European Union Risk Management Plan	
Drug Substance	ChAdOx1-S (recombinant) (AZD1222)
Version Number	7
Succession number	1
Data lock point	10 February 2023
Date of final sign-off	See e-signature page

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP)

FOR

VAXZEVRIA (ChAdOx1-S [RECOMBINANT])

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

ADMINISTRATIVE INFORMATION

Rationale for submitting an updated RMP

This EU RMP (Version 7) has been updated to include data from Pooled Analysis of Oxford Studies (COV001, COV002, COV003, COV005) with the date of cut off (DCO3) 31 December 2021.

EU RMP is also updated with the milestones of Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU/UK]) and COVIDRIVE study (D8111R00017).

References to the SmPC are to the version approved on 10 February 2023.

Summary of significant changes in this RMP

Part I:	No changes
Part II SI:	No changes
Part II SII:	No changes
Part II SIII:	Clinical trial exposure data updated with the DCO3 of pooled analysis data
Part II SIV:	No changes
Part II SV:	Latest cumulative post-marketing exposure data updated (data cut-off date of 31 December 2022)
Part II SVI:	No changes
Part II SVII:	Updated to include DCO3 data from pooled analysis studies.
Part II SVIII:	No changes
Part III:	• The completed studies (COV001, COV002, COV003, COV004 and COV005) and additional PV activities (Pooled analysis data of COV001/2/3/5 studies) are removed from the Table 12. Ongoing and planned additional pharmacovigilance activities • Updated milestones for Post-marketing observational study using existing secondary health data sources (D8111R00006) study and COVIDRIVE study (D8111R00017)
Part IV:	No changes
Part V:	No changes
Part VI:	Updated to reflect changes throughout the EU RMP
Annex	Annex 2: COV studies (COV001/2/3/4/5) and additional PV activities (Pooled analysis data of COV001/2/3/5 studies) are moved from Table I: Planned and ongoing studies to Table II Completed studies. Updated milestones for D8111R00006 [EU/UK]) and D8111R00017 studies. Annex 8: Aligned as per changes in RMP

Details of currently approved RMP

Version number:	Version 6, Succession 3
Approved with procedure:	EMEA/H/C/005675/II/0084/G
Date of approval:	09 February 2023

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	Definition/Explanation
ADR	Averse Drug Reaction
AE	Adverse Event
AEFI	Adverse Event Following Immunisation
AESI	Adverse Event of Special Interest
AMN	Acute Macular Neuroretinopathy
AMOR	Acute Macular Outer Retinopathy
ARDS	Acute Respiratory Distress Syndrome
ATC	Anatomical Therapeutic Chemical
CCDS	Company Core Data Sheet
CDC	Centres for Disease Control and Prevention
CLS	Capillary leak syndrome
CMO	Contract Manufacturing Organization
CSP	Clinical Study Protocol
DCO	Data Cut-Off
DME	Designated Medical Events
DSRU	Drug Safety Research Unit
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
GBS	Guillain-Barré syndrome
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
IBD	International Birth Date

Abbreviation/ Special term	Definition/Explanation
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
ICU	Intensive Care Unit
IIR	Important Identified Risk
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
MSD	Meso Scale Discovery
nAb	Neutralising Antibodies
NITAG	National Immunization Technical Advisory Group
NOEL	No Observed effect level
O/E	Observed Versus Expected
PASS	Post-Authorisation Safety Study(ies)
PAMM	Paracentral Acute Middle Maculopathy
PCR	Polymerase Chain Reaction
PF4	Platelet Factor 4
PL	Package Leaflet
PRR	Proportional Reporting Ratio
PSUR	Periodic Safety Update Report
PT	Preferred Term (MedDRA)
QPPV	Qualified Person Responsible for Pharmacovigilance
RBD	Receptor-Binding Domain
RoR	Reporting Odds Ratio
RMP	Risk Management Plan
S	Spike
SAP	Statistical Analysis Plan
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
TTS	Thrombosis with Thrombocytopenia Syndrome
UK	United Kingdom

Abbreviation/ Special term	Definition/Explanation
US/USA	United States of America
VAED	Vaccine-Associated Enhanced Disease
VAERD	Vaccine-Associated Enhanced Respiratory Disease
VAERS	US Vaccine Adverse Event Reporting System
vp	Viral Particles
WHO	World Health Organization

I. PART I: PRODUCT OVERVIEW

Table 1 Product Overview

Active substance	ChAdOx1-S [recombinant] (AZD1222[a]) (formerly ChAdOx1 nCoV-19)
Pharmacotherapeutic group(s) (ATC Code)	Vaccines, other viral vaccines (J07BX03)
Marketing Authorisation Applicant	AstraZeneca AB, 15185 Södertälje, Sweden
Medicinal products to which this RMP refers	One
Invented name in the EEA	Vaxzevria (formerly COVID-19 Vaccine AstraZeneca)
Marketing authorisation produced	Centralised
	Chemical class: Recombinant replication-deficient viral vector vaccine
Brief description of the product	Summary of mode of action: VAXZEVRIA is a monovalent vaccine composed of a single recombinant, replication-deficient chimpanzee adenovirus (ChAdOx1) vector encoding the S glycoprotein of SARS-CoV-2. The SARS-CoV-2 S immunogen in the vaccine is expressed in the trimeric pre-fusion conformation; the coding sequence has not been modified in order to stabilise the expressed S-protein in the pre-fusion conformation. Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally stimulating neutralising antibody and cellular immune responses.
	Important information about its composition: VAXZEVRIA 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	VAXZEVRIA Summary of Product Characteristics
Indication in the EEA	Current: VAXZEVRIA 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	Current: The VAXZEVRIA primary vaccination course consists of two separate doses of 0.5 mL each. The second dose should be administered between 4 and 12 weeks (28 to 84 days) after the first dose. A booster dose (third dose) of 0.5 mL may be given to individuals who completed the primary vaccination course with Vaxzevria or an mRNA COVID-19 vaccine. The third dose should be administered at least 3 months after completing the primary vaccination course.

Table 1 Product Overview

Pharmaceutical form(s) and strengths	Current: 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: VAXZEVRIA will be referred to by its development number (AZD1222) within this RMP when describing data and studies from the non-clinical and clinical development programme.

II. PART II: SAFETY SPECIFICATION

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

II.1.1 Prevention of COVID-19

Incidence

Coronavirus disease 2019 (COVID-19) is a novel infectious disease, caused by SARS-CoV-2.

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 SARS-CoV-2 as a pandemic in March 2020 (WHO 2020b). As of 05 October 2022, over 615 million confirmed cases of COVID-19 infection have been diagnosed globally with more than 6.5 million deaths (WHO 2022). By 27 September 2022, there had been over 145 million confirmed cases of COVID-19 infection and over 590 thousand deaths in the EU/European Economic Area (ECDC 2022).

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 illness due to COVID-19 increases with age. Early 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 2022 a). Patients with COVID-19 can experience a wide range of symptoms from mild to critical illness (ECDC 2022 a). Older adults, males, and persons with chronic medical conditions, including cardiovascular disease, chronic kidney disease, chronic liver disease, cancer, obesity, diabetes, pre-existing hypertension, pulmonary disease, immunosuppression, and sickle cell disease, are at increased risk of disease severity and/or mortality (Gallo Marin et al 2020, Beaney et al 2022 and ECDC 2022b).

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, Beaney et al 2022). Studies from the United States of America (USA) have also reported increased mortality with COVID-19 in male relative to female patients (Finelli 2021). In the 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). Ethnicity (particularly non-white ethnicity) has been recognized as a predictor for more severe

disease, and/or risk of hospitalisation in numerous studies (Gao 2021). Recent evidence suggests that racial disparities in COVID-19 risk were more pronounced in the early waves of the pandemic, and that such association is mediated mainly by community-level socioeconomic status, contact with suspected or confirmed COVID-19 cases, and lack of access to clinical care (Lo et al 2021,Magesh et al 2021Magesh et al 2021).

The main existing treatment options

Pre-exposure and post-exposure prophylaxis

In December 2020, the first COVID-19 vaccine candidate (COVID-19 mRNA Vaccine BNT162b2) was authorised in the UK on a temporary basis under Regulation 174 of the Human Medicine Regulations 2012 and granted conditional marketing authorisation in the EU for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus in individuals ≥ 16 years of age. That same month, Vaxzevria (previously COVID-19 Vaccine AstraZeneca) temporary authorisation was also issued under UK Regulation 174 for individuals ≥ 18 years of age. In January 2021, Vaxzevria and COVID-19 Vaccine Moderna were granted conditional marketing authorisation in the EU for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus in individuals ≥ 18 years of age. Conditional marketing authorisation in the EU was also granted for COVID-19 Vaccine Janssen in March 2021 and for Nuvaxovid COVID-19 Vaccine (recombinant, adjuvanted) (Novavax CZ a.s.) in December 2021. Subsequently, and as of 04 October 2022, at least 11 different vaccines, utilizing 4 platforms, have been administered globally (WHO 2022). As of October 2022, 172 candidate vaccines are in clinical development and 199 are in pre-clinical investigation (WHO 2022a).

On 11 December 2020, FDA issued the first emergency use authorization (EUA) of Pfizer-BioNTech COVID-19 Vaccine (Comirnaty) for the prevention of COVID-19 in individuals 16 years of age and older. On 18 December 2020, FDA issued an EUA for Moderna COVID-19 Vaccine (Spikevax) for the prevention of COVID-19 in individuals 18 years of age and older. EUA was also issued Janssen COVID-19 Vaccine in February 2021 (FDA 2022).

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. Earlier in the clinical course of disease when SARS-CoV-2 replication is greatest or soon after symptom onset, antivirals and monoclonal antibody therapies are likely to be most effective. Later, anti-inflammatory drugs and immunomodulators may be used to stabilize the hyperinflammatory state that can accompany of COVID-19 in some patients (Cascella et al 2022).

Individuals with mild COVID-19 are managed in the ambulatory setting with supportive care and isolation. Closer monitoring over the time course of those with mild disease is advised for the elderly and those with pre-existing conditions. Where authorized, monoclonal antibody

therapies can be considered for outpatients who are at risk of disease progression (Cascella et al 2022). As of October 2022, CHMP has granted marketing authorizations for 3 mAbs [XEVUDY (sotrovimab), REGKIRONA (regdanvimab), and RONAPREVE (casirivimab/imdevimab)] in the treatment of COVID-19 in patients who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. Patients with moderate, severe and critical disease may be considered for antiviral therapy (eg. VEKLURY [remdesivir], LAGREVIO [mulnupiravir]), and dexamethasone (Cascella et al 2022).

Four anti-SARS-CoV-2 mAb products have received Emergency Use Authorizations (EUAs) from the Food and Drug Administration (FDA). Bamlanivimab plus etesevimab, tixagevimab plus cilgavimab (Evusheld), and bebtelovimab, received EUAs for the treatment of mild to moderate COVID-19 in non-hospitalized patients with laboratory-confirmed SARS-CoV-2 who are at high risk for progressing to severe disease and/or hospitalization. Further treatment options for COVID-19 are currently in clinical development (NIH 2022).

Further treatment options for COVID-19 are currently in clinical development.

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

SARS-CoV-2 infection can be classified into 6 distinct types including asymptomatic, pre-symptomatic infection, as well as mild, moderate, severe and critical illness. Transmission of SARS-CoV-2 may occur from pre-symptomatic, asymptomatic or symptomatic individuals (Cascella et al 2022). Early evidence suggested that viral transmission was possible from asymptomatic individuals (CDC 2020b, Lavezzo et al 2020, Oran and Topol 2020). Estimated rates of asymptomatic SARS-CoV-2 infection, however, vary widely with significant heterogeneity between studies, with an Interquartile Range (IQR) of estimates across 130 studies ranging of 14% to 50% (prediction interval 2% to 90%) (Buitrago-Garcia 2022). Symptomatic patients can experience a range of symptoms from mild to critical illness, with shifts in patterns of reported symptoms relative to dominant variants throughout the pandemic (Schulze 2022). Based on a large cohort study of > 44000 persons with confirmed COVID-19 during the early stages of the pandemic in 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%

These early data are consistent with a meta-analysis including > 280000 persons from 11 countries/regions which estimated the proportion of individuals with severe (and critical) disease as 22.9% (Li 2021). It is worth noting that patterns of clinical outcomes have been

changing throughout the pandemic and along the changing landscape of dominant variants of concern, the widespread use of COVID-19 vaccines, and the improvement in both early detection and management of symptomatic cases. For example, recent research suggested a shift towards atypical but less severe clinical presentation with omicron vs. delta variants (Menni et al 2022).

