basis. This data is included in the weekly data review. Additionally, an eRMR will be generated on a biweekly basis and will be included as a part of surveillance review. The eRMR report will be generated sing the Active Substance High Level value of 'CHADOX1-SARS-COV-2'. A series of filters are applied to the eRMR to identify events requiring review. Examples of these filters include events that are statistically significant (RoR > 1.0), or are Important Medical Events, Designated Medical Events (DME) per the EMA, or have an increase in the number of reported cases.

Qualitative methodology

- *Routine safety data review*: Data from AstraZeneca's safety database will be extracted in the form of specific reports covering the following categories of safety data (in which AZD1222 is captured as a suspect medication):
  - All AEs; stratified by country, seriousness, and age group
  - Fatal AEs

- Serious Unlisted AEs
- All AEs on AstraZeneca's Designated Medical Event (DME) list
- AESI (including important potential risks) (see Section II.7.1 for further details of AESIs)
- Disease specific Standardised MedDRA Queries (SMQs)
- Pregnancy reports
- Special Situations (example: reports of medication error, overdose, lack of efficacy, and potential interactions with other vaccines administered concomitantly)

These reports will be produced and reviewed weekly as part of routine surveillance activities. In addition, daily reports may be produced for cases not yet closed on the safety database to allow for early identification of any potential safety issue. Reports will provide both in-period and cumulative event counts, and comparisons with previous event counts will be conducted to determine if there are any sudden increases or unusual patterns of AE reporting, as population-level exposure to AZD1222 increases over time. Furthermore, these reports will facilitate the identification of potential serious but rare adverse reactions that may be associated with AZD1222 use.

- *Batch-related adverse reactions*: On a monthly basis, a report of AEs by batch number will be generated and analysed against batch distribution data using a gamma-Poisson shrinker model to identify batches with a higher proportion of AE reporting. Batches meeting the threshold for analysis will be examined in further detail in order to identify any safety issues potentially related to the quality of AZD1222.

- *Time-series analysis*: To aid in the identification of changes in case reporting over time, time-series analyses will be considered based on necessity, and subject to the availability of baseline data.

- *Observed versus expected (O/E) analysis*: O/E analysis will be conducted for events/medical concepts provided on the AESI list (see Section II.7.1). The stratified background rates publicly available from the ACCESS program and other industry groups collaborating with Vaccines Europe will be analysed against the observed reports received in AstraZeneca's safety database, using distribution data and/or exposure data collected from EU member countries when made publicly available, on a monthly basis. To account for potential under reporting of AEs, sensitivity analysis will be performed. Where appropriate, standard statistical testing methodology will also be applied. To further enhance background rate identification additional literature review may be conducted if ACCESS data is insufficient or unavailable.

- *Time-to-onset analysis*: An additional signal detection methodology currently under evaluation is time-to-onset analysis. This methodology will consider the amount of lapsed time from vaccine administration to event onset for a given event compared to onset time for all other vaccines for that event.

Mixed methodology

- *Cluster Analysis*: Cluster analyses will be performed on an ad hoc basis (where justified), based on the results of routine surveillance methods described above. Should a cluster analysis be performed as part of the signal detection process, this will be included in the Monthly Safety Summary Report (see Section III.1.4). Justifications will be described for such analyses, and all PTs will be provided.

III.1.1.1 Signal Evaluation

Any potential signal identified through the signal detection processes described in Section III.1.1 will be thoroughly evaluated (utilising all sources of data available) to validate the signal. This will include expanded analysis of all external regulatory database information (EudraVigilance, VigiBase, VAERS), SAPPHIRE case data, literature publications, data from clinical studies, epidemiology data, and O/E analysis of the event(s) of interest. All validated signals will be presented in the Monthly Summary Safety Report (see Section III.1.4).

Following validation of any signal, a further internal safety review will be performed based on AstraZeneca's standard operating procedures. Following this, should there be a reasonable possibility of a causal relationship with AZD1222, appropriate updates will be made to the core product information, which will subsequently be shared with Competent Authorities through standard regulatory processes.

III.1.2 ICSR Reporting

To address the unique challenges associated with a mass vaccination campaign work is ongoing to ensure that the necessary pharmacovigilance infrastructure is in place to address the expected rapid increase in post-marketing individual case safety reports (ICSRs) for processing and regulatory reporting. This will in turn facilitate the rapid provision of high-quality data to support the detection and evaluation of potential safety issues. Some of the measures put in place include scaling of infrastructure and systems, recruitment and training of additional resources, and implementation of specific processes and procedures.

All ICSRs received for AZD1222 will be processed and reported in accordance with the requirements specified in the EMA guidance document entitled 'Detailed Guidance on ICSRs in the context of COVID-19 - Validity and coding of ICSRs (EMA/174312/2020)' (EMA

2020c). Spontaneous cases of Confirmed Vaccination Failure[1] when AZD1222 is used in accordance with its authorisation, will be reported within the required 15 days of receipt.

For all AZD1222 ICSRs received, in addition to data regarding the subject demographics and adverse reaction (including outcome), the following data will also be proactively sought, if not available with the initial report:

- Subjects medical history (inclusive of autoimmune disorders) and concomitant medications
- Vaccination history
- AZD1222 vaccination schedule, including batch number.

Furthermore, in case of a suspected quality defect, detailed specific information regarding batch release specifications, expiry date(s), and distribution and administration-related data (eg, storage and handling conditions for vaccines in the healthcare institutions where vaccination took place) will also be requested.

III.1.3 Specific Adverse Reaction Follow-Up Questionnaires

Targeted follow-up questionnaires will be in place for important potential risks and AESIs.

Applicable targeted follow-up questionnaires for important potential risks are provided in Annex 4.

III.1.4 Monthly Summary Safety Reports

In addition to the submission of Periodic Safety Update Reports (PSURs) at 6-monthly intervals, Summary Safety Reports (also referred to as Simplified PSURs) will be produced at monthly intervals for AZD1222. The key content of each report will be as defined below:

- Estimated exposure from post-marketing experience
- Data in Summary Tabulations:
  - Reference information
  - Cumulative and interval summary tabulations (by High-Level Term [HLT] and System Organ Class [SOC])

[1] Proposed definition for Confirmed Vaccination Failure with AZD1222: 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.
A COVID-19 diagnosis is defined as: Virologically-confirmed SARS-CoV-2 (eg, 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.

  - Overview of data presented in tabulations (AESIs, safety concerns, vaccination errors, and batch analysis)
- Summary of ongoing and closed validated signals
- Changes to Reference Safety Information
- Summary of significant findings from clinical trials during the reporting period
- Health Authority Requests
- Late-breaking Information
- Conclusion and actions (reflecting risk-benefit considerations)
- Appendices:
  - Appendix 1: Summary tabulation of cases per country
  - Appendix 2: Summary tabulation of all adverse reactions, including fatal events (which will be included as a separate tabulation within Appendix 2)
  - Appendix 3: Summary tabulation of AESIs and safety concerns
  - Appendix 4: Summary tabulation of serious unexpected adverse reactions
  - Appendix 5: Summary tabulation of adverse reactions by age group
  - Appendix 6: Summary tabulation of adverse reactions occurring in pregnant women
  - Appendix 7: SMQ and MedDRA search term lists used for AESIs, and RMP safety concerns
  - Appendix 8: Narratives for cases involving AESIs and RMP safety concerns during the reporting period (where relevant)
  - Appendix 9: Line listing of fatal cases during the reporting period
  - Appendix 10: Narratives for fatal cases received during the reporting period (where relevant)
  - Appendix 11: Company Core Data Sheet (CCDS) in effect at the end of the period
  - Appendix 12: Tabular summary of validated safety signals.

Case reports included in all appendices will originate from post-marketing sources, with the data included in Appendices 1-6 stratified as follows:

- Cumulative/Interval (unless otherwise indicated)
- Medically confirmed/Medically unconfirmed
- Serious/Non-serious
- SOC/HLT/PT (Note: stratification by SOC, HLT and PT is applicable only to Appendices 3-6. Appendix 2 will be stratified by SOC/HLT only)

AstraZeneca will endeavour to acquire exposure data, stratified by sex and age from EU Member States, where available. Where such data are not available, exposure data will be included in the report based on doses distributed in each market by AstraZeneca and its License Partners, as part of Pharmacovigilance Safety Agreements.

With regards to AESIs, safety concerns and fatal AEs, the total number of any such events will be discussed in the context of O/E analyses, which will be conducted as part of signal detection activities.

III.1.5 Enhanced Passive Surveillance

Enhanced passive surveillance activities are not planned as an enhanced active surveillance study (D8111R00003 / D8111R00004) is proposed as an additional pharmacovigilance measure (see Section III.2).

III.1.6 Traceability

In order to facilitate traceability of batch numbers for pharmacovigilance signal detection and reporting purposes, stickers detailing relevant brand name and batch numbers will be placed into all cartons of drug product at the Contract Manufacturing Organizations (CMO) packing sites. Two stickers will be provided per dose; hence, 200 stickers will be included in each carton (which has 100 doses based on 0.5 ml per dose), thereby providing stickers for both HCP and patient records. The vaccine carton labelling also includes a scannable 2D barcode that provides batch number and expiry date.

The stickers will include the vaccine name (ie, '*COVID-19 Vaccine AstraZeneca*'), the relevant batch number, and a 2D barcode. As AstraZeneca is using several CMOs for packing purposes, all with unique carton dimensions and size, stickers may vary in size; however, the number of stickers per dose (ie, 2) will remain the same. Traceability instructions for HCPs are provided in the SmPC.

Where regional practices permit, the batch number for AZD1222, if not already provided, will be systematically followed up for each post marketing ICSR. When available, batch information will be included in the AstraZeneca global safety database.

AstraZeneca will also make available Traceability and Vaccination reminder cards for vaccinators to facilitate batch number traceability. These cards are designed to be completed at the time of vaccination and be given to the vaccinee. These cards may be used by Member States where alternative strategies (i.e., the use of electronic records or national mandated vaccination cards) are unavailable. The Traceability and Vaccination reminder cards will contain the following elements:

- Placeholder space for name of vaccinee

- Vaccine brand name and manufacturer name
- Placeholder space for due date and actual date of first and second doses, and space for batch/lot number
- A reminder to retain the card and to bring it to the appointment for the second dose of the vaccine; in addition to a reminder to save the card after the second dose
- QR code that links to an MAH website with additional information on product use
- Placeholder for AE reporting information (national contact points)

At the time of initial vaccine availability, AstraZeneca will provide sufficient quantities of blank Traceability and Vaccination cards to vaccinators in Member States where alternative strategies are unavailable. These cards will also be made available on AstraZeneca websites, where permitted by National Competent Authorities.

III.2 Additional Pharmacovigilance Activities

In order to obtain data to aid the further characterisation of the safety concerns described in Section II.7.3, 4 types of PASS activities are planned, and are presented in Section III.2.1. In order to meet regulatory requirements, each of the planned PASS activities may be conducted by more than one localised clinical study protocol; however, all activities have a consistent study design and planned objectives and endpoints. Details on each planned activity type are therefore presented, rather than presenting information at the individual study level.