Overall, among Chinese patients who developed severe illness, the median time to dyspnoea ranged from 5 to 8 days, the median time to ARDS ranged from 8 to 12 days, and the median time 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. Overall mortality was estimated in a large meta-analysis as 5.6% (Li 2021), with much higher mortality among patients admitted to the ICU ranges from 39% to 72% depending on the study, with improvements seen in ICU mortality over the course of the pandemic (Dennis 2021). 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).

Data from the SEMI-COVID registry in Spain (a retrospective, multi centre national cohort study) demonstrated that immunosuppressed patients admitted to hospital with COVID-19 had significantly longer hospital stays than those without immunosuppression (median 10 days vs 9 days) (Suárez-García et al 2021). Immune suppression in this study was also associated with 60% higher rates of COVID-19-associated mortality compared to patients without immunosuppression, further highlighting the vulnerability of this population to SARS-CoV-2 (Suárez-García et al 2021).

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).
- Acute myocardial infarction especially in patients with severe systemic inflammation and hypercoagulability due to COVID-19 (Long 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)

  - A meta-analysis of studies reporting prevalence of venous thromboembolisms in patients with COVID-19 reported a pooled prevalence of PE of 32% (n = 17 studies) and a pooled prevalence of deep vein thrombosis of 27% (n = 32 studies) (Kollias 2021).
  - Incidence of stroke in COVID-19 patients ranged from 0.4% to 8.1% across 24 cohort studies, with a pooled estimate of stroke occurring in 1.4% of patients with COVID-19 (Nannoni et al 2021).
- Haematological complications including thrombocytopenia and complications including thrombocytopenia and neutrophilia are a hallmark of severe disease (Coopersmith 2021). Hypercoagulability in COVID-19 is well known. Although the exact mechanisms are unclear, it is thought to be linked to cytokine-induced inflammatory response (Abou-Ismail 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), 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).
- 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) and adults in with COVID-19 (Patel et al 2021).
- 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). In a large analysis of electronic health records, the risk of psychiatric outcomes including dementia, mood, anxiety or psychotic disorders were significantly higher in the 6 months following COVID-19 than compared to influenza or other respiratory tract infection (Taquet 2021).
- Long-term complications of COVID-19 (post-acute sequelae) can develop following infection of any severity, affecting up to 1 in 5 people following acute illness from COVID-19. Although sequalae are chronic and often debilitating, long COVID remains poorly characterized in current COVID-19 prevention and treatment strategies (Iqbal 2021). Multiple organ systems can be affected, including respiratory, cardiovascular,

nervous system, musculoskeletal, cutaneous and neuropsychiatric manifestations (Aiyegbusi et al 2021, Ballering et al 2022).

According to early research, 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 2022). More recent data suggest that duration of disease is highly variable, with recovery time dependent on risk factors (including age) and comorbidities (Mizrahi 2020). Duration of symptoms may be higher in individuals with suboptimal immune responses (Dreyer 2021).

Important comorbidities

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). As a result, elderly individuals, and those with these underlying comorbidities were 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 non-clinical 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 was conducted (Study 513351), with findings (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

A non-clinical developmental and reproductive toxicity study was performed to evaluate the effects of AZD1222 on fertility and reproductive processes of female CD-1 mice during the embryo/foetal development phase, and postnatal outcomes during the littering phase. Immunogenicity assessments were also made in dams, foetuses, and pups. There were no vaccine-related unscheduled deaths throughout the study. Furthermore, there were no vaccine-related effects on female reproduction, foetal or pup survival, foetal external, visceral, or skeletal findings, pup physical development, and no abnormal gross pathology findings in pups or dams. Antibody responses raised in dams were maintained throughout gestation and postnatal periods, and seroconversion in foetuses and pups indicate placental and lactational transfer of immunoglobulins. Together with clinical data from non-pregnant people, these

results supported the inclusion of pregnant and breastfeeding people in AZD1222 clinical studies (Stebbings et al 2021a).

In a non-clinical study, the biodistribution of AZD1222 was assessed in mice for 29 days following intramuscular injection. Results show that AZD1222 was safe and well tolerated, with a spread that was largely confined to administration sites and the proximal sciatic nerve, with low levels observed in sites that are involved in rapid clearance of particulates by the reticuloendothelial system. Accordingly, levels of AZD1222 decreased from Day 2 to Day 29, indicating clearance. There were no quantifiable levels of AZD1222 in the blood, brain, spinal cord, reproductive tissue, and mammary gland suggesting a lack of widespread or long-term distribution of AZD1222 vector DNA throughout the body following its administration (Stebbings et al 2021b).

Relevance to human use: Based on these 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.

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 (Study 617078) 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 (Study 513351). 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

Immunogenicity

A post-vaccination SARS-CoV-2 challenge study in rhesus macaques was conducted to evaluate protection and the potential for vaccine-associated enhanced respiratory disease (VAERD) (Non-human Primate Efficacy and Immunogenicity - Study 1). A single administration of AZD1222 significantly reduced viral load in bronchoalveolar lavage fluid and respiratory tract tissue of vaccinated animals as compared to vector controls. None of the vaccinated monkeys developed pulmonary pathology after challenge with SARS-CoV-2. All lungs were histologically normal, and no evidence of viral pneumonia or immune-enhanced inflammatory disease was observed.

Relevance to human use: None. No evidence of VAERD following SARS-CoV-2 challenge in vaccinated rhesus macaques was observed.

Local Tolerance

Local tolerance with AZD1222 has been assessed in a GLP repeat-dose toxicity study in mice (Study 513351), from which findings indicated no erythema or oedema at the injection sites after administration of AZD1222 on any dosing occasion. Non adverse, fully reversible, mixed and/or mononuclear cell inflammation was observed in the subcutaneous tissues and skeletal muscle of the administration sites and adjacent sciatic nerve of animals dosed with AZD1222, however findings were consistent with anticipated findings after IM injection of vaccines.

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

Primary vaccination course with AZD1222

Table 1 provides a breakdown of exposure for the US study (D8110C00001, which included participants from the US [88.7%], Chile [6.8%], and Peru [4.5%]), and for the pooled University of Oxford-sponsored studies (COV001 [UK], COV002 [UK], COV003 [Brazil], and COV005 [South Africa]).

All participants in the US study and most participants in the 4 pooled University of Oxford-sponsored studies, were randomised to receive 2 standard doses of either AZD1222 (at 5.0×10^{10} vp or equivalent) or control. Some participants in the pooled Oxford studies were randomised to single dose cohorts and for some who received 2 doses of AZD1222, one or both the doses were non-standard (ie, low doses of AZD12222 2.2×10^{10} vp or 2.5×10^{10} vp).

Further breakdowns of these exposure data from the US and pooled Oxford studies by age group and sex (Table 2) and race (Table 3) are also provided.

Table -1 Clinical Trial Exposure to AZD1222 (US Study D8110C00001 and Pooled Oxford Studies - Safety Analysis Set)

	US Study D8110C00001[a] n	Pooled Oxford Studies n	Total n
Received at least 1 dose, regardless of dose level (Any dose)	21587	12259[b]	33846
Received a standard dose as the first dose (Dose 1 SD)	21587	10306	31893

[a] Includes all participants who received at least one dose of AZD1222. Participants were classified according to the study intervention they actually received. If a participant received AZD1222 and placebo they were classified as AZD1222.

[b] Participants included in the Any Dose for Safety Analysis Set.

Table 2 Clinical Trial Exposure to AZD1222 by Age Group and Sex (US Study D8110C00001 Pooled Oxford Studies - Safety Analysis Set)

Parameter	Number of participants (%)		
	US Study D8110C00001 (N = 21587)	Pooled Oxford Studies (N = 12259)	Total AZD1222 (N =33846)
Age group at screening (years)			
18 - 64	16760 (77.6)	11003 (89.8)	27763 (82.0)
≥ 65	4827 (22.4)	1256 (10.2)	6083 (18.0)
Sex			
Female	9575 (44.4)	6835 (55.8)	16410 (48.5)
Male	12012 (55.6)	5424 (44.2)	17436 (51.5)

Table 3 Clinical Trial Exposure to AZD1222 by Race (US Study D8110C00001 and Pooled Oxford Studies – Safety Analysis Set)

Race	Number of participants (%)		
	US Study D8110C00001 (N = 21587)	**Pooled Oxford Studies (N = 12259)**	**Total AZD1222 (N =33846)**
White	17061 (79.0)	9253 (75.5)	26314 (77.8)
Asian	947 (4.4)	448 (3.7)	1395 (4.1)
Black or African American	1794 (8.3)	1200 (9.8)	2994 (8.8)
American Indian or Alaska Native	851 (3.9)	-	851 (2.5)
Native Hawaiian or Other Pacific Islander	61 (0.3)	-	61 (0.2)
Other	-	807 (6.6)	807 (2.4)
Mixed/Multiple	510 (2.4)	533 (4.3)	1043 (3.1)
Unknown	101 (0.5)	16 (0.1)	117 (0.3)
Missing	-	2 (< 0.1)	2 (< 0.1)
Not reported	262 (1.2)	-	262 (0.8)

Booster dose (third dose) with AZD1222

Table 4 provides clinical trial exposure for the booster dose of AZD1222 in previously vaccinated individuals with either AZD1222 (V1222) or an mRNA COVID-19 vaccine (VmRNA) from Study D7220C00001(Safety Analysis Set), where the majority of participants were from the UK (>96%):

Table 4 Clinical trial exposure to AZD1222 booster dose (Safety Analysis Set - D7220C00001) for previously vaccinated cohorts):

AZD1222 booster treatment	Primary vaccination and booster dose with AZD1222 (Homologous)	Primary vaccination with mRNA followed by booster dose with AZD1222 (Heterologous)	Total
Safety Analysis Set (N)	367	322	689

Further breakdowns of these exposure data from the D7220C00001 study by age group, sex and race are also provided in Table 5Table 5

Table 5 Clinical trial exposure to AZD1222 booster dose by Age group, Sex and Race (Safety analysis set - D7220C00001)

Parameter	Number of participants (%)	
	Primary vaccination and booster dose with AZD1222 (Homologous) N = 367	**Primary vaccination with mRNA followed by booster dose with AZD1222 (Heterologous) N = 322**
Age group at randomisation (years)		
18 – 64	196 (53.4)	238 (73.9)
≥ 65	171 (46.6)	84 (26.1)
Sex		
Female	170 (46.3)	197 (61.2)
Male	197 (53.7)	125 (38.8)
Race		
White	319 (86.9)	290 (90.1)
Black or African American	2 (0.5)	3 (0.9)
Asian	10 (2.7)	8 (2.5)
Mixed	0	2 (0.6)
Unknown	36 (9.8)	19 (5.9)

Percentages are based on N, the number of subjects in the analysis set for each treatment group.
B1222 represents booster dose of AZD1222

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 US (D8110C00001) and 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 (COPD), 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 '*Interactions with other vaccines*').

Patients with Guillain-Barré syndrome (GBS) or any other demyelinating condition (only excluded from US study D8110C00001)

Reasons for exclusion: Patients with GBS or any other demyelinating condition were excluded from US study D8110C00001 as these individuals may have a higher risk of these demyelinating events.

Considered to be included as missing information: No

Rationale: Very rare events of demyelinating disorders have been reported following vaccination with AZD1222. SmPC includes GBS and transverse myelitis (TM). It is possible that this excluded population may be at a higher risk of these events than the general indicated population. Guillain-Barré syndrome is considered as an important identified risk.

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 6 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	In the US study (D8110C00001), 341 of 21587 participants (1.6%) reported comorbid liver disease at baseline. Exposure data for this population are not available for the pooled Oxford studies.
Patients with renal impairment	In the US study (D8110C00001), 166 of 21587 participants (0.8%) reported comorbid kidney disease at baseline. Exposure data for this population are not available for the pooled Oxford studies.
Patient with controlled cardiovascular disease	In the pooled Oxford studies, 1609 of 12282 participants (13.1%) in the AZD1222 group reported a history of cardiovascular disease at baseline. In the US study (D8110C00001), the following comorbid conditions were reported in the AZD1222 group at baseline: 737 of 21587 participants (3.4%) reported serious heart conditions (such as coronary artery disease, heart failure) and 5851 of 21587 participants (27.1%) reported high blood pressure.