Further to these planned PASS activities, and aligned with regulatory guidance (EMA 2020b), all ongoing clinical studies in the current clinical development plan are also described in Section III.2.1.1, as ongoing data collection in these studies is also anticipated to provide further data with which to characterise the overall AZD1222 safety profile.

III.2.1 Planned Post-authorisation Safety Studies

III.2.1.1 Enhanced Active Surveillance

Study name and title: A Phase IV Enhanced Active Surveillance Study of People Vaccinated with AZD1222. Three EAS studies (D8111R00003 [EU], D8110R00001 [US], and ESR 21-21121[UK; conducted by the DSRU]) are currently proposed using the below overall rationale, objectives, design, population, and milestones.

Rationale and study objectives: The EAS studies aims to enrol and collect safety and tolerability data from volunteers vaccinated with at least 1 dose of AZD1222 in real world setting, in order to strengthen the safety database after AZD1222 availability. In addition, a pregnancy sub-cohort will provide information on outcomes following AZD1222 exposure during (or shortly prior to) pregnancy.

The primary objective of the EAS studies is to assess the safety and tolerability of at least 1 IM dose of AZD1222 in adults ≥ 18 years of age for 3 months after vaccination with the first dose of AZD1222.

The secondary objectives are:

- To assess the longer-term safety and tolerability of at least 1 IM dose of AZD1222 for 18 months after vaccination.
- To assess the safety and tolerability of AZD1222 in participants ≥ 65 year of age and in other key subgroups.
- 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 in neonates/infants born to mothers vaccinated with AZD1222 during pregnancy or within 45 days of the estimated date of conception.

Study design: The proposed EAS studies will be a single arm cohort study of adult volunteers, conducted at participating primary care or general practices or other centres with an ability to administer AZD1222 and follow-up participants. Participants will be identified and enrolled at the receipt of their first dose of AZD1222 in a real-world setting.

Participants will be followed for a up to 18 months post first dose of AZD1222, with medically attended adverse events following immunisation recorded for an initial period and AESIs and safety concerns recorded for up to 18 months post first dose of AZD1222.

The sample size expected to be recruited in this study is approximately 30000 volunteers across all regions.

***Study population*:** Adult volunteers from the EU, UK, and USA.

Milestones:

- *Study Design Concept submission:* 11 December 2020
- *Submission of protocol for review:* 28 January 2021
- *Submission of final study protocol:* 23 February 2021
- *Start of study*: 18 May 2021

- *First interim report*: Q3 2021

III.2.1.2 AZD1222 Pregnancy Registry

Study name and title: Pregnancy Registry of Women Exposed to AZD1222 Immediately Before or During Pregnancy (*study name/code to be confirmed*).

Rationale and study objectives: There are limited data on long term safety and health status in specific populations such as pregnant women.

The primary study objectives are:

- To estimate the risk of selected adverse pregnancy outcomes (ie, spontaneous abortions, stillbirths, and preterm births) in women receiving at least 1 dose of the AZD1222 vaccine during pregnancy or up to a predefined period (eg, 30 days) before estimated date of the LMP.

- To estimate the risk of selected adverse foetal/neonatal outcomes (ie, major congenital malformations and small for gestational age) at birth and up to at least the 12 months of life (to account for diagnosis of major congenital malformations that might be delayed) in infants from pregnancies in which the mothers received the AZD1222 vaccine during pregnancy or up to a predefined period (eg, 30 days) before estimated date of LMP.

Study design: This study will utilise data from a prospective registry, C-VIPER. The pregnancy study is a cohort study, which will include two cohorts of women: pregnant women who received at least 1 dose of AZD1222 while they were pregnant, or within a pre-defined period before becoming pregnant (C-VIPER Cohort); and pregnant women unexposed to COVID-19 vaccine before enrolment who are participants enrolled in the International Coronavirus Exposure in Pregnancy (IRCEP) registry. Both C-VIPER and IRCEP use the same methods to recruit and follow-up women. Women will be followed through the end of their pregnancy (ie, abortion, stillbirth, or live birth) and until the child reaches age 12 months.

Study population: Women aged ≥18, who receive the AZD1222 vaccine at any time while they are pregnant or who become pregnant within a predefined period (eg, 30 days pre-LMP) after being vaccinated will be eligible for inclusion in the treated cohort. A minimum of 500 women exposed to AZD1222, including 200 exposed during the first trimester will be recruited. Unexposed women from IRCEP will be matched to AZD1222 exposed women from C-VIPER by country and gestational age at enrolment.

Milestones:

- *Initial Study Design Concept submission:* 11 December 2020
- *Protocol submission:* 27 January 2021

III.2.1.3 Post-marketing Safety Studies

Post-marketing observational study using existing secondary health data sources

Study name and title: A post-authorisation/post-marketing observational study using existing secondary health data sources to evaluate the association between exposure to AZD1222 and safety concerns *(study code to be confirmed* [US] and D8111R00006 [EU/UK]*)*.

Rationale and study objectives: As more information is required to characterise the safety of the AZD1222 vaccine in conditions of usual care (including populations who were excluded from clinical studies), and to further define the incidence and relative risk of important potential risks and other pre-defined AESIs following immunisation, a post-authorisation observational study using existing secondary health data sources is proposed.

The study objectives are:

- To estimate the incidence of safety concerns and AESIs in recipients and non-recipients of AZD1222, among all populations targeted for vaccination and in the specific populations considered as missing information
- To estimate the relative risk (comparing exposed and unexposed person time) of safety concerns including AESIs among all populations targeted for vaccination and in the specific populations considered as missing information
- To characterise the use of AZD1222 among all populations targeted for vaccination and in the specific populations considered as missing information.

Study design: This is a retrospective, longitudinal cohort study using population-based automated health care data to ascertain vaccination details, patient characteristics, and outcomes of interest.

The study observation period starts on the date of the first AZD1222 vaccination (index date) and will end at 2 years after the index date, or earlier if other censoring rules apply (eg, death, leaving database). A minimum prior period of one year of database history will be required to collect information on patient characteristics and prior risks.

Study population: All patients exposed to AZD1222 with a date of vaccination (preferably batch date) and a minimum of 12 months of prior history in the database.

Milestones:

- *Study Design Concept submission:* 18 December 2020
- *Submission of study protocol for review:* 01 April 2021

Post-marketing safety study in patients receiving immunosuppressant medication or with primary immunodeficiency

Study name and title: Post-marketing safety study in patients receiving immunosuppressant medication or with primary immunodeficiency *(study name/code to be confirmed)*.

Rationale and study objectives: To evaluate the safety profile of AZD1222 in patients receiving immunosuppressant medication(s) or with primary immunodeficiency, in order to provide additional data to support the characterisation of the area of missing information of *'Use in immunocompromised patients'*. This study will aggregate results using a meta-analytical approach across multiple datasets from the UK, EU and US, with the aim of aggregating a sufficient sample size in order to discharge the risk of an event rate less than or equal to 1 in 10000.

Study design: Under development.

Study population: To be determined.

Milestones:

- *Submission of study protocol:* 01 November 2021

Interventional study in immunocompromised subjects

Study name and title: Interventional study in immunocompromised subjects *(study name/code to be confirmed)*.

Rationale and study objectives: To evaluate the safety profile of AZD1222 in patients receiving immunosuppressant medication(s) or with primary immunodeficiency, in order to provide additional data to support the characterisation of the area of missing information of *'Use in immunocompromised patients'*.

Study design: Under development.

Study population: To be determined.

Milestones:

- *Submission of study protocol:* 28 February 2021

III.2.1.4 Post-marketing Effectiveness Study

Study name and title: A post-authorization/post-marketing retrospective cohort study to evaluate the effectiveness of the AZD1222 vaccine to prevent serious COVID-19 infection in conditions of usual care *(study code to be confirmed* [US] and D8111R00005 [EU/UK]*)*.

Rationale and Study Objectives

The effectiveness of vaccines in real-world setting may differ from efficacy estimated from clinical registration studies. At the time of regulatory approval, efficacy of AZD1222 will have been demonstrated in randomised clinical studies, but information about the effectiveness of this vaccine under real-world conditions will be lacking. One of the proposed approaches to address this is through a public-private partnership with COVIDRIVE, leveraging an existing brand-specific influenza vaccine effectiveness platform (DRIVE).

The primary objective is to estimate brand specific vaccine effectiveness against laboratory-confirmed SARS-CoV-2 among (primarily) hospitalised patients, overall and by age group (eg, < 18, 18 to 64 and ≥ 65 years old), after adjusting for potential confounders.

Study Design

The current proposed study design is an observational, primary data, active-surveillance hospital-based and/or Primary Care study, following a pre-defined study design (eg, test-negative design), which will be carried out in each participating site. However, final study design and data collection methodology is an outstanding subject for consortium decision in the next period of the public-private partnership set-up.

Study Population

Patients fulfilling COVID-19 case definition (eg, European Centre for Disease Prevention and Control [ECDC] definition) are enrolled at hospitals (or Primary Care) and tested for the virus of interest.

Milestones:

- *Submission of study protocol:* Directed by COVIDRIVE consortium, expected March 2021

III.2.2 Ongoing Clinical Studies

In addition to the planned PASS (which are designed to address specific AZD1222 safety concerns), data from all ongoing pivotal AZD1222 clinical studies are also crucial in contributing to the ongoing evaluation of AZD1222 safety concerns and in further characterising the AZD1222 safety profile overall. These studies are not considered PASS; however, are included in this EU RMP as additional pharmacovigilance activities in accordance with COVID-19 RMP-specific regulatory guidance (EMA 2020b).

III.2.2.1 Study COV001

Study name and title: Study COV001 - A Phase I/II Study to Determine Efficacy, Safety, and Immunogenicity of the Candidate Coronavirus Disease (COVID-19) Vaccine ChAdOx1 nCoV-19 in UK Healthy Adult Volunteers.

Rationale and study objectives*:* This study was initiated as the first-in-human study employing candidate vaccine AZD1222 (ChAdOx1 nCoV-19).

The primary objectives of this study are to assess safety and efficacy of AZD1222 against COVID-19. Key secondary objectives are to assess the reactogenicity profile, and the cellular and humoral immunogenicity of AZD1222.

Study design: This is an ongoing, Phase I/II, single-blinded, controlled, individually randomised study of AZD1222 or active control (licensed MenACWY) administered via an IM injection into the deltoid. This study involves multiple dosing regimens, comprising both single and booster dosing groups, with an overall sample size of up to 1090 participants. All participants will be followed up for 12 months from last vaccination visit. This study is being conducted in the UK.

Study population: Healthy adults aged 18 to 55 years recruited in the UK.

Planned study timelines:

- *Final study report due*: Q1 2022

III.2.2.2 Study COV002

Study name and title: Study COV002 - A Phase II/III Study to Determine the Efficacy, Safety, and Immunogenicity of the Candidate Coronavirus Disease (COVID-19) Vaccine ChAdOx1 nCoV-19.