Table 6 Exposure of Special Populations Included or not Included in the Clinical Development Programme

Type of special population	Exposure
Patient with controlled respiratory disease	In the pooled Oxford studies, 1288 of 12282 participants (10.5%) in the AZD1222 group reported a history of respiratory disease at baseline. In the US study (D8110C00001), the following comorbid respiratory diseases were reported in the 21587 AZD1222 group participants at baseline: 2142 (9.9%) reported asthma, 297 (1.4%) reported chronic obstructive pulmonary disease, 1 (< 0.1%) reported cystic fibrosis, and 33 (0.2%) reported pulmonary fibrosis.
Immunocompromised patients	In the US study (D8110C00001), 5 of the 21587 participants in the AZD1222 group (< 0.1%) reported lower immune health at baseline due to solid organ transplant. Exposure data for this population are not available for the pooled Oxford studies.
Subpopulations carrying relevant genetic polymorphisms	Data not collected in the clinical development programme.

II.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

II.5.1 Method used to calculate exposure

The post-marketing exposure data included in this section are presented by the number of doses distributed and the number of doses administered. All doses of VAXZEVRIA are intended for the same indication and route of administration.

For doses distributed, detailed vaccinee-level data (eg, gender, ethnicity, and age category) are not available.

II.5.2 Exposure

The VAXZEVRIA International Birth Date (IBD) is 29 December 2020; however, the first dose of vaccine administered in the post-marketing setting was on 04 January 2021 in the UK.

Cumulatively, up to 31 December 2022, global post-marketing exposure (by doses distributed) to VAXZEVRIA was estimated to be 3.02 billion doses. Cumulative regional data are presented in Table 7.

Table 7 VAXZEVRIA cumulative exposure (based on doses distributed) from IBD to 31 December 2022, by Region/Country/Collaboration

Region[b]	Exposure by doses distributed
Europe	248197720
International	680370580
North America	33267900
Japan	62720740
Serum Institute of India (licensing partner)[a]	1745773940
Fiocruz (licensing partner)[a]	209957440
R-Pharm (licensing partner) [a]	10358700
BKT [a]	30000000
Global	3020647020

[a] Data from Serum Institute of India, BKT, and R-Pharm is as of 30 June 2022 and from Fiocruz is as of 31 December 2022.

[b] Where AstraZeneca (AZ) is the Marketing Authorisation Holder, dose volumes cited represent doses dispatched from AZ manufacturing sites and contracted manufacturing sites. The destinations noted 'Region' represent what is known at the time of dispatch. Country to country donations may or may not be reflected dependent on the timing and type of donation'

BKT Biokangtai

Vaccine doses administered is a subset of doses distributed. Cumulative up to 31 December 2022, global post-marketing exposure (by doses administered) to Vaxzevria was estimated to be 2.35 billion doses including booster doses and are summarised in Table 8.

Table 8 VAXZEVRIA cumulative exposure (by doses administered), by Region/Country

Region/Country[a]	Exposure by doses administered		
	Dose 1	Dose 2	Dose 3/Dose 4/ Boosters
European Union	38935859	29830777	31951
United Kingdom	24725401	24141350	59155
Australia	6710682	6644072	479167
Argentina	10181628	9944079	6643766
Bangladesh	20769391	19503709	15968643
Guatemala	2038088	1612254	837482
Malaysia	2047982	2027704	1631803
Japan	58689	59160	0
Canada	2236627	577088	1788
Columbia	5761263	3886086	2039794
Ecuador	1764549	1470105	5039008
Iran	5601073	5045996	3779468
Brazil	62269829	56441002	32863466
Chile	410045	139643	2656600
Nepal	5506364	4789110	4703764
Peru	2244579	2110451	3747778
Saint Lucia	37850	34810	0
Taiwan	8072530	7164623	60558
Thailand	14098645	28682204	5923245
New Zealand	3317	3646	2076
Uruguay	46687	44454	179
Afghanistan	975338		
Philippines	22135134		
India	1745211297		
Ghana	10545038		
Lebanon	722870		
Iraq	717233		
South Korea	20348873		
Mexico	49783383		

[a]The data cut off for Iraq is 29 August 2021

The data cut off for Afghanistan is 30 April 2022

The data cut off for United Kingdom is 12 September 2022

The data cut off for Nepal is 25 September 2022

The data cut off for Mexico is 01 October 2022

The data cut off for Saint Lucia is 18 October 2022

The data cut off for Thailand is 25 November 2022

The data cut off for Philippines and Peru is 30 November 2022

The data cut off for Canada is 04 December 2022

The data cut off for New Zealand is 06 December 2022

The data cut off for Ghana is 09 December 2022

The data cut off for EU is 11 December 2022. *EU - AZ vaccine administration data for Germany is not available

The data cut off for Iran and South Korea is 17 December 2022

The data cut off for Australia is 21 December 2022

The data cut off for Brazil and Taiwan is 25 December 2022

The data cut off for Chile and India is 26 December 2022

The data cut off for Colombia and Japan is 27 December 2022

The data cut off for Argentina, Malaysia, Bangladesh, Ecuador, Guatemala, Lebanon and Uruguay is 28 December 2022

The weekly administered data is subject to change every week. The administered data for the PBRER reporting interval is derived by subtracting the previous report's cumulative from current cumulative values (Current Cumulative - Previous Cumulative = Current Interval) across all the Countries. Therefore, the negative values here is due to a greater cumulative value from previous report in comparison to current report.

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

Potential for misuse for illegal purposes

VAXZEVRIA 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 were evaluated in order to formulate the initial list of identified risks (adverse drug reactions [ADRs]), in addition to the important potential risks described within the initial approved version of this Risk Management Plan (RMP) (Version 1, Succession 5). Risks that were not included in the initial list of safety concerns (including supporting rationales) are presented in Section II.7.1.1, with safety concerns relevant for inclusion in the initial approved RMP and their justifications presented in Section II.7.1.2.

Further to these sections, a list of adverse events of special interest (AESIs) 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

The following topics were not considered relevant for inclusion in the list of safety concerns at the time of initial EU RMP approval:

- 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 common or 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 initial EU RMP

Important identified risks

There were no important identified risks for AZD1222 at the time of initial EU RMP approval.

Important potential risk

The following topics were classified as important potential risks for AZD1222 at the time of initial EU RMP approval:

- 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 were classified as missing information for AZD1222 at the time of initial EU RMP approval:

- 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. While 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 immunocompromised 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, while 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. While 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 current list of AESIs applicable to AZD1222 is presented in Table 9. 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 post-authorisation safety studies (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 9 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/adults (MIS-C/A)
	Sudden Death
	Anosmia, ageusia
Eye disorder	Acute macular neuroretinopathy (AMN)/ Acute macular outer retinopathy (AMOR)/ Paracentral acute middle maculopathy (PAMM)
Immunological	Autoimmune thyroiditis
	Anaphylaxis
	Type III hypersensitivity reactions
	Giant cell arteritis (GCA)
Respiratory	Acute respiratory distress syndrome (ARDS)
Neurologic	Guillain-Barré syndrome (GBS)
	Peripheral neuropathy and polyneuropathy
	Multiple sclerosis, transverse myelitis, and other demyelinating disorders
	Optic neuritis / neuromyelitis optica spectrum disorder

Body System/Classification	AESI
	Non-infectious encephalitis (inc. acute disseminated encephalomyelitis) / Non-infectious encephalopathy
	Myasthenia gravis
	Bell's palsy
	Generalised Convulsion (Seizures)
	Narcolepsy
Cardiovascular system	Myocarditis / Pericarditis
	Myocardial infarction
	Acute cardiac injury including microangiopathy, cardiogenic shock, heart failure, stress cardiomyopathy
	Postural orthostatic tachycardia syndrome
Circulatory system/Haematological	Thrombocytopenia, including immune thrombocytopenia
	Embolic and thrombotic events (thrombosis)
	Thrombosis with thrombocytopenia syndrome (TTS)
	Capillary leak syndrome (CLS)
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
	Chilblain-like lesions

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/PRAC/73244/2022) (EMA 2022). These considerations are therefore discussed below for completeness:

Reactogenicity

As of 31 December 2021, in the pooled Oxford studies, solicited local and systemic adverse events (AEs) were reported by 73.4 % and 72.8% of evaluated participants in the pooled Dose 1 SD safety dataset (N = 10306), respectively, within the first 7 days following any dose of

AZD1222. In the control group (MenACWY vaccine active control or saline placebo; N = 10141), solicited local and systemic AEs were reported by 48.9% and 60.8% 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.

Additionally, for the US study (D8110C00001), in the safety analysis set, 1956 participants in the AZD1222 group and 981 participants in the placebo group were evaluated for solicited AEs within 7 days after any vaccination. Solicited local and systemic AEs were reported by 74.1% (1440 participants) and 71.6% of participants (1395 participants), respectively, within the first 7 days following any vaccination with AZD1222. In the placebo group, solicited local injection site and systemic AEs were reported by 24.4% (239 participants) and 53.0% of participants (519 participants), respectively.

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.

Reactogenicity in AZD1222 as a Booster Dose

In study D7220C00001, the frequency of solicited local and systemic AEs in participants receiving a homologous booster of AZD1222 who were previously vaccinated with AZD1222 (N=367) was 59.5% and 59.1%, respectively. The frequency of solicited local and systemic AEs in participants receiving a heterologous booster of AZD1222 who were previously vaccinated with an mRNA vaccine (N=322) was 75.5% and 78.9%, respectively, which is similar to the reactogenicity observed in participants receiving a first dose of AZD1222 in previous clinical studies. Across both groups who received a booster dose of AZD1222, most solicited AEs were mild or moderate in intensity and generally resolved within a few days.

In the COV001 study, the observed reactogenicity in participants who received a single homologous booster dose (third dose) following a 2-dose primary vaccination course of AZD1222 was consistent with the known reactogenicity profile of COVID-19 Vaccine

AstraZeneca and was lower after the third dose compared with after the first dose (Flaxman et al 2021).

In the published study RHH 001, a Phase 4 randomized single-blind study conducted in Brazil, 304 participants received a single booster dose (third dose) of AZD1222 following a 2-dose primary vaccination course with an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac) (Clemens et al 2022). The reported reactogenicity profile was consistent with the known reactogenicity profile of AZD1222.

Overall, based on available data, the reactogenicity of either a homologous or heterologous booster dose of AZD1222, has been shown to be consistent with the reactogenicity profile of AZD1222 when administered as a primary vaccination course.

Formulation and preparation aspects of the vaccine

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.

AZD1222 does not form infectious particles in vaccinated individuals. Shedding from vaccinated individuals to unvaccinated close contacts does not occur, as the vaccine is injected via IM route. As AZD1222 is replication-deficient, it does not replicate in vaccinated individuals, so transmission does not occur.

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 study discontinuation rate in the pooled Oxford studies (any dose group; N = 12259) as of 31 December 2021 indicates that early discontinuation from the study for any reason was very low in the AZD1222 arm (n = 1621 participants [13.2%]). In the US study (D8110C00001), the incidence of study discontinuation was low; a total of < 0.1% (3 participants) in the AZD1222 group and < 0.1% (5 participants) in the placebo group discontinued the study due to AEs within 28 days following any vaccination. A total of 1.2% (266 participants) in the AZD1222 group and 1.5% (160 participants) in the placebo group discontinued study intervention due to AEs following any vaccination.

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, while 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 0).

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

The planned and ongoing PASS activities will follow participants for varying lengths of time to allow meaningful data collection for the evaluation of long-term safety and effectiveness (see Section III.2.1).

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:

1 Remain blinded in the trial per the Clinical Study Protocol (CSP).
2 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:
   (a) If a participant has received active treatment with AZD1222:
      (i) 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.
      (ii) If the participant has received 2 doses of AZD1222 the investigator will recommend that they continue in the study.
   (b) 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.
3 For study D7220C00001, all participants will be followed for safety for 6 months (180 days) post-vaccination of booster dose.

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 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 are 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 are 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

A re-assessment of the safety concerns has been conducted in line with Good Pharmacovigilance Practices (GVP) Module V – Risk Management Systems (Revision 2) and currently available post-marketing and clinical trial data. The important potential risk of "Nervous system disorders, including immune-mediated neurological conditions" is renamed as "Immune-mediated neurological conditions" as per the below rationale: .

II.7.2.1 Nervous system disorders including immune mediated neurological conditions:

The important potential risk 'Nervous system disorders, including immune mediated neurological condition' is renamed as 'Immune mediated neurological conditions'.

Nervous system disorders includes a wide spectrum of conditions and symptoms; many of which like headache, dizziness, somnolence, lethargy, paraesthesia and hypoaesthesia are well characterised in section 4.8 of EU SmPC and hence could be considered as 'non-important' identified risks. Non-serious nervous system events do not have an impact on the overall benefit risk.

Cumulatively as of 28 June 2022, a total of 36033 cases of immune mediated neurological conditions were identified from literature, clinical studies, non-interventional studies and spontaneous sources. Overall, in clinical studies there were no clinically meaningful imbalances in the incidence of neurological AESIs.

Immune mediated neurological conditions could result in serious consequences (including life threating and fatal) if not identified and treated early and also associated with significant disability. As there are no clear mechanism of immune mediated neurological conditions following vaccination with VAXEVRIA, unknown risk factors and still gaps in characterisation, this risk is retained as important potential risk.

II.7.3 Details of important identified risks, important potential risks and missing information

Presentation of important identified risks and important potential risks

II.7.3.1 Important Identified Risk: Thrombosis with thrombocytopenia syndrome

Potential mechanisms

The exact mechanism of thrombosis with thrombocytopenia syndrome (TTS) following immunisation with AZD1222 is unknown. Several hypothetical biologic mechanisms (eg, vaccine induction of Platelet Factor 4 (PF4 autoantibodies) have been proposed to explain the pathophysiology of thromboembolic events with thrombocytopenia following vaccination (Greinacher et al 2021). Among them a study by Baker et al 2021, proposes an interaction between the ChAdOx1 vaccine vector used in COVID-19 Vaccine AstraZeneca and PF4; however, it is unknown if the adenoviral ChAdOx1 interaction with PF4 is actually platelet activating or thrombogenic (causal of blood clots). Greinacher et al 2021 suggested that ChAdOx1 itself or proteins contained within the vaccine can bind to PF4 to form immune complexes which may drive a B-cell response causing high-titer anti-PF4 antibodies resulting in TTS. However, none of these hypotheses have been confirmed.

Evidence source(s) and strength of evidence

There were no reports of thrombosis concurrent with thrombocytopenia in the AZD1222 clinical development programme. Very rare events of serious TTS (including fatal events), have been observed following vaccination with AZD1222 during post-authorisation use.

Characterisation of the risk

TTS, in some cases accompanied by bleeding, has been observed very rarely following vaccination with AZD1222. This includes severe cases presenting as venous thrombosis, including unusual sites such as cerebral venous sinus thrombosis, splanchnic vein thrombosis, as well as arterial thrombosis, concomitant with thrombocytopenia. The majority of these cases occurred within the first 21 days following vaccination and some events had a fatal outcome. The reporting rates after the second dose are lower compared to after the first dose.

Risk factors and risk groups

There are no known risk factors for the development of thrombosis with thrombocytopenia following vaccination.

Preventability

Prevention of TTS in the context of COVID-19 vaccination is currently unknown. As described in Section 4.4 of the SmPC, healthcare professionals should be alert to the signs and symptoms of thromboembolism and/or thrombocytopenia. Vaccinated individuals should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, leg pain, persistent abdominal pain following vaccination.

Individuals diagnosed with thrombocytopenia/ thrombosis within three weeks after vaccination with AZD1222, should be actively investigated for signs of thrombosis/thrombocytopenia.

TTS requires specialised clinical management. Healthcare professionals should consult applicable guidance and/or consult specialists (eg, haematologists, specialists in coagulation) to diagnose and treat this condition.

Impact on the risk-benefit balance of the product

TTS is a potentially life-threatening event if not recognised or managed appropriately, may result in persistent or significant disability or incapacity. TTS requires immediate medical intervention.

Public health impact

The public health benefit of vaccination is considered to outweigh the very rare occurrence of these events.

II.7.3.2 Important Identified Risk: Thrombocytopenia, including immune thrombocytopenia

Potential mechanism

The exact mechanism of thrombocytopenia, including immune thrombocytopenia following immunisation with AZD1222 is unknown.

Evidence source(s) and strength of evidence

Very rare cases of thrombocytopenia, including immune thrombocytopenia (ITP), have been observed following vaccination with AZD1222 during post-authorisation use.

Characterisation of the risk

Cases of thrombocytopenia, including immune thrombocytopenia (ITP), have been reported after receiving Vaxzevria, typically within the first four weeks after vaccination. Very rarely, these presented with very low platelet levels (< 20,000 per μL) and/or were associated with

bleeding. Some of these cases occurred in individuals with a history of immune thrombocytopenia. Cases with fatal outcome have been reported. In the clinical development programme, in the primary analysis of the study D8110C00001(DCO 05 March 2021), thrombocytopenia was reported in 2 participants (< 0.1%) in the AZD1222 group, and immune thrombocytopenia was reported in 1 participant each (< 0.1%) in both AZD1222 group and the placebo group. In the long-term safety analysis at 6-months data cut-off (30 July 2021) when censored at the time of EUA vaccination, one additional event of thrombocytopenia was reported in a participant in the AZD 1222 group. None of these events were serious.

Risk factors and risk groups

There are no known risk factors for the development of thrombocytopenia following vaccination. In general, individuals with a history of thrombocytopenic disorder, such as immune thrombocytopenia, the risk of developing low platelet levels should be considered before administering the vaccine and platelet monitoring is recommended after vaccination as described in Section 4.4 of the SmPC.

Preventability

Prevention of thrombocytopenia including immune thrombocytopenia in the context of COVID-19 vaccination is currently unknown. Individuals diagnosed with thrombosis within three weeks after vaccination with Vaxzevria, should be actively investigated for signs of thrombocytopenia as described in Section 4.4 of the SmPC.

Impact on the risk-benefit balance of the product

Thrombocytopenia including immune thrombocytopenia if not recognised or managed appropriately can lead to bleeding which can be a potentially life threatening event. Thrombocytopenia with associated bleeding requires immediate medical intervention.

Public health impact

The public health benefit of vaccination is considered to outweigh the very rare occurrence of these events.

II.7.3.3 Important Identified Risk: Guillain-Barré syndrome

Potential mechanism

Exact mechanism of GBS following immunization with AZD1222 is unknown. Although the underlying etiology and pathophysiology of GBS are not completely understood, it is believed that immune stimulation plays a central role in its pathogenesis (Sejvar et al 2011).

Evidence source(s) and strength of evidence

In the US study (D8110C00001), 1 SAE of a demyelinating event initially reported as Guillain-Barre syndrome occurred in a participant enrolled in the AZD1222 group. The SAE of GBS was subsequently amended to an SAE of Chronic inflammatory demyelinating

polyradiculoneuropathy. Very rare events of GBS have been observed following vaccination with AZD1222 during post-authorisation use.

Characterisation of the risk

Very rare events of GBS have been observed following vaccination with AZD1222 in the post-authorisation setting. These reports of GBS have been associated temporally after vaccination and resulted in fatal outcome in isolated cases. The majority of the GBS cases were reported in vaccinees < 69 years of age. Pharmacoepidemiologic studies suggest an increased rate of GBS after the 1st dose of AZD1222 in the first 4-6 weeks after vaccination (Keh et al 2021 and Maramattom et al 2021).

Risk factors and risk groups

There are no known risk factors for the development of GBS following vaccination. In general, infection with the bacteria Campylobacter jejuni is one of the most common risk factors for GBS. People also can develop GBS after having the flu or other infections such as cytomegalovirus and Epstein-Barr virus. On very rare occasions, people develop GBS in the days or weeks after getting a vaccination (CDC 2019).

Preventability

As described in SmPC section 4.4, the healthcare professionals should be alert of GBS signs and symptoms to ensure correct diagnosis, in order to initiate adequate supportive care and treatment, and to rule out other causes.

Impact on the risk-benefit balance of the product

GBS, though rare, is the most common cause of acute flaccid paralysis and if not recognised or managed appropriately, may result in persistent or significant disability or incapacity, and hence requires immediate medical intervention.

Public health impact

Occurrence of GBS following AZD1222 vaccine is very rare and as such the public health benefit of vaccination is considered to outweigh the very rare potential occurrences of such events.

II.7.3.4 Important Potential Risk: Thrombosis

Potential mechanisms

The mechanism of thrombosis following immunisation is unknown.

Evidence source(s) and strength of evidence

Very rare events of serious thrombosis, including thrombosis with and without co-reported thrombocytopenia and thrombosis in unusual sites associated with rapid decline in platelet count known as TTS, have been observed following vaccination with AZD1222 during post-authorisation use.

Characterisation of the risk

Serious events of arterial and venous thrombosis have been reported following vaccination with AZD1222 during post-authorisation use. In the pooled Oxford studies, thromboembolic events were reported in 0.1% (18/12,257 participants) in the AZD1222 group and 0.3% (34/11,962 participants) in the control group. There were no reports of cerebral venous sinus/cerebral venous thrombosis or splanchnic vein thrombosis; 1 event of mesenteric vein thrombosis was reported in the control group in the Oxford studies. No concurrent AEs of thrombocytopenia or platelet count decrease were reported in participants with a thromboembolic event. In the primary analysis of the US study (DCO 05 March 2021), thromboembolic events (MedDRA SMQ Embolic and thrombotic events) reported during the double-blind period were balanced: 0.1% (23/21,587 participants) in the AZD1222 group and < 0.1% (9/10,792 participants) in the placebo group. In the long-term safety analysis at 6-months data cut-off (30 July 2021) when censored at the time of EUA vaccination, thromboembolic events were reported in 0.3% of participants (68 participants) in the AZD1222 group (exposure adjusted rate of < 0.01/patient-year) and 0.1% of participants (14 participants) in the placebo group (< 0.01/patient-year).

Risk factors and risk groups

There are no known risk factors identified for the development of thrombosis following vaccination.

Preventability

Prevention of thrombosis in the context of COVID-19 vaccination is currently unknown. As described in Section 4.4 of the SmPC, healthcare professionals should be alert to the signs and symptoms of thromboembolism. Vaccinated individuals should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain, leg swelling, leg pain, persistent abdominal pain following vaccination. Additionally, individuals with neurological symptoms including severe or persistent headaches, blurred vision, confusion, or seizures after vaccination should seek prompt medical attention.

Individuals diagnosed with thrombosis/thrombocytopenia within 3 weeks after vaccination with AZD1222 should be actively investigated for signs of thrombocytopenia/thrombosis.

Impact on the risk-benefit balance of the product

Thrombosis is a potentially life-threatening event, and if not recognised or managed appropriately, may result in persistent or significant disability or incapacity, and hence requires immediate medical intervention.

Public health impact

The public health benefits of vaccination is considered to outweigh the very rare occurrence of these events.

II.7.3.5 Important Potential Risk: 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).

Very rare events of immune-mediated neurological conditions have been observed following vaccination with AZD1222 during post-authorisation use.

Characterisation of the risk

A review of the events in the pooled safety dataset in the MedDRA System Organ Class (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, in clinical studies there were no clinically meaningful imbalances in the incidence of neurological AESIs. In the pooled Oxford studies as of 31 December 2021, neurologic or neuroinflammatory AESIs were reported in 1.0% (121/12,259 participants) in the AZD1222 group and 1.0% (117/11,962 participants) in the control group. In the primary analysis of the US study (DCO 05 March 2021), neurologic or neuroinflammatory AESIs were reported in 0.6 % (121/21,587 participants) in the AZD1222 group 0.4 % (48/10,792 participants) in the placebo group. In the long-term safety analysis at 6-months data cut-off (30 July 2021) when censored at the time of EUA vaccination, neurologic or neuroinflammatory AESIs were reported in 0.6% of participants (137 participants) in the AZD1222 group (exposure adjusted rate of 0.01/patient-year) and 0.5% of participants (51 participants) in the placebo group (0.01/patient-year).

Furthermore, in the pooled Oxford studies no clinically meaningful imbalance was noted in the incidence of AESIs of neuroinflammatory disorders, which were reported in 10 participants (0.1%) in the AZD1222 group and 6 participants (< 0.1%) in the control group in the pooled safety dataset (any dose group). Of these, the most frequently reported events were nonserious AEs of facial paralysis, occurring in 4 participants in the AZD1222 group and 3 participants in the control group. In the primary analysis of the US study (DCO 05 March 2021), there were 5 participants reported nonserious AEs of facial paralysis, all in the AZD1222 group. In the long-term safety analysis at 6-months data cut-off (30 July 2021) when censored at the time of EUA vaccination, 3 additional participants reported nonserious AEs of facial paralysis in the AZD 1222 group.

In the pooled Oxford studies, there were 4 SAEs of demyelinating events: 3 cases in the AZD1222 group (1 case of transverse myelitis, and 2 case of multiple sclerosis in a participant with pre-existing, but previously unrecognised, multiple sclerosis), and 1 case of myelitis in the control group. In the primary analysis of the US study (DCO 05 March 2021), there was 1 SAE of a demyelinating event: a participant in the AZD1222 group had an AE initially reported as Guillain-Barre syndrome, which was subsequently diagnosed as an SAE of Chronic inflammatory demyelinating polyradiculoneuropathy. In the long-term safety analysis at 6-months data cut-off (30 July 2021) when censored at the time of EUA vaccination, one additional SAE was reported in a participant who experienced demyelinating polyneuropathy.