Rationale and study objectives: The primary objectives of this study are to assess efficacy and safety of AZD1222 (ChAdOx1 nCoV-19) against COVID-19 in adults aged 18 years and older in the UK.

Key secondary objectives are to assess the reactogenicity profile of AZD1222; to assess efficacy of AZD1222 against severe and non-severe COVID-19; to assess humoral immunogenicity of AZD1222; to assess cellular immunity AZD1222 in older adults; and to assess the safety and immunogenicity of a booster dose of AZD1222 in older adults aged 56 years or greater (two-dose schedule).

Study design*:* This is an ongoing, Phase II/III, participant-blinded, individually randomised controlled trial, investigating either a single dose or 2-doses of AZD1222 or licensed MenACWY vaccine via IM injection.

This study comprises 11 separate investigational groups of participants, with each group investigating a specific dosing regimen and age group. The groupings of participants investigated this study are:

- Adults aged 18 to 55 years
- Adults aged 56 to 69 years
- Adults aged 70 years or older
- Adults aged 18 to 55 years who previously received a ChAdOx1 vectored vaccine (maximum 60 participants)
- HIV infected adults (aged 18 to 55 years) who were stable on antiretroviral therapy (maximum 60 participants)

All participants will be followed up for 12 months from last vaccination visit. This study is being conducted in the UK.

Study population: Adult volunteers aged at least 18 years.

Planned study timelines:

- *Final study report due*: Q2 2022

III.2.2.3 Study COV003

Study name and title: Study COV003 - A Randomised, Controlled, Phase III Study to Determine the Safety, Efficacy, and Immunogenicity of the Non-Replicating ChAdOx1 nCoV-19 Vaccine.

Rationale and study objectives*:* The primary objective of this study is to evaluate the efficacy of AZD1222 against COVID-19 disease confirmed with polymerase chain reaction (PCR).

Key secondary objectives are to evaluate the safety, tolerability and reactogenicity profile of AZD1222; to evaluate the efficacy of AZD1222 against severe and non-severe COVID-19 disease; and to evaluate the humoral and cellular immunogenicity of AZD1222.

Study design: This is an ongoing, Phase III, controlled, randomised, single-blind study conducted in adults with high exposure to COVID-19, who are administered two-doses of AZD1222 or MenACWY and saline placebo by means of an IM injection with co-administered paracetamol. All participants will be followed up for 12 months from last vaccination visit. This study is being conducted in Brazil.

Study population*:* Adult participants over the age of 18. Recruitment focused on healthcare professionals and those with likely high known exposure to COVID-19; eg, health professionals, students, residents and professionals who perform health care activities such as

nurses and nursing technicians, pharmacists, doctors, physiotherapists, speech therapists and radiology technicians.

Participants in older age groups (56 to 69 years, and 70 years and above) were to be recruited at the investigators' discretion. For this patient population the likelihood of COVID-19 exposure was to be judged on a case-by-case basis, regardless of previous occupation.

Planned study timelines:

- *Final study report due*: Q2 2022

III.2.2.4 Study COV004

Study name and title: Study COV004 – A Phase IB/II Single-Blinded, Randomised, Controlled Study to Determine Safety, Immunogenicity and Efficacy of the Candidate Coronavirus Disease (COVID-19) Vaccine ChAdOx1 nCoV-19 in Adults in Kenya

Rationale and study objectives: The primary objectives of this study are to assess the safety, tolerability and reactogenicity profile of the candidate vaccine ChAdOx1 nCoV-19; and to assess immunogenicity of ChAdOx1 nCoV-19.

Key secondary objectives are to assess humoral immunogenicity of ChAdOx1 nCoV-19 at early and late timepoints; to assess cellular immunogenicity of ChAdOx1 nCoV-19; and to assess efficacy of ChAdOx1 nCoV-19 against COVID-19.

Study design: This is an ongoing, Phase IB/II single-blinded, randomized, controlled study of a single dose ChAdOx1 nCoV-19 vaccine among adults in Kenya. Participants are to be followed up for 12 months.

Study population: Healthy adults aged 18-55 years.

Planned study timelines:

- *Final study report due*: *2022*

III.2.2.5 Study COV005

Study name and title: Study COV005 - An Adaptive Phase I/II Randomised Placebo-controlled Trial to Determine Safety, Immunogenicity and Efficacy of Non-Replicating ChAdOx1 SARS-CoV-2 Vaccine in South African Adults Living Without HIV; and Safety and Immunogenicity in Adults Living with HIV.

Rationale and study objectives*:* The primary objectives of this study in the HIV-uninfected participants group are to assess the safety, tolerability and reactogenicity profile of AZD1222; and to assess the efficacy of AZD1222 against all-severity COVID-19. Key secondary objectives in the HIV-uninfected participants group are to assess efficacy of AZD1222 against

COVID-19 of differing severity; and to assess cellular and humoral immunogenicity of AZD1222.

In adults living with HIV, the primary objectives of this study are to assess the safety, tolerability and reactogenicity profile of AZD1222 in people living with HIV; and to assess cellular and humoral immunogenicity of AZD1222 in people living with HIV after one and two doses of vaccine. The secondary objective in this participant group is to descriptively compare immune responses to AZD1222 in people living with HIV to HIV-uninfected individuals, overall and stratified by COVID-19 serostatus at enrolment.

Study design*:* This is an ongoing, Phase I/II, double-blinded, placebo-controlled, individually randomised study of AZD1222 or placebo will be administered via an IM injection into the deltoid. All participants receive 2 doses of AZD1222 or placebo, 4 weeks (21 to 35 days) apart. Participants are to be followed over the duration of the study (through to 365 days post-randomisation). This study is being conducted in South Africa.

Study population: Adult participants aged 18 to 65; both healthy HIV-uninfected; and generally-well people living with HIV in South Africa.

Planned study timelines:

- *Final study report due*: Q2 2022

III.2.2.6 Study D8110C00001

Study name and title: Study D8110C00001 – A Phase III Randomized, Double-blind, Placebo-controlled Multicentre Study in Adults to Determine the Safety, Efficacy, and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19.

Rationale and study objectives: The primary objectives of this study are to estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of COVID-19 in adults ≥ 18 years of age; to assess the safety and tolerability of 2 IM doses of AZD1222 compared to placebo in adults ≥ 18 years of age; and to assess the reactogenicity of 2 IM doses of AZD1222 compared to placebo in adults ≥ 18 years of age (Substudy only).

Key secondary objectives are to estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of SARS-CoV-2 infection; to estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of symptomatic COVID-19 using CDC criteria; to estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of University of Oxford-defined symptomatic COVID-19; to estimate the efficacy of 2 IM doses of AZD1222 compared to placebo in the prevention of COVID-19 in all study participants, regardless of evidence of prior SARS-CoV-2 infection; to estimate the efficacy of

2 IM doses of AZD1222 compared to placebo for the prevention of severe or critical symptomatic COVID-19; and to estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of COVID-19-related Emergency Department visits.

Study design: This is an ongoing, Phase III randomised, double-blind, placebo-controlled multicentre study assessing the safety, efficacy, and immunogenicity of AZD1222 compared to saline placebo for the prevention of COVID-19. Participants receive 2 IM doses of either AZD1222 or saline placebo, 4 weeks apart, on Days 1 and 29. All participants will remain on study for 2 years following administration of first dose of study intervention (Day 730). This study is being conducted in the USA, Chile, and Peru.

Study population: Adult participants ≥ 18 years of age who are healthy or have medically-stable chronic diseases, and are at increased risk for SARS-CoV-2 acquisition and COVID-19.

Planned study timelines:

- *Interim analysis*: *Q1 2021*

III.2.2.7 Study D8111C00002

Study name and title: Study D8111C00002 – A Phase I/II Randomized, Double-blind, Placebo-controlled Multicentre Study in Participants Aged 18 Years or Older to Determine the Safety and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19.

Rationale and study objectives: The primary objectives of this study are to assess antibody responses to AZD1222 Spike antigen following 2 IM doses of AZD1222 or placebo; and to assess the safety, tolerability, and reactogenicity profile of the candidate vaccine AZD1222.

Key secondary objectives are to assess antibody responses to AZD1222 RBD antigen following 2 IM doses of AZD1222 or placebo; to assess time course of antibody to AZD1222 Spike and RBD antigens of AZD1222 (MSD serology assay); to assess the function of nAb against SARS-CoV-2 spike protein; to assess the safety of the candidate vaccine AZD1222; to describe occurrence of symptomatic COVID-19 in recipients of AZD1222 and placebo; and to describe occurrence of severe COVID-19 and seroresponse to non-Spike SARS-CoV-2 antigens.

Study design: This is a multicentre, randomised, double-blind, parallel-group, placebo-controlled, 52-week Phase I/II study. Participants receive 2 IM doses of either AZD1222 or placebo, administered 4 weeks apart. Participants are to be followed up for 12 months (365 days). This study is being conducted in Japan.

Study population: The study has 2 cohorts with different age populations. Cohort C includes healthy participants aged 18 to 55 years. Cohort D includes healthy elderly participants aged ≥ 56 years.

Planned study timelines:

- *Interim analysis: Q1 2021*
- *Primary analysis*: *Q2 2021*

III.3 Summary Table of Additional Pharmacovigilance Activities

A summary of the studies included in the pharmacovigilance plan is provided in Table III-2.