Risk factors and risk groups

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

Preventability

Prevention of 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.

II.7.3.6 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 (EMA 2021b, EMA 2021c, FDA 2020).

Characterisation of the risk

In the AZD1222 clinical programme, there was no evidence of an association between AZD1222 and VAED/VAERD; proportionally more AESIs based on study specific lists of terms related to COVID-19[1] occurred in the control group than among AZD1222 recipients. In the pooled Oxford studies as of 31 December 2021, COVID-related AESIs were reported in 0.5% (66/12,259 participants) in the AZD1222 group and 1.0% (118/11,962 participants) in the control group. There have been no confirmed post-marketing reports of VAED/VAERD. In the primary analysis of the US study (DCO 05 March 2021), COVID-related AESIs were reported in 1.7% (374/21,587 participants) in the AZD1222 group and 3.4% (362/10,792 participants) in the placebo group. In the long-term safety analysis at 6-months data cut-off (30 July2021) when censored at the time of EUA vaccination, COVID-related AESIs were reported in 3.2% of participants (697 participants) in the AZD1222 group (exposure adjusted rate of 0.06/patient-year) and 4.3% of participants (461 participants) in the placebo group (0.13/patient-year).

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

[1] Based on the selected terms: Acute lung injury, Acute respiratory distress syndrome, Pneumonitis, Coronavirus infection, COVID-19, COVID-19 pneumonia, Multisystem inflammatory syndrome in children, SARS-CoV-2 sepsis, Suspected COVID-19

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

Presentation of missing information

II.7.3.7 Missing Information: Use during pregnancy and while breastfeeding

Evidence source

Data from more than 400 case reports of pregnant women or women who became pregnant after receiving AZD1222 do not suggest unusual patterns of pregnancy complications or foetal/neonatal outcomes. No increased risk of maternal thrombosis in combination with thrombocytopenia has been observed. Preliminary non-clinical safety studies have not indicated any concern to date and available non-clinical, clinical and post-marketing data do not suggest a risk to breastfed new borns /infants.

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 further characterising the safety profile in this population, is considered necessary.

Population in need of further characterisation

Use of AZD1222 in pregnant and breastfeeding women is investigated in the ongoing PASS activities (a post-marketing observational study using existing secondary health data sources, and a pregnancy registry; see Section III.2.1 for further details).

II.7.3.8 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 and ongoing PASS activities (post-marketing observational study using existing secondary health data sources, Systematic literature review, see Section III.2.1 and III.2.2) for further details).

II.7.3.9 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) is investigated in the ongoing PASS activity (a post-marketing observational study using existing secondary health data sources; see Section III.2.1 for further details).

II.7.3.10 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 from AZD1222 clinical studies to date that the safety profile of this population differs from 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 is investigated in the ongoing PASS activity (a post-marketing observational study using existing secondary health data sources; see Section III.2.1 for further details).

II.7.3.11 Missing Information: Interactions with other vaccines

Evidence source

There is currently limited information regarding the safety, immunogenicity, and efficacy of AZD1222 when co-administered with other vaccines concurrently seasonal illness vaccines.

While there is currently no evidence to suggest the safety profile or efficacy of AZD1222 when co-administered with other vaccines would be impacted, given the paucity of data, the possibility of an interaction causing an altered safety profile or reduced efficacy of either AZD1222 or the co-administered vaccine 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) is investigated in the ongoing PASS activity (a post-marketing observational study using existing secondary health data sources; see Section III.2.1 for further details). Vaccines to be evaluated include the influenza and pneumococcal vaccines.

II.7.3.12 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. While 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 ongoing PASS activity (a post-marketing observational study using existing secondary health data sources; see Section III.2.1 for further details) and through follow-up in ongoing clinical studies in the AZD1222 clinical development programme (see Section III.2.2).

For the US study, long-term safety of AZD1222 has been evaluated through the 6-month data cut-off (31 July 2021). Relevant safety results through the 6-month data cut-off are presented for the Important identified risks and Important potential risks in section II.7.3. Overall, safety results at the 6-month data cut-off were generally consistent with safety findings at the primary analysis, with no new or emerging safety issues identified.

II.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

A summary of safety concerns for AZD1222 is presented in Table 10

Table 10 Summary of Safety Concerns

Important identified risks	• Thrombosis with thrombocytopenia syndrome • Thrombocytopenia, including immune thrombocytopenia • Guillain-Barré syndrome
Important potential risks	• Thrombosis • Immune-mediated neurological conditions • Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)
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 to vaccine risk management in the context of the COVID-19 pandemic (EMA 2022, 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 are supplemented as described below.

Data sources that are used for signal detection and the frequency of their review are listed in Table 11.

Table 11 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])	Monthly
EudraVigilance Data Analysis System (EVDAS) Electronic Reaction Monitoring Report (eRMR)	Quarterly
US Vaccine Adverse Event Reporting System (VAERS)	Monthly
Literature (Embase and Insight Meme)	Monthly
All Clinical Trial AEs from AZ and non-AZ sponsored studies	Monthly
Batch distribution data	Monthly

Due to the unique nature in which safety data are obtained for AZD1222 (both in methods of data collection and in volume of data), multiple methods for the evaluation of data retrieved from the above data sources are utilised for signal detection. These data sources are 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 is 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 are downloaded and integrated into the AstraZeneca Global Safety Database on a daily basis. These data are included in the quarterly data review. Additionally, an eRMR is generated on a monthly basis and is included as a part of surveillance review. The eRMR report is generated using the Active Substance High Level value of 'COVID-19 VACCINE ASTRAZENECA (CHADOX1 NCOV-19)'. 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 are 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 DME list

- AESIs (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 are produced and reviewed monthly 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 provide both in-period and cumulative event counts, and comparisons with previous event counts are 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 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 is generated and analysed against batch distribution data using an observed vs expected analysis model to identify batches with a higher number of AEs than expected being reported based on the volume distributed for that lot. Batches meeting the threshold for analysis are 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 is 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 are 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 6 - monthly basis. To account for potential under reporting of AEs, sensitivity analysis is performed. Where appropriate, standard statistical testing methodology are also 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 Periodic Safety Update 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 PSUR (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

All ICSRs received for AZD1222 are 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 [2] when AZD1222 is used in accordance with its authorisation, will be reported within the required 15 days of receipt.

For all AZD1222 ICSRs received, data regarding the subject, the reporter, the adverse reaction, suspect drug(s) and product batch number are proactively sought.

Additionally, for all AZD1222 ICSRs received other than non-serious listed ICSRs, further data including, but not limited to, the subject's medical history, concomitant medications, vaccination and reaction dates, and outcome are actively followed up.

[2] 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.

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 are in place for important potential risks and AESIs.

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

III.1.4 Summary Safety Reports

PSURs will serve as the tool for discussion of any safety topics as well as other standard pharmacovigilance activities. The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

III.1.5 Enhanced Passive Surveillance

Enhanced passive surveillance activities are not planned as other additional pharmacovigilance measures are in place (see Section III.2.1).

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 are placed into all cartons of drug product at the Contract Manufacturing Organizations (CMO) packing sites. Two stickers are provided per dose; hence, 200 stickers are 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 include the vaccine name (ie, '*COVID-19 Vaccine AstraZeneca*' or '*VAXZEVRIA*'), 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) remains the same. Traceability instructions for HCPs are provided in the SmPC.

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

AstraZeneca also makes 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 (ie, the use of electronic records or national mandated vaccination cards) are unavailable. The Traceability and Vaccination reminder cards 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 a Marketing Authorisation Holder 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 are also available on AstraZeneca websites, where required 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, a number of PASS activities are planned, which are presented in Section III.2.1. It is noted that in order to meet regulatory requirements, some of the planned PASS activities may be conducted under more than one localised protocol.

Further to these PASS activities, and aligned with regulatory guidance (EMA 2022), all ongoing clinical studies in the current clinical development plan are also described in Section III.2.2, 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 Post Marketing safety studies

III.2.1.1 Pregnancy Registry

Study name and title:	Pregnancy Registry of Women Exposed to AZD1222 Immediately Before or During Pregnancy as part of the C-VIPER Registry Consortium (D8110C00003; Pregistry-sponsored).
Rationale and study objectives:	There are limited data on long term safety and health status in specific populations such as pregnant women. The study objective is to estimate the risk of the most common obstetric outcomes (pregnancy losses, placentation disorders, gestational diabetes, premature

	delivery, and COVID-19), neonatal outcomes (congenital anomalies, low birth weight for gestational age, neonatal intensive care unit admission, and COVID-19), and infant outcomes (height for age, weight for height, developmental milestones until one year of age, and COVID-19) among pregnant women exposed to AZD1222 from 30 days prior to the first day of the LMP to end of pregnancy and their offspring relative to a matched unexposed reference group.
Study design:	This study will utilise data from a prospective registry, C-VIPER, an international, prospective, observational cohort study of pregnant women vaccinated from 30 days prior to the first day of the LMP to end of pregnancy to prevent COVID-19. It includes follow-up of liveborn infants to one year of age. 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 years old, 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 Dec 2020 • Protocol submission: 27 Jan 2021 • Start of study: 17 May 2021 • First interim report / First quarterly update: 30 Sep 2021 • Statistical analysis plan (SAP): 15 Jan 2022 • Semi-annual report (period of 1 Jun to 30 Nov each year): Jan 2022/ Jan 2023 • Quarterly update (period of 1 Dec to 28th Feb following year): Apr 2022 • Annual update report (period of 1 June to 31 May following year): Jul 2022/Jul 2023/Jul 2024/Jul 2025 • Final Report: Jul 2026

III.2.1.2 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 to evaluate the association between exposure to AZD1222 and safety concerns using existing secondary health data sources and D8111R00006 [EU/UK]).
Rationale and study objectives:	The purpose of this study is to further define the incidence and relative risk of safety concerns and AESIs among adults vaccinated with AZD1222 and 3 different comparator cohorts: concurrent individuals who have not received any vaccination for COVID-19, active comparators (2 dose vaccinees only), and historical comparators – overall and in subpopulations of interest. The AZD1222 cohort will be matched, as applicable, independently to the 3 different comparator cohorts on calendar date of vaccination, age, sex, region, prior COVID 19, and status according to each of the five special populations. Matching will be done with replacement in a ratio of 1 vaccinated to 1 comparator subject. Where appropriate, the study will also use a self-controlled risk interval (SCRI) design. The primary study objectives are as follows: 1. To describe the baseline characteristics of all subjects in the matched population.

	2. To describe, among subjects who receive a first dose of AZD1222(i.e., in the all AZD1222 vaccinated first dose population), the timing and type of second dose of any COVID-19 vaccine (AZD1222 or other) over the study period. 3. To describe the incidence rates (IRs) of prespecified AESIs in subjects who received at least 1 dose of AZD1222 in the matched population and subjects who did not receive any vaccination against COVID-19 (concurrent unvaccinated comparators) in the matched population. 4. To estimate the relative and absolute risk of prespecified AESIs in subjects who received at least 1 dose of AZD1222 compared with concurrent unvaccinated comparators in the matched populations, using a retrospective cohort design and an SCRI design. The secondary study objectives are as follows: 1. To describe the baseline characteristics of all subjects in the matched population among the specific populations considered to have missing information. 2. To describe, among subjects who receive a first dose of AZD1222, (i.e., in the all AZD1222 vaccinated first dose population), the timing and type of second dose of any COVID-19 vaccine (AZD1222 or other) over the study period among the specific populations considered to have missing information. 3. To describe the IRs of prespecified AESIs in subjects who received at least 1 dose of AZD1222 in the matched population and subjects who did not receive any vaccination against COVID-19 (concurrent unvaccinated comparators) in the matched population, among the specific populations considered to have missing information. 4. To estimate the relative and absolute risk of prespecified AESIs in subjects who received at least 1 dose of AZD1222 compared with concurrent unvaccinated comparators in the matched populations, among the specific populations considered to have missing information, using a retrospective cohort design and an SCRI design. Exploratory objectives are as follows: 1. To describe the IRs of prespecified AESIs in subjects who received an mRNA vaccine against COVID-19 (either Comirnaty or Spikevax) (active comparators) and in subjects from the pre-pandemic period (2017-2018) (historical comparators) in the matched population. 2. To estimate the relative and absolute risk of prespecified AESIs in subjects who received at least 1 dose of AZD1222 in the matched population compared with historical comparators in the matched population. 3. To estimate the relative and absolute risk of prespecified AESIs in subjects who received 2 doses of AZD1222 in the matched population compared with subjects who received 2 doses of active comparator (Comirnaty or Spikevax as per homologous vaccination regimen) in the matched population.
Study design/period:	This is a multinational, retrospective, longitudinal cohort study using population-based automated health care data to ascertain vaccination details, patient characteristics, and outcomes of interest. The study period will start on 04 January 2021, when the vaccine was first used in the UK, and will end approximately 24 months after it is introduced in the last country among participating data sources.

Study population:	• The source population will comprise all individuals registered in each of the healthcare data sources. • The AZD1222 cohort will be identified based on the first vaccination with AZD1222 (index date). • A concurrent unvaccinated comparator cohort will be identified among subjects who have not received any vaccination for COVID-19 matched (to the extent possible) on the vaccinee's index date, age, sex, prior diagnosis of COVID-19, and status according to each of the 5 special populations. • The active comparator cohort will be identified based on the first second consecutive vaccination with an mRNA vaccine (Comirnaty or Spikevax) matched (to the extent possible) on the vaccinee's index date (second dose), age, sex, prior diagnosis of COVID-19, and status according to each of the 5 special populations. • A historical comparator cohort will be identified among subjects who were enrolled in the study data sources at any time during 2017 and 2018 matched on age, sex, and status according to each of the 5 special populations.
Milestones:	The milestones below are only for the D8111R00006 study: • Study Design Concept submission: 18 Dec 2020 • Submission of study protocol: 01 Apr 2021 • Submission of final study protocol: 15 Jul 2021 • Statistical analysis plan submission: Nov 2021 • Progress report: Oct 2021 • Interim report 1: Apr 2022 • Feasibility report for comparative analysis: August 2023 • Final report of study results: Jun 2024

In vitro interaction with PF4 and/or platelets

Study name and title:	In vitro interaction of AZD1222 or spike protein with PF4 and/or platelets (MS1222-0001)/ (MS1222-0004)/ (MS1222-0005).
Rationale and study objectives:	To test the interaction of AZD1222 or spike protein with PF4 and/or platelets to further characterise the possible mechanisms and to identify the possible triggers of platelet activation after vaccination.
Study design:	Computational prediction of spike interaction with PF4: Modelling possible interaction of spike protein with PF4 as a potential mechanism. The study objectives are to test AZD1222 interaction with platelets, PF4, and anti-PF4, and to test platelet activation in vitro in the presence of AZD1222 and naïve sera, AZD1222 and vaccinated sera, Spike and naïve sera, and Spike and vaccinated sera.
Study population:	In vitro assay involving sera from Covid/Vaccine naïve individuals and AZD1222 vaccinated individuals. Platelets will be sourced from healthy donors.
Milestones:	• Computational interaction prediction (final report): 01 Jul 2021 (MS1222-0001) • Binding assays testing AZD1222 interaction with the above (final report):01 Sep 2021 (MS1222-0004) • Platelet activation in response to complexes defined above (final report):01 Oct 2021 (MS1222-0005)

HIT antibodies in vaccinated sera

Study name and title:	Are HIT antibodies increased in the sera of vaccinated individuals MS1222-0003
Rationale and study objectives:	Thrombosis events are characterised as being similar to a HIT-like event. This study will test sera of vaccinated individuals for the presence of such antibodies to further characterise the possible mechanisms and to identify the possible triggers of platelet activation after vaccination.
Study design:	Using clinical trial material, pre-dose, and post-dose 1 and dose 2 test for the presence and quantity of HIT antibodies.
Study population:	AZD1222 clinical trial participants.
Milestones:	• Final report: 01 Aug 2021.

In vitro expression of Spike protein

Study name and title:	In vitro expression of spike protein following transduction by AZD1222 (MS1222-0002)
Rationale and study objectives:	The objective of this study is to address the question of spike expression by cells transduced by AZD1222 to further characterize the possible mechanisms and to identify the possible triggers of platelet activation after vaccination.
Study design:	Cells will be transduced in vitro by AZD1222 and spike protein will be measured in the cell and supernatant by ELISA. Western blot will determine if the spike protein is full length, or with cleaved S1 fragment.
Study population:	Not applicable - In vitro cell line.
Milestones:	• Final study report submission: 07 Jul 2021

Biodistribution study

Study name and title:	AZD1222 (ChAdOx1-nCovd-19): A Single Dose Intramuscular Vaccine Biodistribution Study in the Mouse (1169DM)
Rationale and study objectives:	The objective of this study is to determine the biodistribution of AZD1222 when given by single IM injection to mice to further characterize the possible mechanisms and to identify the possible triggers of platelet activation after vaccination.
Study design:	Single dose toxicity, parallel design
Study population:	80 mice (40 males/40 females)
Milestones:	• Final study report submission: 30 Apr 2021

UK vaccine effectiveness study: National Health Service

Study name and title:	Real-world effectiveness of the Oxford/AstraZeneca COVID-19 vaccine in England (D8111R00007)
Rationale and study objectives:	The objective of this study is to evaluate the effectiveness of the AZD1222 in England

Study design:	Observational retrospective cohort study
Study population:	English population greater or equal to 16 years of age
Milestones:	Final study report: Q1 2023

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 (D8111R00005/ D8111R00017 [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 consortium study protocol (D8111R00005 - directed by the COVIDRIVE consortium): Mar 2021. • Submission of AstraZeneca-specific study protocol (D8111R00017): 30 Apr 2021 • Submission of final AstraZeneca-specific study (D8111R00017): 15 Jul 2021 • First interim report: Q2 2022 • Second interim report: Q4 2022 • Third interim report: Q2 2023 • Final Report: Q4 2023

Thrombotic thrombocytopenia syndrome (D8111R00010)

Study name and title:	An assessment of a relationship between the exposure to COVID-19 vaccines and risk of thrombotic thrombocytopenia syndrome[a]
Rationale and study objectives:	A very rare syndrome of TTS has been reported following exposure to COVID-19 vaccine. No causal association with COVID-19 vaccination has yet been established. The objective of this study is to evaluate an association between COVID-19 vaccine exposure and the TTS.

Study design:	A retrospective study using linked secondary databases in England. Data for the definitive study accessed through the NHS Digital Trusted Research Environment (TRE), providing national data coverage. Primary care data will be linked with vaccination, hospitalization, COVID-19 test results, mortality data. Initial exploratory analyses will be conducted using the Oxford-Royal College of General Practitioners sentinel network, ORCHID network database. Two primary study designs will be considered, a case control study and a self-controlled case series (SCCS). A cohort analysis will be considered, in addition or as an alternative to either of the primary study designs, pending feasibility assessment of the follow-up time.
Study population:	All patients, in England who are present in the integrated health records of NHS Digital TRE and/or Oxford Royal College of General Practitioners Clinical Informatics Digital Hub (ORCHID) database at the start of study period.
Milestones:	Progress report : Q1 2023 Submission of final study report: Q2 2023

[a] Thrombotic thrombocytopenia syndrome is also referred as Thrombosis with Thrombocytopenia Syndrome

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 included in this EU RMP as additional pharmacovigilance activities in accordance with COVID-19 RMP-specific regulatory guidance (EMA 2022).

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 objective of this study is to assess the efficacy and safety of AZD1222 against COVID-19.
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.
Milestones:	• Final study report due: 31 Mar 2023

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 objective of this study is to assess efficacy and safety of AZD1222 (ChAdOx1 nCoV-19) against COVID-19 in adults aged 18 years and older in the UK.
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. 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.
Milestones:	• Final study report due: 31 Mar 2023

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).
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.
Milestones:	• Final study report due: 31 Mar 2023

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.
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.
Milestones:	• Final study report due: 31 Mar 2023

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. 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.
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.
Milestones:	• Final study report due: 31 Mar 2023

Study D8110C00001

Study name and title:	Study D8110C00001 – A Phase III Randomized, Double-blind, Placebo-controlled Multicenter 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).
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.
Milestones:	• Primary efficacy analysis: Q2 2021 • Final study report due: Q4 2023.

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.
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.
Milestones:	• Interim analysis: Q1 2021 • Primary analysis: Q2 2021.

III.2.3 Other additional PV activities'

A systematic literature review for studies evaluating adverse events of Vaxzevria in patients taking immunosuppressant medications and/or with primary immunodeficiency

Activity name and title:	A systematic literature review for studies evaluating adverse events of Vaxzevria™ in patients taking immunosuppressant medications and/or with primary immunodeficiency D8111R00020
Rationale and 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 review will synthesize the current evidence and assess the level of knowledge on the frequency of adverse events in an immunocompromised population after receiving Vaxzevria.
Design:	Systematic Literature Review
Population:	Patients taking immunosuppressant medications and/or with primary immunodeficiency.
Milestones:	• Submission of study protocol: Q4 2022

	• Final report : Q1 2023

Pooled analysis of COV001/2/3/5 studies

Activity name and title:	Final analysis from the pooled pivotal studies including COV001, COV002, COV003, and COV005
Objectives:	Final analysis from the pooled pivotal studies to confirm on the efficacy and safety of Vaxzevria
Milestones:	• Final report : 31 March 2023

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

A summary of the studies and activities included in the pharmacovigilance plan is provided in Table 12.

Table 12 Ongoing and planned additional pharmacovigilance activities

Study name / title Status	Study code	Summary of activity objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – Required additional pharmacovigilance activities					
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 Status: Ongoing	D8110C00001	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 (Sub study only)	• Thrombosis with thrombocytopenia syndrome • Thrombosis • Thrombocytopenia, including immune thrombocytopenia • Guillain-Barré syndrome • Immune-mediated neurological conditions • Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Long-term safety	Primary efficacy analysis Final report	Q2 2021 Q4 2023
Pregnancy Registry Pregnancy Registry of Women Exposed to AZD1222 Immediately Before or During Pregnancy as Part of the C-VIPER Registry Consortium.	D8110C00003 (Pregistry-sponsored)	To estimate the risk of the most common obstetric outcomes (pregnancy losses, placentation disorders, gestational diabetes, premature delivery, and COVID-19), neonatal outcomes (congenital anomalies, low birth weight for gestational age, neonatal intensive care unit	• Use during pregnancy and while breastfeeding	Initial Study Design Concept submission Protocol submission Start of study	11 Dec 2020 27 Jan 2021 17 May 2021

Table 12 Ongoing and planned additional pharmacovigilance activities

Study name / title Status	Study code	Summary of activity objectives	Safety concerns addressed	Milestones	Due dates
Status: Ongoing		admission, and COVID-19), and infant outcomes (height for age, weight for height, developmental milestones until one year of age, and COVID-19) among pregnant women exposed to AZD1222 from 30 days prior to the first day of the LMP to end of pregnancy and their offspring relative to a matched unexposed reference group.		First interim report / First quarterly update SAP Semi-annual report Quarterly update Annual Update Final report	30 Sep 2021 15 Jan 2022 Jan 2022/ Jan 2023 Apr 2022 Jul 2022/Jul 2023/Jul 2024/Jul 2025 Jul 2026
Post-marketing observational study using existing secondary health data sources	D8111R00006 (EU/UK)	To evaluate the incidence and relative risk of safety concerns and AESIs.	• Thrombosis with thrombocytopenia syndrome • Thrombosis • Thrombocytopenia, including immune thrombocytopenia • Guillain-Barré syndrome • Immune-mediated neurological conditions	Study Design Concept submission	18 Dec 2020
				Protocol submission	01 Apr 2021
				Final protocol submission	15 July 2021

Table 12 Ongoing and planned additional pharmacovigilance activities

Study name / title Status	Study code	Summary of activity objectives	Safety concerns addressed	Milestones	Due dates
A post-authorisation/post-marketing observational study to evaluate the association between exposure to AZD1222 and safety concerns using existing secondary health data sources. Status: Ongoing			• Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) • 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	Statistical analysis plan submission	Nov 2021
				Progress report	Oct 2021
				Interim report 1	Apr 2022
				Feasibility report for comparative analysis	Aug 2023
				Final report of study results	Jun 2024
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	D8111R00005 Master Protocol (EU/UK) D8111R00017 AZ protocol (EU/UK)	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 (D8111R00005), Directed by COVI-DRIVE consortium	Mar 2021
				Protocol submission (D8111R00017), AstraZeneca-specific study protocol	30 Apr 2021
				Protocol submission (D8111R00017), AstraZeneca-specific final study protocol	15 Jul 2021

Table 12 Ongoing and planned additional pharmacovigilance activities

Study name / title Status	Study code	Summary of activity objectives	Safety concerns addressed	Milestones	Due dates
with COVIDRIVE utilizing primary data collected prospectively through the COVIDRIVE platform. Status: Ongoing				First interim report (D8111R00017)	Q2 2022
				Second interim report (D8111R00017)	Q4 2022
				Final report (D8111R00017)	Q4 2023
D8111R00007 Real-world effectiveness of the Oxford/AstraZeneca COVID-19 vaccine in England Status: Ongoing	D8111R00007	To evaluate the effectiveness of the AZD1222 in England	• Not applicable	Final Study report	Q1 2023

Table 12 Ongoing and planned additional pharmacovigilance activities

Study name / title Status	Study code	Summary of activity objectives	Safety concerns addressed	Milestones	Due dates
D8111R00010 An assessment of a relationship between the exposure to COVID-19 vaccines and risk of thrombotic thrombocytopenia syndrome Status: Ongoing	D8111R00010	To evaluate an association between COVID-19 vaccine exposure and thromboembolic events occurring with thrombocytopenia (thrombotic thrombocytopenia syndrome; TTS).	• Thrombosis with thrombocytopenia syndrome;	Progress report Final Study report	Q1 2023 Q2 2023
Category 3 : Other additional PV activities					
A systematic literature review for studies evaluating adverse events of Vaxzevria in patients taking immunosuppressant medications and/or with primary immunodeficiency * Status: Ongoing	D8111R00020	To evaluate the safety profile of AZD1222 in patients receiving immunosuppressant medication(s) or with primary immunodeficiency	• Use in immunocompromised patients	Protocol submission Final report	Q4 2022 Q1 2023

*Metanalytic study design replaced with Systemic literature review with associated milestones

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 13.