Table III-2 Ongoing and planned additional pharmacovigilance activities

Activity type and description Status	Study name/code	Summary of activity objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - *Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation*					
None					
Category 2 – *Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances*					
Study COV001 A Phase I/II Study to Determine Efficacy, Safety, and Immunogenicity of the Candidate Coronavirus Disease (COVID-19) Vaccine ChAdOx1 nCoV-19 in UK Healthy Adult Volunteers • **Status**: Ongoing	• COV001	*Primary Objectives:* • To assess efficacy of AZD1222 against COVID-19 • To assess the safety of AZD1222 *Key secondary Objectives:* • To assess the reactogenicity profile of AZD1222 • To assess cellular and humoral immunogenicity of AZD1222	• Nervous system disorders, including immune-mediated neurological conditions • Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) • Anaphylaxis • Long-term safety	Final report	Q1 2022

Table III-2 Ongoing and planned additional pharmacovigilance activities

Activity type and description Status	Study name/code	Summary of activity objectives	Safety concerns addressed	Milestones	Due dates
Study COV002 A Phase II/III Study to Determine the Efficacy, Safety, and Immunogenicity of the Candidate Coronavirus Disease (COVID-19) Vaccine ChAdOx1 nCoV-19 • **Status**: Ongoing	• COV002	*Primary Objectives:* • To assess efficacy and safety of AZD1222 against COVID-19 in adults aged 18 years and older in the UK *Secondary Objectives:* • To assess the reactogenicity profile of AZD1222 • To assess efficacy of AZD1222 against severe and non-severe COVID-19 • To assess humoral immunogenicity of AZD1222 • To assess cellular immunity of AZD1222 in older adults • To assess the safety and immunogenicity of a booster dose of AZD1222 in older adults aged 56 years or older (two-dose schedule).	• Nervous system disorders, including immune-mediated neurological conditions • Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) • Anaphylaxis • Long-term safety	Final report	Q2 2022
Study COV003 A Randomised, Controlled, Phase III Study to Determine the Safety, Efficacy, and Immunogenicity of the Non-Replicating ChAdOx1 nCoV-19 Vaccine • **Status**: Ongoing	• COV003	*Primary Objective:* • To evaluate the efficacy of AZD1222 vaccine against COVID-19 disease confirmed with PCR *Secondary Objectives:* • To evaluate the safety, tolerability and reactogenicity profile of AZD1222 • To evaluate the efficacy of AZD1222 against severe and non-severe COVID-19 disease • To evaluate the humoral immunogenicity of AZD1222 • To assess the cellular immunogenicity of AZD1222.	• Nervous system disorders, including immune-mediated neurological conditions • Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) • Anaphylaxis • Long-term safety	Final report	Q2 2022

Table III-2 Ongoing and planned additional pharmacovigilance activities

Activity type and description Status	Study name/code	Summary of activity objectives	Safety concerns addressed	Milestones	Due dates
Study COV005 An Adaptive Phase I/II Randomised Placebo-controlled Trial to Determine Safety, Immunogenicity and Efficacy of Non-Replicating ChAdOx1 SARS-CoV-2 Vaccine in South African Adults Living Without HIV, and Safety and Immunogenicity in Adults Living with HIV • **Status**: Ongoing	• COV005	*Primary Objective:* • To assess the safety of AZD1222 in healthy HIV-uninfected adults • To assess efficacy of AZD1222 against COVID-19 • To assess the safety of the candidate vaccine AZD1222 in adults living with HIV • To evaluate the immunogenicity of AZD1222 after first and second doses of vaccine in adults living with HIV *Secondary Objectives:* • To assess the immunogenicity of AZD1222 in healthy HIV-uninfected adults.	• Nervous system disorders, including immune-mediated neurological conditions • Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) • Anaphylaxis • Use in immunocompromised patients • Long-term safety	Final report	Q2 2022
D8110C00001 A Phase III Randomized, Double-blind, Placebo-controlled Multicentre Study in Adults to Determine the Safety, Efficacy, and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19	• D8110C00001	*Primary Objectives:* • To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of COVID-19 in adults ≥ 18 years of age • To assess the safety and tolerability of 2 IM doses of AZD1222 compared to placebo in adults ≥ 18 years of age • To assess the reactogenicity of 2 IM doses of AZD1222 compared to placebo in adults ≥ 18 years of age (Substudy only) *Key Secondary Objectives:* • To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the	• Nervous system disorders, including immune-mediated neurological conditions • Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) • Anaphylaxis • Long-term safety	Interim analysis	Q1 2021

Table III-2 Ongoing and planned additional pharmacovigilance activities

Activity type and description Status	Study name/code	Summary of activity objectives	Safety concerns addressed	Milestones	Due dates
Status: Ongoing		prevention of SARS-CoV-2 infection • To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of symptomatic COVID-19 using CDC criteria • To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of University of Oxford-defined symptomatic COVID-19 • To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo in the prevention of COVID-19 in all study participants, regardless of evidence of prior SARS-CoV-2 infection • To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of severe or critical symptomatic COVID-19 • To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of COVID-19-related Emergency Department visits			

Table III-2 Ongoing and planned additional pharmacovigilance activities

Activity type and description Status	Study name/code	Summary of activity objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - *Required additional pharmacovigilance activities*					
Enhanced active surveillance A Phase IV Enhanced Active Surveillance Study of People Vaccinated with AZD1222 • **Status**: Planned	• D8111R00003 (EU) • D8110R00001 (US) • ESR 21-21121 (UK; DSRU-sponsored))	*Primary Objectives:* • To assess the safety and tolerability of at least 1 IM dose of AZD1222 in adults ≥ 18 years of age for 3 months after vaccination with the first dose of AZD1222. *Secondary Objectives:* • To assess the longer-term safety and tolerability of at least 1 IM dose of AZD1222 for 18 months after vaccination • To assess the safety and tolerability of AZD1222 in participants ≥ 65 year of age and in other key subgroups • 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 in neonates/infants born to mothers vaccinated with AZD1222 during pregnancy or within 45 days of the estimated date of conception.	• Nervous system disorders, including immune-mediated neurological conditions • Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) • Anaphylaxis • Use during pregnancy and while breastfeeding • Use in immunocompromised patients • Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) • Use in patients with autoimmune or inflammatory disorders • Interactions with other vaccines • Long-term safety	Study Design Concept submission	11 Dec 2020
				Protocol submission for review	28 Jan 2021
				Final protocol submission	23 Feb 2021
				Start of study	18 May 2021
				First interim report	Q3 2021

Table III-2 Ongoing and planned additional pharmacovigilance activities

Activity type and description Status	Study name/code	Summary of activity objectives	Safety concerns addressed	Milestones	Due dates
AZD1222 Pregnancy Registry Pregnancy Registry of Women Exposed to AZD1222 Immediately Before or During Pregnancy • **Status**: Planned	• *Study code to be confirmed*	*Primary Objectives:* • To estimate the risk of selected adverse pregnancy outcomes (ie, spontaneous abortions, stillbirths, and preterm births) in women receiving at least 1 dose of the AZD1222 vaccine during pregnancy or up to a predefined period (eg, 30 days) before estimated date of LMP • To estimate the risk of selected adverse foetal/neonatal outcomes (ie, major congenital malformations and small for gestational age) at birth and up to at least the 12 months of life (to account for diagnosis of major congenital malformations that might be delayed) in infants from pregnancies in which the mothers received the AZD1222 vaccine during pregnancy or up to a predefined period (eg, 30 days) before estimated date of LMP.	• Use during pregnancy and while breastfeeding	Initial Study Design Concept submission	11 Dec 2020
				Protocol submission	27 Jan 2021

Table III-2 Ongoing and planned additional pharmacovigilance activities

Activity type and description Status	Study name/code	Summary of activity objectives	Safety concerns addressed	Milestones	Due dates
Post-marketing observational study using existing secondary health data sources A post-authorisation/post-marketing observational study using existing secondary health data sources to evaluate the association between exposure to AZD1222 and safety concerns. • **Status**: Planned	• *Study code to be confirmed* (US) • D8111R00006 (EU/UK)	*Primary Objectives:* • To estimate the incidence of safety concerns and AESIs in recipients and non-recipients of AZD1222, among all populations targeted for vaccination and in the specific populations considered as missing information • To estimate the relative risk (comparing exposed and unexposed person time) of safety concerns including AESIs among all populations targeted for vaccination and in the specific populations considered as missing information • To characterise the use of AZD1222 among all populations targeted for vaccination and in the specific populations considered as missing information	• Nervous system disorders, including immune-mediated neurological conditions • Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) • Anaphylaxis • Use during pregnancy and while breastfeeding • Use in immunocompromised patients • Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) • Use in patients with autoimmune or inflammatory disorders • Interactions with other vaccines • Long-term safety	Study Design Concept submission	18 Dec 2020
				Protocol submission	01 Apr 2021
Post-marketing safety study in patients receiving immunosuppressant medication or with primary immunodeficiency • **Status**: Planned	• *Study code to be confirmed*	*Primary objective:* • To evaluate the safety profile of AZD1222 in patients receiving immunosuppressant medication(s) or with primary immunodeficiency	• Use in immunocompromised patients	Study protocol submission	01 Nov 2021

Table III-2 Ongoing and planned additional pharmacovigilance activities

Activity type and description Status	Study name/code	Summary of activity objectives	Safety concerns addressed	Milestones	Due dates
Interventional study in immunocompromised subjects • **Status**: Planned	• *Study code to be confirmed*	*Primary objective:* • To evaluate the safety profile of AZD1222 in patients receiving immunosuppressant medication(s) or with primary immunodeficiency	• Use in immunocompromised patients	Protocol submission	28 Feb 2021
Post-marketing effectiveness study Post-authorisation/ Post-marketing retrospective cohort study to evaluate the effectiveness of the AZD1222 vaccine to prevent serious COVID-19 infection in conditions of usual care through public-private partnership with COVIDRIVE utilizing primary data collected prospectively through the COVIDRIVE platform. **Status**: Planned	• D8111R00005 (EU/UK) • *Study code to be confirmed* (US)	*Primary Objective:* • To estimate brand specific vaccine effectiveness against laboratory-confirmed SARS-CoV-2 in hospitalized patients, overall and by age group (< 18, 18-64 and ≥ 65 years old), after adjusting for potential confounders.	*Not applicable*	Protocol submission	Directed by COVI-DRIVE consortium, expected March 2021

Table III-2 Ongoing and planned additional pharmacovigilance activities

Activity type and description Status	Study name/code	Summary of activity objectives	Safety concerns addressed	Milestones	Due dates
Study COV004 A Phase IB/II Single-Blinded, Randomised, Controlled Study to Determine Safety, Immunogenicity and Efficacy of the Candidate Coronavirus Disease (COVID-19) Vaccine ChAdOx1 nCoV-19 in Adults in Kenya • **Status**: Ongoing	• COV004	*Primary Objectives:* • To assess the safety, tolerability and reactogenicity profile of the candidate vaccine ChAdOx1 nCoV-19 • To assess immunogenicity of ChAdOx1 nCoV-19 *Secondary Objectives:* • To assess humoral immunogenicity of ChAdOx1 nCoV-19 at early and late timepoints • To assess cellular immunogenicity of ChAdOx1 nCoV-19 • To assess efficacy of ChAdOx1 nCoV-19 against COVID-19	• Nervous system disorders, including immune-mediated neurological conditions • Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) • Anaphylaxis • Long-term safety	Final report	2022

Table III-2 Ongoing and planned additional pharmacovigilance activities

Activity type and description Status	Study name/code	Summary of activity objectives	Safety concerns addressed	Milestones	Due dates
D8111C00002 A Phase I/II Randomized, Double-blind, Placebo-controlled Multicentre Study in Participants Aged 18 Years or Older to Determine the Safety and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19 • **Status**: Ongoing	• D8111C00002	*Primary Objectives:* • To assess antibody responses to AZD1222 Spike antigen following 2 IM doses of AZD1222 or placebo. • To assess the safety, tolerability, and reactogenicity profile of the candidate vaccine AZD1222. *Secondary Objectives:* • To assess antibody responses to AZD1222 RBD antigen following 2 IM doses of AZD1222 or placebo. • To assess time course of antibody to AZD1222 Spike and RBD antigens of AZD1222 (MSD serology assay) • To assess the function of nAb against SARS-CoV-2 spike protein • To assess the safety of the candidate vaccine AZD1222. • To describe occurrence of symptomatic COVID-19 in recipients of AZD1222 and placebo. • To describe occurrence of severe COVID-19 and seroresponse to non-Spike SARS-CoV-2 antigens.	• Nervous system disorders, including immune-mediated neurological conditions • Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) • Anaphylaxis • Long-term safety	Interim analysis	Q1 2021
				Primary analysis	Q2 2021

IV. PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

V. PART V: RISK MINIMISATION MEASURES

V.1 Routine Risk Minimisation Measures

A summary of routine risk minimisation measures per safety concern are provided in Table V-1.

Table V-1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Potential Risks	
Nervous system disorders, including immune-mediated neurological conditions	None
Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	None
Anaphylaxis	**Routine risk communication:** • SmPC Sections 4.3 and 4.4 • PL Section 2
Missing Information	
Use during pregnancy and while breastfeeding	**Routine risk communication:** • SmPC Section 4.6 • PL Section 2
Use in immunocompromised patients	**Routine risk communication:** • SmPC Section 4.4 • PL Section 2
Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)	None
Use in patients with autoimmune or inflammatory disorders	None
Interactions with other vaccines	**Routine risk communication:** • SmPC Section 4.5 • PL Section 2
Long-term safety	None

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table V-2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risks		
Nervous system disorders, including immune-mediated neurological conditions	None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Specific adverse reaction follow-up questionnaire (to be sent for immune-mediated neurological conditions only) **Additional pharmacovigilance activities:** • EAS • Post-marketing observational study using existing secondary health data sources • Study COV001 • Study COV002 • Study COV003 • Study COV004 • Study COV005 • Study D8110C00001 • Study D8111C00002
Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Specific adverse reaction follow-up questionnaire **Additional pharmacovigilance activities:** • EAS • Post-marketing observational study using existing secondary health data sources • Study COV001 • Study COV002 • Study COV003 • Study COV004 • Study COV005 • Study D8110C00001 • Study D8111C00002

Table V-2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Anaphylaxis	**Routine risk communication:** • SmPC Sections 4.3 and 4.4 • PL Section 2	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Specific adverse reaction follow-up questionnaire **Additional pharmacovigilance activities:** • EAS • Post-marketing observational study using existing secondary health data sources • Study COV001 • Study COV002 • Study COV003 • Study COV004 • Study COV005 • Study D8110C00001 • Study D8111C00002
Missing Information		
Use during pregnancy and while breastfeeding	**Routine risk communication:** • SmPC Section 4.6 • PL Section 2	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • EAS • AZD1222 Pregnancy Registry • Post-marketing observational study using existing secondary health data sources
Use in immunocompromised patients	**Routine risk communication:** • SmPC Section 4.4 • PL Section 2	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • EAS • Post-marketing observational study using existing secondary health data sources • Post-marketing safety study in patients receiving immunosuppressant medication or with primary immunodeficiency • Interventional study in immunocompromised patients • Study COV005

Table V-2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)	None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • EAS • Post-marketing observational study using existing secondary health data sources
Use in patients with autoimmune or inflammatory disorder	None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • EAS • Post-marketing observational study using existing secondary health data sources
Interactions with other vaccines	**Routine risk communication:** • SmPC Section 4.5 • PL Section 2	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • EAS • Post-marketing observational study using existing secondary health data sources
Long-term safety	None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • EAS • Post-marketing observational study using existing secondary health data sources • Study COV001 • Study COV002 • Study COV003 • Study COV004 • Study COV005 • Study D8110C00001 • Study D8111C00002

VI. PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR AZD1222

Summary of risk management plan for COVID-19 Vaccine AstraZeneca (AZD1222; ChAdOx1-S [recombinant])

This is a summary of the risk management plan (RMP) for COVID-19 Vaccine AstraZeneca (also referred to as AZD1222). The RMP details important risks of COVID-19 Vaccine AstraZeneca, how these risks can be minimised, and how more information will be obtained about COVID-19 Vaccine AstraZeneca 's risks and uncertainties (missing information).

COVID-19 Vaccine AstraZeneca's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how COVID-19 Vaccine AstraZeneca should be used.

This summary of the RMP for COVID-19 Vaccine AstraZeneca should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of COVID-19 Vaccine AstraZeneca's RMP.

VI.1 The medicine and what it is used for

COVID-19 Vaccine AstraZeneca is authorised for active immunisation to prevent COVID-19 caused by SARS CoV 2, in individuals 18 years of age and older. It contains Chimpanzee Adenovirus encoding the SARS CoV 2 Spike glycoprotein (ChAdOx1-S) as the active substance, and it is given by intramuscular injection only, preferably in the deltoid muscle.

Further information about the evaluation of COVID-19 Vaccine AstraZeneca’s benefits can be found in COVID-19 Vaccine AstraZeneca’s EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine’s webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/covid-19-vaccine-astrazeneca.

VI.2 Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of COVID-19 Vaccine AstraZeneca, together with measures to minimise such risks and the proposed studies for learning more about COVID-19 Vaccine AstraZeneca's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of COVID-19 Vaccine AstraZeneca is not yet available, it is listed under 'missing information' below.

VI.2.1 List of important risks and missing information

Important risks of COVID-19 Vaccine AstraZeneca are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of COVID-19 Vaccine AstraZeneca. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table VI-1 List of important risks and missing information

Important identified risks	None
Important potential risks	• Nervous system disorders, including immune-mediated neurological conditions • Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) • Anaphylaxis

Table VI-1 List of important risks and missing information

Missing Information	• Use during pregnancy and while breastfeeding • Use in immunocompromised patients • Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) • Use in patients with autoimmune or inflammatory disorders • Interactions with other vaccines • Long-term safety

VI.2.2 Summary of important risks

Table VI-2 Important potential risk: Nervous system disorders, including immune-mediated neurological conditions

Evidence for linking the risk to the medicine	The association between vaccines and acute demyelinating events has been assessed in a range of studies and expert reviews, including a population-based analysis of nearly 64 million vaccine doses in the United States, which concluded that if there is an association between transverse myelitis and vaccines, it is < 2 per million doses of live-zoster and live-attenuated influenza vaccines, and < 1 per million doses for other vaccines. Moreover, demyelinating diseases occur more frequently with infections than with vaccination. Taken together, the evidence is inconclusive regarding a causal relation between contemporary vaccines and acute demyelinating events. Overall, there were no clinically meaningful imbalances in the incidence of neurological AESIs between the AZD1222 group (n = 64 participants [0.5%]) and the control group (n = 79 participants [0.7%]) in the pooled safety dataset (any dose group).
Risk factors and risk groups	There are no known risk factors for the development of neurological conditions following vaccination.
Risk minimisation measures	None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: • Enhanced Active Surveillance (EAS) • Post-marketing observational study using existing secondary health data sources • Study COV001 • Study COV002 • Study COV003 • Study COV004 • Study COV005 • Study D8110C00001 • Study D8111C00002 See section VI.2.3 of this summary for an overview of the post-authorisation development plan.

Table VI-3 Important potential risk: Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)

Evidence for linking the risk to the medicine	There is a theoretical concern that vaccination against SARS-CoV-2 may be associated with enhanced severity of COVID-19 episodes which would manifest as VAED/VAERD. Vaccine-associated enhanced disease was observed in children given formalin-inactivated whole-virus vaccines against respiratory syncytial virus and measles virus, and findings from experimental models of SARS-CoV and MERS-CoV infection suggest that VAED/VAERD may be possible in certain conditions.
Risk factors and risk groups	There are no known risk factors identified for VAED/VAERD.
Risk minimisation measures	None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: • EAS • Post-marketing observational study using existing secondary health data sources • Study COV001 • Study COV002 • Study COV003 • Study COV004 • Study COV005 • Study D8110C00001 • Study D8111C00002 See section VI.2.3 of this summary for an overview of the post-authorisation development plan.

Table VI-4 Important potential risk: Anaphylaxis

Evidence for linking the risk to the medicine	The risk of anaphylaxis is idiosyncratic in nature, with anaphylaxis risk after all vaccines estimated to be 1.31 (95% CI, 0.90-1.84) per million vaccine doses. No serious or acute events of anaphylaxis were reported in AZD1222 clinical trials, and therefore the risk of anaphylaxis is a theoretical concern based on data from other vaccines (as a class of medications). There were no serious reports of anaphylaxis, and no reported acute allergic reactions in the AZD1222 clinical development programme.
Risk factors and risk groups	Almost all components of a vaccine (including excipients) may be considered as potential triggers of an allergic reaction, and therefore known hypersensitivity to any component of AZD1222 and/or a history of allergic reactions are considered to be risk factors for the development of anaphylaxis.
Risk minimisation measures	**Routine risk communication:** • SmPC Sections 4.3 and 4.4 • PL Section 2

Table VI-4 Important potential risk: Anaphylaxis

Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: • EAS • Post-marketing observational study using existing secondary health data sources • Study COV001 • Study COV002 • Study COV003 • Study COV004 • Study COV005 • Study D8110C00001 • Study D8111C00002 See section VI.2.3 of this summary for an overview of the post-authorisation development plan.

Table VI-5 Missing information: Use during pregnancy and while breastfeeding

Risk minimisation measures	**Routine risk minimisation measures** • SmPC Section 4.6 • PL Section 2
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: • EAS • AZD1222 Pregnancy Registry • Post-marketing observational study using existing secondary health data sources See section VI.2.3 of this summary for an overview of the post-authorisation development plan.

Table VI-6 Missing information: Use in immunocompromised patients

Risk minimisation measures	**Routine risk minimisation measures** • SmPC Section 4.4 • PL Section 2
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: • Study COV005 • EAS • Post-marketing observational study using existing secondary health data sources • Post-marketing safety study in patients receiving immunosuppressant medication or with primary immunodeficiency • Interventional study in immunocompromised patients See section VI.2.3 of this summary for an overview of the post-authorisation development plan.

Table VI-7 Missing information: Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders)

Risk minimisation measures	None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: • EAS • Post-marketing observational study using existing secondary health data sources See section VI.2.3 of this summary for an overview of the post-authorisation development plan.

Table VI-8 Missing information: Use in patients with autoimmune or inflammatory disorders

Risk minimisation measures	None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: • EAS • Post-marketing observational study using existing secondary health data sources See section VI.2.3 of this summary for an overview of the post-authorisation development plan.

Table VI-9 Missing information: Interactions with other vaccines

Risk minimisation measures	**Routine risk minimisation measures** • SmPC Section 4.5 • PL Section 2
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: • EAS • Post-marketing observational study using existing secondary health data sources See section VI.2.3 of this summary for an overview of the post-authorisation development plan.

Table VI-10 Missing information: Long-term safety

Risk minimisation measures	None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: • EAS • Post-marketing observational study using existing secondary health data sources • Study COV001 • Study COV002 • Study COV003 • Study COV004 • Study COV005 • Study D8110C00001 • Study D8111C00002 See section VI.2.3 of this summary for an overview of the post-authorisation development plan.