Table 13 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
Thrombosis with thrombocytopenia syndrome	Routine risk communication: • SmPC Section 4.3, 4.4 and 4.8 • PL Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Sections 4.3 and 4.4 • PL Section 2 and 4
Thrombocytopenia, including immune thrombocytopenia	Routine risk communication: • SmPC Section 4.8 • PL Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 • PL Section 2
Guillain-Barré syndrome	Routine risk communication: • SmPC Section 4.8 • PL Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 • PL Section 2
Important Potential Risks	
Thrombosis	Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4

Table 13 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Immune-mediated neurological conditions	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4 • PL Section 2
Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)	None
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 14 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Thrombosis with thrombocytopenia syndrome	Routine risk minimisation measures: • SmPC Sections 4.3, 4.4 and 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire

Table 14 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• PL Sections 2 and 4	Additional pharmacovigilance activities: • Biodistribution study (1169DM) • In vitro expression of Spike protein (MS1222-0002) • HIT antibodies in vaccinated sera (MS1222-0003) • In vitro interaction with PF4 and/or platelets (MS1222-0001/MS1222-0004/MS1222-0005) • D8111R00010 • Post-marketing observational study using existing secondary health data sources D8111R00006 [EU]) • Study COV001 • Study COV002 • Study COV003 • Study COV004 • Study COV005 • Study D8110C00001 • Study D8111C00002
Thrombocytopenia, including immune thrombocytopenia	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.8 PL Sections 2 and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU]) • Study COV001 • Study COV002 • Study COV003 • Study COV004 • Study COV005 • Study D8110C00001 Study D8111C00002
Guillain-Barré syndrome	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.8 PL Sections 2 and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU]) • Study COV001

Table 14 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		• Study COV002 • Study COV003 • Study COV004 • Study COV005 • Study D8110C00001 Study D8111C00002
Important Potential Risks		
Thrombosis	Routine risk minimisation measures: SmPC Sections 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU]) • Study COV001 • Study COV002 • Study COV003 • Study COV004 • Study COV005 • Study D8110C00001 Study D8111C00002
Immune-mediated neurological conditions	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.8 • PL Section 2 and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: • Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU]) • Study COV001 • Study COV002 • Study COV003 • Study COV004 • Study COV005 • Study D8110C00001 • Study D8111C00002
Vaccine-associated enhanced disease (VAED), including vaccine-associated	None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities:

Table 14 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
enhanced respiratory disease (VAERD)		• Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU]) • Study COV001 • Study COV002 • Study COV003 • Study COV004 • Study COV005 • Study D8110C00001 • Study D8111C00002
Missing Information		
Use during pregnancy and while breastfeeding	Routine risk minimisation measures: • SmPC Section 4.6 • PL Section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Pregnancy Registry (D8110C00003) • Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU])
Use in immunocompromised patients	Routine risk minimisation measures: • SmPC Section 4.4 • PL Section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU]) • Systematic literature review (D8111R00020) • Study COV005
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: • Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU])
Use in patients with autoimmune or inflammatory disorder	None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities:

Table 14 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
		• Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU])
Interactions with other vaccines	Routine risk minimisation measures: • SmPC Section 4.5 PL Section 2	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU])
Long-term safety	None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU]) • 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 VAXZEVRIA (previously COVID-19 vaccine AstraZeneca) (AZD1222; ChAdOx1-S [recombinant])

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

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

This summary of the RMP for VAXZEVRIA 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 VAXZEVRIA's RMP.

VI.1 THE MEDICINE AND WHAT IT IS USED FOR

VAXZEVRIA 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 VAXZEVRIA's benefits can be found in VAXZEVRIA'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/vaxzevria-previously-covid-19-vaccine-astrazeneca.

VI.2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of VAXZEVRIA, together with measures to minimise such risks and the proposed studies for learning more about VAXZEVRIA'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 VAXZEVRIA is not yet available, it is listed under 'missing information' below.

VI.2.1 List of important risks and missing information

Important risks of VAXZEVRIA 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 VAXZEVRIA. 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 15 List of important risks and missing information

Important identified risks	• Thrombosis with thrombocytopenia syndrome • Thrombocytopenia, including immune thrombocytopenia • Guillain-Barré syndrome
Important potential risks	• Thrombosis • Immune-mediated neurological conditions • Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)
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 16 Important identified risk: Thrombosis with thrombocytopenia syndrome

Evidence for linking the risk to the medicine	Very rare events of serious thrombosis with thrombocytopenia syndrome (TTS) (including fatal events), have been observed following vaccination with AZD1222 during post-authorisation use. There have been no reports of TTS in the AZD1222 clinical development programme.
Risk factors and risk groups	There are no known risk factors for the development of thrombosis with thrombocytopenia following vaccination.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.3, 4.4 and 4.8 • PL Sections 2 and 4

Table 16 Important identified risk: Thrombosis with thrombocytopenia syndrome

Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Biodistribution study (1169DM) • In vitro expression of Spike protein • HIT antibodies in vaccinated sera • In vitro interaction with PF4 and/or platelets • D8111R00010 • Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU]) • 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-17 Important identified risk: Thrombocytopenia, including immune thrombocytopenia

Evidence for linking the risk to the medicine	Very rare cases of thrombocytopenia, including immune thrombocytopenia (ITP), have been observed following vaccination with AZD1222 during post-authorisation use
Risk factors and risk groups	There are no known risk factors for the development of thrombocytopenia following vaccination. In general, individuals with a history of thrombocytopenic disorder, such as immune thrombocytopenia, the risk of developing low platelet levels should be considered before administering the vaccine and platelet monitoring is recommended after vaccination as described in Section 4.4 of the SmPC
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU]) • Study COV001 • Study COV002 • Study COV003 • Study COV004 • Study COV005 • Study D8110C00001

Table VI-17 Important identified risk: Thrombocytopenia, including immune thrombocytopenia

	• Study D8111C00002 See Section VI.2.3 of this summary for an overview of the post-authorisation development plan.

Table VI-18 Important identified risk: Guillain-Barré syndrome

Evidence for linking the risk to the medicine	In the US study (D8110C00001), 1 SAE of a demyelinating event initially reported as Guillain-Barre syndrome occurred in a participant enrolled in the AZD1222 group. The SAE of GBS was subsequently amended to an SAE of Chronic inflammatory demyelinating polyradiculoneuropathy. Very rare events of GBS have been observed following vaccination with AZD1222 during post-authorisation use.
Risk factors and risk groups	There are no known risk factors for the development of GBS following vaccination. In general, infection with the bacteria Campylobacter jejuni is one of the most common risk factors for GBS. People also can develop GBS after having the flu or other infections such as cytomegalovirus and Epstein-Barr virus. On very rare occasions, people develop GBS in the days or weeks after getting a vaccination (CDC, 2019).
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU]) • 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-19 Important potential risk: Thrombosis

Evidence for linking the risk to the medicine	Very rare events of serious thrombosis have been observed following vaccination with AZD1222 during post authorisation use. Overall, there have been no clinically meaningful imbalances in the incidence of events of thrombosis between the AZD1222 and control groups in the AZD1222 clinical development programme.

Risk factors and risk groups	There are no known risk factors identified for the development of thrombosis following vaccination.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.4
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU]) • 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 20 Important potential risk: 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 have been no clinically meaningful imbalances in the incidence of neurological AESIs between the AZD1222 and control groups in the AZD1222 clinical development programme. Very rare events of immune-mediated neurological conditions have been observed following vaccination with AZD1222 during post-authorisation use.
Risk factors and risk groups	There are no known risk factors for the development of neurological conditions following vaccination.
Risk minimisation measures	SmPC Section 4.4 and 4.8, PL section 2 and 4
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU]) • Study COV001 • Study COV002 • Study COV003

Table 20 Important potential risk: Immune-mediated neurological conditions

	• 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-21 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. Overall, there is no evidence of an association between AZD1222 and VAED/VAERD; proportionally more AESIs related to COVID-19 have occurred in the control/placebo groups than among AZD1222 recipients in the AZD1222 clinical development programme. There have been no confirmed post-marketing reports of VAED/VAERD.
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: • Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU]) • 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 22 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: • Pregnancy Registry (D8110C00003) • Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU]) See Section VI.2.3 of this summary for an overview of the post-authorisation development plan.

Table 23 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: • Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU]) • Systematic literature review (D8111R00020) • Study COV005 See Section VI.2.3 of this summary for an overview of the post-authorisation development plan.

Table 24 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: • Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU]) See Section VI.2.3 of this summary for an overview of the post-authorisation development plan.

Table 25 Missing information: Use in patients with autoimmune or inflammatory disorders

Risk minimisation measures	None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU]) See Section VI.2.3 of this summary for an overview of the post-authorisation development plan.

Table VI-26 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: • Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU]) See Section VI.2.3 of this summary for an overview of the post-authorisation development plan.

Table VI-27 Missing information: Long-term safety

Risk minimisation measures	None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Post-marketing observational study using existing secondary health data sources (D8111R00006 [EU]) • 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

Studies and activities in the post authorisation development plan are as follows:

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).

Registry of Women Exposed to AZD1222 Immediately Before or During Pregnancy as part of the C-VIPER Registry Consortium (D8110C00003; Pregistry-sponsored)

Purpose of the study: The study objective is to estimate the risk of the most common obstetric outcomes (pregnancy losses, placentation disorders, gestational diabetes, premature delivery, and COVID-19), neonatal outcomes (congenital anomalies, low birth weight for gestational age, neonatal intensive care unit admission, and COVID-19), and infant outcomes (height for age, weight for height, developmental milestones until one year of age, and COVID-19) among pregnant women exposed to AZD1222 from 30 days prior to the first day of the LMP to end of pregnancy and their offspring relative to a matched unexposed reference group.

A post-authorisation/post-marketing observational study to evaluate the association between exposure to AZD1222 and safety concerns using existing secondary health data source (D8111R00006 [EU/UK])

Purpose of the study: The study objective is to evaluate the incidence and relative risk of safety concerns and adverse events of special interest (AESIs).

An assessment of a relationship between the exposure to COVID-19 vaccines and risk of thrombotic thrombocytopenia syndrome

Purpose of the study: To investigate the association of vaccine exposure with venous thrombotic events and thrombocytopenia using multiple study design approaches

Evaluation of effectiveness of AZD1222 in the United Kingdom

Purpose of the study: To evaluate the effectiveness of AZD1222 in England using National Health Service data

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])

Purpose of the study: 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.

A systematic literature review for studies evaluating adverse events of Vaxzevria in patients taking immunosuppressant medications and/or with primary immunodeficiency

Purpose of the activity: 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 review will synthesize the current evidence and assess the level of knowledge on the frequency of adverse events in an immunocompromised population after receiving Vaxzevria.