VI.2.3 Post-authorisation development plan

VI.2.3.1 Studies which are conditions of the marketing authorisation

The following studies are specific obligations of the marketing authorisation:

- **Study COV001 - A Phase I/II Study to Determine Efficacy, Safety, and Immunogenicity of the Candidate Coronavirus Disease (COVID-19) Vaccine ChAdOx1 nCoV-19 in UK Healthy Adult Volunteers**
  - *Purpose of the study:* This study was initiated as the first-in-human study employing candidate vaccine AZD1222 (ChAdOx1 nCoV-19). The primary objectives of this study are to assess safety and efficacy of AZD1222 against COVID-19. Key secondary objectives are to assess the reactogenicity profile, and the cellular and humoral immunogenicity of AZD1222.

- **Study COV002 - A Phase II/III Study to Determine the Efficacy, Safety, and Immunogenicity of the Candidate Coronavirus Disease (COVID-19) Vaccine ChAdOx1 nCoV-19.**
  - *Purpose of the study:* The primary objectives of this study are to assess efficacy and safety of AZD1222 (ChAdOx1 nCoV-19) against COVID-19 in adults aged 18 years and older in the UK. Key secondary objectives are to assess the reactogenicity profile of AZD1222; to assess efficacy of AZD1222 against severe and non-severe COVID-19; to assess humoral immunogenicity of AZD1222; to assess cellular immunity AZD1222 in older adults; and to assess the safety and immunogenicity of a booster dose of AZD1222 in older adults aged 56 years or greater (two-dose schedule).

- **Study COV003 - A Randomised, Controlled, Phase III Study to Determine the Safety, Efficacy, and Immunogenicity of the Non-Replicating ChAdOx1 nCoV 19 Vaccine.**
  - *Purpose of the study:* The primary objective of this study is to evaluate the efficacy of AZD1222 against COVID-19 disease confirmed with polymerase chain reaction (PCR). Key secondary objectives are to evaluate the safety, tolerability and reactogenicity profile of AZD1222; to evaluate the efficacy of AZD1222 against severe and non-severe COVID-19 disease; and to evaluate the humoral and cellular immunogenicity of AZD1222.

- **Study COV005 - An Adaptive Phase I/II Randomised Placebo-controlled Trial to Determine Safety, Immunogenicity and Efficacy of Non-Replicating ChAdOx1 SARS CoV-2 Vaccine in South African Adults Living Without HIV; and Safety and Immunogenicity in Adults Living with HIV.**
  - *Purpose of the study:* The primary objectives of this study in the HIV-uninfected participants group are to assess the safety, tolerability and reactogenicity profile of AZD1222; and to assess the efficacy of AZD1222 against all-severity COVID-19. Key secondary objectives in the HIV-uninfected participants group are to assess efficacy of AZD1222 against COVID-19 of differing severity; and to assess cellular and humoral immunogenicity of AZD1222.

    In adults living with HIV, the primary objectives of this study are to assess the safety, tolerability and reactogenicity profile of AZD1222 in people living with HIV; and to assess cellular and humoral immunogenicity of AZD1222 in people living with HIV after one and two doses of vaccine. The secondary objective in this participant group is to descriptively compare immune responses to AZD1222 in people living with HIV to HIV-uninfected individuals, overall and stratified by COVID-19 serostatus at enrolment.

- **Study D8110C00001 – A Phase III Randomized, Double-blind, Placebo-controlled Multicentre Study in Adults to Determine the Safety, Efficacy, and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19.**
  - *Purpose of the study:* The primary objectives of this study are to estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of COVID-19 in adults ≥ 18 years of age; to assess the safety and tolerability of 2 IM doses of AZD1222 compared to placebo in adults ≥ 18 years of age; and to assess the reactogenicity of 2 IM doses of AZD1222 compared to placebo in adults ≥ 18 years of age (Substudy only).

    Key secondary objectives are to estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of SARS-CoV-2 infection; to estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of symptomatic COVID-19 using CDC criteria; to estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of University of Oxford-defined symptomatic COVID-19; to estimate the efficacy of 2 IM doses of AZD1222 compared to placebo in the prevention of COVID-19 in all study participants, regardless of evidence of prior SARS-CoV-2 infection; to estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of severe or critical symptomatic COVID-19; and to estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of COVID-19-related Emergency Department visits.

VI.2.3.2 Other studies in post-authorisation development plan

Other studies in the post authorisation development plan are as follows:

- **A Phase IV Enhanced Active Surveillance (EAS) Study of People Vaccinated with AZD1222 (D8111R00003 [EU] / D8110R00001 [US] / ESR 21-21121 [UK; DSRU-sponsored)**

  Purpose of the study: This EAS study proposal aims to enrol and collect safety and tolerability data from volunteers vaccinated with at least one dose of AZD1222 in real world setting, in order to strengthen the safety database after AZD1222 availability. In addition, a pregnancy sub-cohort will provide information on outcomes following AZD1222 exposure during (or shortly prior to) pregnancy. The primary objective of the EAS study is to assess the safety and tolerability of at least one IM dose of AZD1222 in adults ≥ 18 years of age for 3 months after vaccination with the first dose of AZD1222. The secondary objectives are to assess the longer-term safety and tolerability of at least one IM dose of AZD1222 for 18 months after vaccination; to assess the safety and tolerability of AZD1222 in participants ≥ 65 year of age and in other key subgroups; to estimate the frequency of select pregnancy outcomes in women vaccinated with AZD1222 during pregnancy or within 45 days of the estimated conception date; and to estimate the frequency of select outcomes in neonates/infants born to mothers vaccinated with AZD1222 during pregnancy or within 45 days of the estimated date of conception.

- **AZD1222 Pregnancy Registry - Registry of Women Exposed to AZD1222 Immediately Before or During Pregnancy**
  - *Purpose of the study:* There are limited data on long term safety and health status in specific populations such as pregnant women. The study objectives are estimate the risk of selected adverse pregnancy in women receiving at least one dose of the AZD1222 vaccine during pregnancy or up to a predefined period (eg, 30 days) before estimated date of last menstrual period (LMP), and to estimate the risk of selected adverse foetal/neonatal outcomes at birth and up to at least the 12 months of life in infants from pregnancies in which the mothers received the AZD1222 vaccine during pregnancy or up to a predefined period (eg, 30 days) before estimated date of LMP.

- **A post-authorisation/post-marketing observational study using existing secondary health data sources to evaluate the association between exposure to AZD1222 and safety concerns (D8111R00006 [EU/UK] / *Study code to be confirmed* [US])**
  - *Purpose of the study:* As more information is required to characterise the safety of the AZD1222 vaccine in conditions of usual care (including populations who were excluded from clinical studies), and to further define the incidence and relative risk of important potential risks and other pre-defined adverse events of special interest (AESIs) following immunisation, a post-authorisation observational study using existing secondary health data sources is proposed. The study objectives are to estimate the incidence of safety concerns and AESIs in recipients and non-recipients of AZD1222 among all populations targeted for vaccination and in the specific populations considered as missing information, to estimate the relative risk of safety concerns including AESIs among all populations targeted for vaccination and in the specific populations considered as missing information, and to characterise the use of AZD1222 among all populations targeted for vaccination and in the specific populations considered as missing information.

- **Post-marketing safety study in patients receiving immunosuppressant medication or with primary immunodeficiency**
  - *Purpose of the study:* To evaluate the safety profile of AZD1222 in patients receiving immunosuppressant medication(s) or with primary immunodeficiency, in order to provide additional data to support the characterisation of the area of missing information of *'Use in immunocompromised patients'*. This study will aggregate results using a meta-analytical approach across multiple datasets from the UK, EU and US, with the aim of aggregating e a sufficient sample size in order to discharge the risk of an event rate less than or equal to 1 in 10000.

- **Interventional study in immunocompromised subjects**
  - *Purpose of the study:* To evaluate the safety profile of AZD1222 in patients receiving immunosuppressant medication(s) or with primary immunodeficiency, in order to provide additional data to support the characterisation of the area of missing information of *'Use in immunocompromised patients'*.

- **A post-authorization/post-marketing retrospective cohort study to evaluate the effectiveness of the AZD1222 vaccine to prevent serious COVID-19 infection in conditions of usual care (D8111R00005 [EU/UK] / *Study code to be confirmed* [US])**
  - *Purpose of the study:* The effectiveness of vaccines in real-world setting may differ from efficacy estimated from clinical registration studies. At the time of regulatory approval, efficacy of AZD1222 will have been demonstrated in randomised clinical studies, but information about the effectiveness of this vaccine under real-world conditions will be lacking. One of the proposed approaches to address this is through a public-private partnership with COVIDRIVE, leveraging an existing brand-specific influenza vaccine effectiveness platform (DRIVE). The primary objective is to estimate brand specific vaccine effectiveness against laboratory-confirmed SARS-CoV-2 among (primarily) hospitalized patients, overall and by age group (eg, < 18, 18 to 64 and ≥ 65 years old), after adjusting for potential confounders.

- **Study COV004 – A Phase IB/II Single-Blinded, Randomised, Controlled Study to Determine Safety, Immunogenicity and Efficacy of the Candidate Coronavirus Disease (COVID-19) Vaccine ChAdOx1 nCoV-19 in Adults in Kenya**
  - *Purpose of the study:* The primary objectives of this study are to assess the safety, tolerability and reactogenicity profile of the candidate vaccine ChAdOx1 nCoV-19; and to assess immunogenicity of ChAdOx1 nCoV-19. Key secondary objectives are to assess humoral immunogenicity of ChAdOx1 nCoV-19 at early and late timepoints; to assess cellular immunogenicity of ChAdOx1 nCoV-19; and to assess efficacy of ChAdOx1 nCoV-19 against COVID-19.

- **Study D8111C00002 – A Phase I/II Randomized, Double-blind, Placebo-controlled Multicentre Study in Participants Aged 18 Years or Older to Determine the Safety and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19.**
  - *Purpose of the study:* The primary objectives of this study are to assess antibody responses to AZD1222 Spike antigen following 2 IM doses of AZD1222 or placebo; and to assess the safety, tolerability, and reactogenicity profile of the candidate vaccine AZD1222.

    Key secondary objectives are to assess antibody responses to AZD1222 RBD antigen following 2 IM doses of AZD1222 or placebo; to assess time course of antibody to AZD1222 Spike and RBD antigens of AZD1222 (MSD serology assay); to assess the function of nAb against SARS-CoV-2 spike protein; to assess the safety of the candidate vaccine AZD1222; to describe occurrence of symptomatic COVID-19 in recipients of AZD1222 and placebo; and to describe occurrence of severe COVID-19 and seroresponse to non-Spike SARS-CoV-2 antigens.

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EU RMP Part VII Annex 4

Drug Substance ChAdOx1-S (recombinant) (AZD1222)

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR COVID-19 VACCINE ASTRAZENECA (ChAdOx1-S [RECOMBINANT])

Part VII Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

TABLE OF CONTENTS

1. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

The following specific adverse reaction follow-up questionnaires will be used to collect further information on important potential risks:

- Questionnaire (COVID-19 Vaccine AstraZeneca) –Immune-mediated neurological conditions
- Questionnaire (COVID-19 Vaccine AstraZeneca) – COVID-19/ Vaccine failure and including Vaccine-associated enhanced disease (VAED)
- Questionnaire (COVID-19 Vaccine AstraZeneca) –Anaphylaxis

AstraZeneca

Questionnaire for immune-mediated neurological conditions

AZ Date of Receipt:_____
AZ Case ID#: _____

1. Reporter's Information

Reporter's Name:	Is Reporter a healthcare professional? ☐ No ☐ Yes, If yes, please provide specialty:	Telephone #: Fax #:
Reporter's Address:	Reporter's Signature:	Date *(DD/MM/YY)*:

2. Patient's Details

Initials: Sex: ☐ Male ☐ Female Date of Birth (*DD/MM/YYYY*): Age (*years*):

3. Adverse Event Details

Adverse Event(s)	Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	Outcome	
			☐ Recovered ☐ Event ongoing	☐ Recovered with sequelae ☐ Patient died ☐ Unknown
			☐ Recovered ☐ Event ongoing	☐ Recovered with sequelae ☐ Patient died ☐ Unknown
			☐ Recovered ☐ Event ongoing	☐ Recovered with sequelae ☐ Patient died ☐ Unknown

In the event of Death, please provide the cause of death (*please provide copy of autopsy report, if available).*
Was the patient hospitalized for the event(s)? ☐ No ☐ Yes

Please tick appropriate diagnosis:
☐ Guillain-Barré syndrome
☐ Multiple sclerosis
☐ Optic neuritis
☐ Myelitis Transverse
☐ Other demyelinating disease (provide details)
☐ Encephalitis
☐ Encephalopathy
Other, specify: _____

What signs and symptoms did the patient experience?

☐ Leg weakness	☐ Cardiac arrhythmias	☐ Lethargy	☐ Depression	☐ Paraparesis
☐ Facial paralysis	☐ Headache	☐ Delirium	☐ Meningismus	☐ Paralysis
☐ Loss of deep tendon reflexes	☐ Neck stiffness	☐ Confusional State	☐ Sensory loss	☐ Respiratory muscle involvement
☐ Bowel/Bladder dysfunction	☐ Photophobia	☐ Decreased level of consciousness	☐ Paraesthesia	☐ Spasticity
☐ Blood pressure fluctuation/orthostatic drop	☐ Seizures If seizures, please specify type_____ No of episodes:_____	☐ Cognitive dysfunction (Attention span Concentration, Memory, Judgement)	☐ Motor dysfunction	☐ Muscle cramping secondary to spasticity
☐ Ataxia	Duration of longest seizure episode:_____		☐ Hemiparesis	

Were there any complications caused by the above event(s)? ☐ No ☐ Yes
If 'Yes', please provide a brief statement of complications from the event(s):

4. COVID-19 Vaccine AstraZeneca

Indication:	Dose 1 received ☐ No ☐ Yes Date of Vaccination *(DD/MM/YY)*: Batch/Lot number:
	Dose 2 received ☐ No ☐ Yes Date of Vaccination *(DD/MM/YY)*: Batch/Lot number: If dose 2 was not received, was it due to the adverse event

AstraZeneca

Questionnaire for immune-mediated neurological conditions

AZ Date of Receipt:_____
AZ Case ID#: _____

5. How was the patient treated?

Was treatment provided? ☐ No ☐ Yes
If Yes, Please provide the details of treatment: _____

☐ Intravenous immunoglobulin - ***please specify:*** _____
☐ Plasmapheresis
☐ Supportive therapy - ***please specify:*** _____
☐ Other treatments - ***please specify:*** _____

6. Other Suspect Drugs

Please only include other drugs you consider to be causality related to the adverse event(s) and not concomitant medications.

Suspect Drug Name	Indication	Daily Dosage	Route	Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	Was suspect drug withdrawn?
						☐ No ☐ Yes
						☐ No ☐ Yes
						☐ No ☐ Yes

If any of the above drugs were stopped, did the event(s) improve after stopping?
☐ No ☐ Yes ☐ Not applicable, If applicable, please provide Date Drug was Stopped/Altered *(DD/MM/YY)*: _____

Did the event(s) recur after reintroduction?
☐ No ☐ Yes ☐ Not applicable, If applicable, please provide Date Drug was Reintroduced *(DD/MM/YY)*: _____

7. Concomitant Drugs/ Concomitant Vaccines

Please exclude drugs used to treat the event(s). List all medications taken by the patient, including over-the-counter drugs, supplements, and herbal preparations. (attached a list if available).

Concomitant Drug Name (including Batch/Lot number)	Indication	Daily Dosage	Route	Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	Was concomitant drug withdrawn?
						☐ No ☐ Yes
						☐ No ☐ Yes
						☐ No ☐ Yes
						☐ No ☐ Yes
						☐ No ☐ Yes

8. Relevant Medical History/Concurrent Diseases

Medical History			Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*
Respiratory or gastrointestinal infection	☐ No	☐ Yes		
Recent immunization (eg. Rabies Vaccination, influenza)	☐ No	☐ Yes		
Nutritional deficiency: Vitamin B12, vitamin E; copper	☐ No	☐ Yes		
Neoplastic disease	☐ No	☐ Yes		
Conditions that cause spinal cord compression/ Conditions that resulted in spinal cord radiation	☐ No	☐ Yes		
Drugs/toxins (epidural anesthesia, chemotherapeutic agents)	☐ No	☐ Yes		
Lymphoma	☐ No	☐ Yes		
HIV positive	☐ No	☐ Yes		
Systemic lupus erythematosus	☐ No	☐ Yes		
Vasculitis	☐ No	☐ Yes		
Connective tissue / autoimmune diseases	☐ No	☐ Yes		

Other, please specify:

Is the patient being treated or under medical care for the condition(s) identified above? ☐ Yes ☐ No

9. Laboratory Results- Before/During/After Treatment- Please provide details of the following relevant lab tests (attached test results if available).		
Test	**Date**	**Results**
CSF		
EEG		
Neuroimaging (MRI/CT)		
Oligoclonal Bands		
IgG index, IgG synthesis rate		
Nerve conduction studies/ needle electromyography		
Nerve biopsy		
Blood serum for antiganglioside antibody detection AIDP: various antibodies AMAN: GM1a, GM1b, GD1a and GalNAc-GD1a antibodies AMSAN: GM1, GD1a Fisher syndrome: GQ1b and GT1a antibodies Onco-neural antibodies		
Acute and convalescent sera (A/C serum)		
Complete Blood Count		
Serum C-reactive protein		
Serum Electrolytes		
Imaging results (X-ray/CT/MRI, etc.)		
Liver Function tests		
Rheumatoid factor (RF)		
Anti-nuclear antibodies (ANA)		
Other investigations (Evoked Potential tests, Ophthalmologic examination, Electrophysiologic examination, Myelography, Viral serology, tests for bacterial infections) :		
Other, please specify: Please provide and attach results of any relevant laboratory and diagnostic procedures performed, if available		

Thank you for completing this form.

AstraZeneca

Questionnaire for
COVID-19/ Vaccine Failure and Vaccine-Associated Enhanced Disease (VAED)

AZ Date of Receipt:_____
AZ Case ID#: _____

1. Reporter's Information

Reporter's Name:

Is Reporter a healthcare professional?
☐ No ☐ Yes, If yes, please provide specialty:

Telephone #:

Fax #:

Reporter's Address:

Reporter's Signature:

Date *(DD/MM/YY):*

2. Patient's Details

Initials:

Sex: ☐ Male ☐ Female

Date of Birth (*DD/MM/YYYY*):

Age (*years*):

3. Adverse Event Details

Adverse Event(s)	Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	Outcome	
			☐ Recovered ☐ Event ongoing	☐ Recovered with sequelae ☐ Patient died ☐ Unknown
			☐ Recovered ☐ Event ongoing	☐ Recovered with sequelae ☐ Patient died ☐ Unknown
			☐ Recovered ☐ Event ongoing	☐ Recovered with sequelae ☐ Patient died ☐ Unknown

In the event of death, please provide the cause of death (*please provide copy of autopsy report, if available).*

Was the patient hospitalized for the event(s)?
☐ No ☐ Yes

Did the patient have testing for SARS-CoV-2?
☐ Yes ☐ No ☐ Unknown
If yes, specify type of testing: _____
(Please specify date of test and type of test – e.g., nasal swab reverse transcription–polymerase chain reaction (RT-PCR) test or nucleic acid amplification–based test (NAAT) or antigen test)

Does the patient have SARS-CoV-2 antibodies at diagnosis?
☐ Yes ☐ No ☐ Unknown
_____
(Please specify date of test, whether IgM /IgG or both and the titer if available)

Was/Is the patient admitted to an Intensive Care Unit?
☐ Yes ☐ No ☐ Unknown
If 'Yes' please provide details

In the absence of a positive SARS-CoV-2 test, what findings suggested a diagnosis of COVID-19 infection?

How many days from the SARS-CoV2 diagnosis did it take before the SARS-CoV2 antigen test became negative?

Have any pre-existing diseases worsened during the SARS-CoV-2 infection (please specify)
☐ Yes ☐ No ☐ Unknown

Please provide information on any new or worsened symptoms/signs during the COVID-19 illness experienced (including date of onset/worsening)

Respiratory system
☐ Dyspnea
☐ Cough
☐ Cyanosis
☐ COVID-pneumonia
☐ Acute Respiratory Distress Syndrome (ARDS)
☐ Lower respiratory tract disease
☐ Respiratory failure
☐ Pulmonary hemorrhage
☐ Radiographic abnormalities
☐ Others

Cardiovascular system
☐ Acute cardiac injury
☐ Pericarditis
☐ Myocarditis
☐ Cardiogenic shock
☐ Others

Hematopoietic and Immune system
☐ Coagulopathy
☐ Thrombocytopenia
☐ Deep vein thrombosis
☐ Disseminated intravascular coagulation
☐ Vasculitis
☐ Pulmonary embolism
☐ Others

Inflammatory markers
☐ Elevated cytokines
☐ Others

AstraZeneca

Questionnaire for
COVID-19/ Vaccine Failure and Vaccine-Associated Enhanced Disease (VAED)

AZ Date of Receipt:_____
AZ Case ID#: _____

Renal system	Gastrointestinal and hepatic system	Central Nervous System	Other System
☐ Renal dysfunction	☐ Vomiting	☐ Altered mental status	☐ Acute arthritis
☐ Acute kidney injury	☐ Diarrhea	☐ Convulsions/seizures	☐ Dermatological
☐ Others	☐ Jaundice	☐ Cranial nerve involvement	☐ Multisystem inflammatory syndrome [MIS])
	☐ Acute liver injury	☐ Unconsciousness	☐ Multiorgan failure (please specify which organ systems were affected)
	☐ Others	☐ Others	☐ Death

Were there any complications caused by the event(s)? ☐ No ☐ Yes
If 'Yes' please provide a brief statement of any complications from the event(s):

4. COVID-19 Vaccine AstraZeneca

Indication:	Dose1 received ☐ No ☐ Yes Date of Vaccination *(DD/MM/YY)*: Batch/Lot number:
	Dose2 received ☐ No ☐ Yes Date of Vaccination *(DD/MM/YY)*: Batch/Lot number: If dose 2 was not received, was it due to the adverse event

5. How was the patient treated?

Did the patient receive any additional therapies for COVID-19? ☐ No ☐ Yes

Therapy	Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	Dose/Any additional information
☐ Remdesivir			
☐ Hydroxychloroquine/chloroquine			
☐ Azithromycin			
☐ Corticosteroids			
☐ Plasmapheresis			
☐ Other (Please Specify)			

6. Other Suspect Drugs

Please only include other drugs you consider to be causality related to the adverse event(s) and not concomitant medications.

Suspect Drug Name	Indication	Daily Dosage	Route	Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	Was suspect drug withdrawn?
						☐ No ☐ Yes
						☐ No ☐ Yes
						☐ No ☐ Yes

If any of the above drugs were stopped, did the event(s) improve after stopping?
☐ No ☐ Yes ☐ Not applicable, If applicable, please provide Date Drug was Stopped/Altered *(DD/MM/YY)*: _____

Did the event(s) recur after reintroduction?
☐ No ☐ Yes ☐ Not applicable, If applicable, please provide Date Drug was Reintroduced *(DD/MM/YY)*: _____

7. Concomitant Drugs/ Concomitant Vaccines

Please exclude drugs used to treat the event(s). List all medications taken by the patient, including over-the-counter drugs, supplements, and herbal preparations. (attached a list if available).

Concomitant Drug Name (including Batch/Lot number)	Indication	Daily Dosage	Route	Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	Was concomitant drug withdrawn?
						☐ No ☐ Yes
						☐ No ☐ Yes

AstraZeneca

Questionnaire for
COVID-19/ Vaccine Failure and Vaccine-Associated Enhanced Disease (VAED)

AZ Date of Receipt:_____
AZ Case ID#: _____

						☐ No ☐ Yes
						☐ No ☐ Yes
						☐ No ☐ Yes

8. Relevant Medical History/Concurrent Diseases

Medical History			Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*
Respiratory or gastrointestinal infection	☐ No	☐ Yes		
Recent immunization	☐ No	☐ Yes		
Lymphoma	☐ No	☐ Yes		
HIV positive	☐ No	☐ Yes		
Systemic lupus erythematosus	☐ No	☐ Yes		
Vasculitis	☐ No	☐ Yes		
Other autoimmune disorders	☐ No	☐ Yes		
Hypertension	☐ No	☐ Yes		
Diabetes	☐ No	☐ Yes		
Heart Disease (please specify)	☐ No	☐ Yes		
Lung Disease (please specify)	☐ No	☐ Yes		
Kidney disease (please specify)	☐ No	☐ Yes		
Obesity	☐ No	☐ Yes		
Current or Former Smoker If Yes, please provide details	☐ No	☐ Yes		

Other, please specify:

Is the patient being treated or under medical care for the condition(s) identified above?
☐ Yes ☐ No

9. Laboratory Results- Before/During/After Treatment- Please provide and attach results of any relevant laboratory and diagnostic procedures performed, if available. Especially laboratory findings suggestive of VAED/VAERD.

Test	Date	Results
Test for SARS-CoV-2 by PCR, or other commercial or public health assay		
Imaging for COVID-Pneumonia (e.g.CXR, CT)		
Evidence of hypoxemia (e.g. PaO2/FiO2 [P/F ratio], SpO2/FiO2 [S/F ratio]), hypercapnia (PaCO2) or acidosis (pH)		
Hematology (e.g. leucocyte count [including neutrophil and lymphocyte counts], hemoglobin, platelet count, coagulation parameters [PT, PTT, D Dimer, INR], fibrinogen, B and T cell function assays)		
Clinical chemistry (e.g. serum creatinine, glomerular filtration rate [GFR], liver enzymes, bilirubin, albumin, B-type natriuretic peptide [BNP], troponin)		
Other, please specify: Please provide and attach results of any relevant laboratory and diagnostic procedures performed, if available		

Thank you for completing this form.

AstraZeneca

Questionnaire for Anaphylaxis

AZ Date of Receipt:_____
AZ Case ID#: _____

1. Reporter's Information

Reporter's Name:	Is Reporter a healthcare professional? ☐ No ☐ Yes, If yes, please provide specialty:	Telephone #: Fax #:
Reporter's Address:	Reporter's Signature:	Date *(DD/MM/YY):*

2. Patient's Details

Initials:	Sex: ☐ Male ☐ Female If female, pregnant ☐ No ☐ Yes, If yes, please provide details:	Date of Birth (*DD/MM/YYYY*): Age (*years*):

Race: ☐ White ☐ Black or African American ☐ Native American ☐ Alaska Native ☐ Native Hawaiian ☐ Asian ☐ Other ☐ Refused or Unknown
Ethnic Group: ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Unknown

3. Adverse Event Details

Adverse Event(s)	Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	Time of Event (Hour/minutes after immunisation)	Outcome	
				☐ Recovered ☐ Event ongoing	☐ Recovered with sequelae If yes, please specify: ☐ Patient died ☐ Unknown
				☐ Recovered ☐ Event ongoing	☐ Recovered with sequelae If yes, please specify: ☐ Patient died ☐ Unknown
				☐ Recovered ☐ Event ongoing	☐ Recovered with sequelae If yes, please specify: ☐ Patient died ☐ Unknown

In the event of Death, please provide the cause of death (*please provide copy of autopsy report, if available).*

Was the patient hospitalized for the anaphylaxis? ☐ *No* ☐ *Yes*

Major Criteria (Please check all that apply)

Dermatologic or mucosal	Cardiovascular	Respiratory
☐ Generalised urticaria (hives) or generalised erythema ☐ Angioedema (Not hereditary angioedema), localized or generalised ☐ Generalised pruritus with skin rash ☐ Others, please specify	☐ Measured hypotension (_____) ☐ Clinical diagnosis of uncompensated shock, indicated by the combination of at least 3 of the following: • *Tachycardia* • *Capillary refill time >3 s* • *Reduced central pulse volume* • *Decreased level of consciousness or loss of consciousness* ☐ Others, please specify	☐ Bronchospasm (bilateral wheezing) ☐ Stridor ☐ Upper airway swelling (lip, tongue, throat, uvula, or larynx) ☐ Respiratory distress—2 or more of the following: • *Tachypnoea* • *Increased use of accessory respiratory muscles (sternocleidomastoid, intercostals, etc.)* • *Recession* • *Cyanosis* • *Grunting* ☐ Others, please specify

AstraZeneca

Questionnaire for Anaphylaxis

AZ Date of Receipt:_____
AZ Case ID#: _____

Minor Criteria (Please check all that apply)

Dermatologic or mucosal	Cardiovascular:	Respiratory	Gastrointestinal
☐ Generalised pruritus without skin rash ☐ Generalised prickle sensation ☐ Localized injection site urticaria ☐ Red and itchy eyes	☐ Reduced peripheral circulation as indicated by the combination of at least 2 of • *tachycardia and* • *A capillary refill time of >3 s without hypotension* • *A decreased level of consciousness*	☐ Persistent dry cough ☐ Hoarse voice ☐ Difficulty breathing without wheeze or stridor ☐ Sneezing, rhinorrhea ☐ Sensation of throat closure	☐ Diarrhea ☐ Abdominal pain ☐ Vomiting ☐ Nausea Laboratory ☐ Mast cell tryptase elevation > upper normal limit

4. COVID-19 Vaccine AstraZeneca

Indication:	Dose 1 received ☐ No ☐ Yes Date of Vaccination *(DD/MM/YY)*: Batch/Lot number:
	Dose 2 received ☐ No ☐ Yes Date of Vaccination *(DD/MM/YY)*: Batch/Lot number: If dose 2 was not received, was it due to the adverse event

5. How was the patient treated?

Therapy	Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	Dose/Any additional information
☐ CPR			
☐ Oxygen			
☐ IV fluid challenge			
☐ Bronchodilators			
☐ Epinephrine			
☐ Corticosteroids			
☐ Antihistamines			
☐ Other (Please Specify)			

6. Other Suspect Drugs

Please only include other drugs you consider to be causality related to the adverse event(s) and not concomitant medications.

Suspect Drug Name	Indication	Daily Dosage	Route	Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	Was suspect drug withdrawn?
						☐ No ☐ Yes
						☐ No ☐ Yes
						☐ No ☐ Yes

If any of the above drugs were stopped, did the event(s) improve after stopping?
☐ No ☐ Yes ☐ Not applicable, If applicable, please provide Date Drug was Stopped/Altered *(DD/MM/YY)*: _____

Did the event(s) recur after reintroduction?
☐ No ☐ Yes ☐ Not applicable, If applicable, please provide Date Drug was Reintroduced *(DD/MM/YY)*: _____

AstraZeneca

Questionnaire for Anaphylaxis

AZ Date of Receipt:_____
AZ Case ID#: _____

7. Concomitant Drugs/Concomitant Vaccines Please exclude drugs used to treat the event(s). List all medications taken by the patient, including over-the-counter drugs, supplements, and herbal preparations.

Concomitant Drug Name	Indication	Daily Dosage	Route	Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	Was concomitant drug withdrawn?
						☐ No ☐ Yes
						☐ No ☐ Yes
						☐ No ☐ Yes

8. Relevant Medical History/Concurrent Diseases

Medical History		Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*
History of allergy to vaccines, vaccine components,	☐ No ☐ Yes		
Asthma	☐ No ☐ Yes		
Eczema	☐ No ☐ Yes		
Urticaria/hives	☐ No ☐ Yes		
Hypotension	☐ No ☐ Yes		
Immunosuppressive disorders	☐ No ☐ Yes		
Food allergies (please specify)	☐ No ☐ Yes		
Other allergies (e.g. dust, dog, cat, mold) (please specify)	☐ No ☐ Yes		

Has the patient previously developed hypersensitivity reaction, acute allergic reaction and anaphylaxis, injections site reactions with vaccines, excipients or other medications?

☐ Yes ☐ No

If yes, which medications did the patient react to and when was the last reaction and what was the time to onset of the reaction after exposure to the medication?

Has the patient been treated with antihistamines, prednisone, or other medication for any prior hypersensitivity/anaphylaxis/allergic reaction, events?

☐ Yes ☐ No

If yes, please describe the event and the treatment provided:

9. Laboratory Results- Before/During/After Treatment- Please provide and attach results of any relevant laboratory and diagnostic procedures performed, if available. Especially the physical examination details

Physical examination results of the patients:

Please provide and attach results of mast cell tryptase test and any other relevant laboratory and diagnostic procedures performed, if available:

Thank you for completing this form.