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EU RMP Part VII Annex 4

Drug Substance ChAdOx1-S (recombinant) (AZD1222)

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR VAXZEVRIA (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 identified and potential risks:

- Questionnaire (VAXZEVRIA) – Thrombosis in combination with thrombocytopenia, Thrombosis with thrombocytopenia syndrome [TTS]/ Embolic and thrombotic events (Thrombosis)/ Thrombocytopenia, including immune thrombocytopenia
- Questionnaire (VAXZEVRIA) – Immune-mediated neurological conditions
- Questionnaire (VAXZEVRIA) – COVID-19/ Vaccine failure and including Vaccine-associated enhanced (respiratory) disease (VAED/VAERD)/ Anosmia/ Ageusia

*Subject to national health authority agreement

AstraZeneca

Questionnaire for Thrombosis in combination with thrombocytopenia, Thrombosis with thrombocytopenia syndrome (TTS)/ Embolic and thrombotic events (Thrombosis)/ Thrombocytopenia, including immune thrombocytopenia

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 #:
Reporter's Address:	Reporter's Signature:	Date *(DD/MM/YY):*

2. Patient's Details

Initials:

Gender at birth: ☐ Male ☐ Female
For female, currently Pregnant ?:
☐ No ☐ Yes

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)***	**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

*In the event of Death, please provide the cause of death (please provide copy of autopsy report, if available).*Was the patient hospitalized for Thrombosis, Thrombosis with thrombocytopenia syndrome or Thrombocytopenia? ☐ No ☐ Yes

Please tick appropriate diagnosis; If yes, please could you provide the following further information, if available:

☐ Thrombosis with thrombocytopenia syndrome (Date DD/MMM/YYYY):
☐ Thrombosis (Date DD/MMM/YYYY):
☐ Thromocytopenia (platelet count <150 X 109/L) (Date DD/MMM/YYYY):

How was thrombosis diagnosed?

Imaging study:
☐ Ultrasound -Doppler
☐ Computed Tomography (CT scan)
☐ Magnetic resonance venography/arteriography (MRV/MRA)
☐ Echocardiogram
☐ Perfusion V/Q scan
☐ Conventional angiography/Digital subtraction angiography
Others, please specify the details

☐ Surgical (Procedure that confirms the presence of a thrombus (e.g. Thrombectomy):
Please specify the details: _____

☐ Pathology (consistent with thrombosis/thromboembolism including biopsy or autopsy):
Please specify the details:_____

Please provide details about the site of Thrombosis (please check all that is applicable. Also provide the date of diagnosis)

☐ Arterial thrombosis
☐ Venous thrombosis
☐ Small vessels thrombosis
☐ Cerebral thrombosis
☐ Cerebrovascular venous sinus thrombosis
☐ Splanchnic vein thrombosis
☐ Coronary thrombosis
☐ Pulmonary thrombosis (emboli or thrombosis)
☐ Leg extremities thrombosis
☐ Hepatic thrombosis
☐ Renal thrombosis|
☐ Ocular thrombosis
☐ Adrenal thrombosis

AstraZeneca

Questionnaire for Thrombosis in combination with thrombocytopenia, Thrombosis with thrombocytopenia syndrome (TTS) /Embolic and thrombotic events (Thrombosis)/ Thrombocytopenia, including immune thrombocytopenia

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

Others please specify:

Please provide details of bleeding events

☐ Purpura
☐ Bruising
☐ Non palpable petechiae
☐ Epistaxis (bleeding from nose)
☐ Gingival bleeding
☐ Gastro-intestinal bleeding
☐ Intra-cranial bleeding
☐ Other bleeding, specify:

Please check below if the patient had any of the signs and symptoms

Neurological:	Cardiovascular/Respiratory:	Gastrointestinal and hepatic system	Muscular:	General:
☐ Headache ☐ Seizures If seizures, please specify type_____ No of episodes:_____ Duration of longest seizure episode:_____ ☐ Photophobia ☐ blurred vision ☐ double vision ☐ sudden visual loss ☐ temporary loss of vision in one eye ☐ Unconsciousness ☐ Altered mental status	☐ Chest pain/discomfort ☐ Palpitations ☐ Dyspnoea ☐ Cough ☐ Cyanosis ☐ Respiratory failure	☐ Abdominal pain	☐ pain in legs ☐ difficulty walking ☐ instability ☐ paralysis with weak muscles ☐ problems with coordination ☐ paralysis of one side of the body Speech: ☐ difficulty speaking ☐ slurred speech	☐ fatigue ☐ lightheadedness Sensory ☐ pins and needles ☐ reduced sensation of touch ☐ numbness

If any other signs and symptoms, please, specify:_____

Were there any complications caused by the Thrombosis with thrombocytopenia syndrome / Embolic and thrombotic events (Thrombosis)/ Thrombocytopenia?
☐ No ☐ Yes
If 'Yes', please provide a brief statement of complications:

4. COVID-19 Vaccine

Dose 1 received: ☐ No ☐ Yes Date and time of vaccination (DD/MM/YY / hh:mm): Batch/Lot #:

Is this covid-19 vaccine AstraZeneca: ☐ No ☐ Yes If no, name of the vaccine (vaccine brand name or manufacturer):

Dose 2 received: ☐ No ☐ Yes Date and time of vaccination (DD/MM/YY / hh:mm): Batch/Lot #:

Is this covid-19 vaccine AstraZeneca : ☐ No ☐ Yes If no, name of the vaccine (vaccine brand name or manufacturer):

Any other additional dose of COVID-19 vaccine received after 1 dose or 2 dose series of COVID 19 vaccine: ☐ No ☐ Yes
Date and time of vaccination (DD/MM/YY / hh:mm): Batch/Lot #:
Name of the vaccine (vaccine brand name or manufacturer):

AstraZeneca

Questionnaire for Thrombosis in combination with thrombocytopenia, Thrombosis with thrombocytopenia syndrome (TTS) /Embolic and thrombotic events (Thrombosis)/ Thrombocytopenia, including immune thrombocytopenia

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

5. How was the patient treated?

Was treatment provided? ☐ No ☐ Yes

Please specify the details of the treatment (including dose/start date):

☐ Anticoagulant drugs

☐ Intravenous immunoglobulin

☐ Platelet transfusions

☐ Plasma exchange

Others please specify: _____

6. Other Suspect Drugs

Please only include other drugs you consider to be causally 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) reoccur after reintroduction?
☐ No ☐ Yes ☐ Not applicable, If applicable, please provide Date Drug was Reintroduced *(DD/MM/YY)*: _____

7. Concomitant Drugs/ Vaccines *(Non Covid Vaccines administered in the last 4 weeks) 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/ Concomitant Vaccine	Indication	For vaccines please enter Batch/Lot #	Daily Dosage	Route	Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	Was concomitant drug withdrawn?
							☐ No ☐ Yes
							☐ No ☐ Yes
							☐ No ☐ Yes

8. Please provide information on Relevant Medical History/Concurrent Diseases/ Treatments

Medical History		Start Date (if applicable) (DD/MM/YY)	Stop date (if applicable) (DD/MM/YY)
Previous thrombotic/embolic event	☐ No ☐ Yes		
History of Covid-19 (please provide the date of diagnosis)	☐ No ☐ Yes		
CNS tumor/metastases	☐ No ☐ Yes		
Haemophilia/other coagulation disorders	☐ No ☐ Yes		
History of Heparin induced Thrombocytopenia	☐ No ☐ Yes		
History of Primary immune thrombocytopenia/ Thrombocytopenia	☐ No ☐ Yes		
History of Drug induced immune thrombocytopenia	☐ No ☐ Yes		
Anticoagulation / previous heparin use	☐ No ☐ Yes		
Therapeutic thrombolysis	☐ No ☐ Yes		
Sickle cell disease	☐ No ☐ Yes		
Disseminated intravascular coagulation	☐ No ☐ Yes		

AstraZeneca

Questionnaire for Thrombosis in combination with thrombocytopenia, Thrombosis with thrombocytopenia syndrome (TTS) /Embolic and thrombotic events (Thrombosis)/ Thrombocytopenia, including immune thrombocytopenia

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

Cancer with disseminated intravascular coagulation	☐ No ☐ Yes		
Cancer with bone marrow infiltration or suppression (eg, lymphoma, leukemia, some solid tumors)	☐ No ☐ Yes		
Renal failure	☐ No ☐ Yes		
Liver failure	☐ No ☐ Yes		
Hypersplenism due to chronic liver disease	☐ No ☐ Yes		
Hypertension	☐ No ☐ Yes		
Valvular heart disease	☐ No ☐ Yes		
Atrial fibrillation	☐ No ☐ Yes		
Atherosclerosis	☐ No ☐ Yes		
Ischaemic heart disease	☐ No ☐ Yes		
Endocarditis	☐ No ☐ Yes		
Sudden hypotension	☐ No ☐ Yes		
Peripheral vascular disease	☐ No ☐ Yes		
Inflammatory vascular disease	☐ No ☐ Yes		
Diabetes mellitus	☐ No ☐ Yes		
Infections (eg HIV, Hepatitis C, Intracellular parasites)	☐ No ☐ Yes		
Sepsis	☐ No ☐ Yes		
Rheumatologic/autoimmune disorders (eg, systemic lupus erythematosus, rheumatoid arthritis)	☐ No ☐ Yes		
Trauma	☐ No ☐ Yes		
Nutrient deficiencies (eg, vitamin B12, folate, copper)	☐ No ☐ Yes		
Myelodysplasia	☐ No ☐ Yes		
Surgical procedures	☐ No ☐ Yes		
Obesity	☐ No ☐ Yes		
Alcohol consumption	☐ No ☐ Yes		
Tobacco smoking	☐ No ☐ Yes		

Other, please specify:

Were there any adverse events experienced with the previous Covid -19 vaccines,if yes, please provide the details (including date of vaccination, date of event, treatment and outcome of the event):

9. Laboratory Results- Before/During/After Treatment Please provide details of the relevant lab tests as applicable (attach results if available).

Test	**Date** (DD/MM/YY)	**Results**
Complete blood count (CBC)		
Platelet count (before vaccination)		
Platelet count (after vaccination) – please provide details of all the values		
Peripheral blood smear		
Bone marrow biopsy		
Blood group (Rh)		
Direct antiglobulin test		
Erythrocyte sedimentation rate (ESR)		
Serum C-reactive protein (CRP)		
Prothrombin time (PT)		
Activated partial thromboplastin time (APTT)		
Heparin-induced Thrombocytopenia (HIT) PF4 Antibody : Immunoassay (AcusStar)		

AstraZeneca

Questionnaire for Thrombosis in combination with thrombocytopenia, Thrombosis with thrombocytopenia syndrome (TTS) /Embolic and thrombotic events (Thrombosis)/ Thrombocytopenia, including immune thrombocytopenia

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

Heparin-induced Thrombocytopenia (HIT) PF4 Antibody ELISA		
PF4-serotonin release assay		
D-dimers, fibrinogen levels		
Serum anti-platelet antibodies		
Partial thromboplastin time (PTT)		
INR		
Total cholesterol		
Anticardiolipin (ELISA) IgM		
Anticardiolipin (ELISA) IgG		
Anti-beta 2 glycoprotein I		
Anti-prothrombin		
H pylori, HIV, HCV		
Random / Fasted blood glucose		
Ultrasound (e.g. carotid, cardiac)		
ECG		
MRI		
CT		
Cerebral angiography		
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 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 #:

Reporter's Address:

Reporter's Signature:

Date *(DD/MM/YY):*

2. Patient's Details

Initials:

Gender at birth: ☐ Male ☐ Female

For female, currently Pregnant ?: ☐ No ☐ Yes

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)*	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
☐ Paraesthesia/hypoaesthesia

Other, specify: _____

What signs and symptoms did the patient experience?

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

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

Dose 1 received: ☐ No ☐ Yes Date and time of vaccination (DD/MM/YY / hh:mm): Batch/Lot #:

Is this covid-19 vaccine AstraZeneca: ☐ No ☐ Yes If no, name of the vaccine (vaccine brand name or manufacturer):

Dose 2 received: ☐ No ☐ Yes Date and time of vaccination (DD/MM/YY / hh:mm): Batch/Lot #:

Is this covid-19 vaccine AstraZeneca : ☐ No ☐ Yes If no, name of the vaccine (vaccine brand name or manufacturer):

AstraZeneca

Questionnaire for immune-mediated neurological conditions

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

Any other additional dose of COVID-19 vaccine received after 1 dose or 2 dose series of COVID 19 vaccine: ☐ No ☐ Yes

Date and time of vaccination (DD/MM/YY / hh:mm): Batch/Lot #:

Name of the vaccine (vaccine brand name or manufacturer):

.

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 causally 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) reoccur after reintroduction?

☐ No ☐ Yes ☐ Not applicable, If applicable, please provide Date Drug was Reintroduced *(DD/MM/YY)*: _____

7. Concomitant Drugs/ Concomitant Vaccines

(Non Covid Vaccines administered in the last 4 weeks) 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. (attach a list if available).

Concomitant Drug Name / Concomitant Vaccine	Indication	For vaccines please enter Batch/Lot #	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 anaesthesia, 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 **Were there any adverse events experienced with the previous Covid -19 vaccines, if yes, please provide the details (including date of vaccination, date of event, treatment and outcome of the event):**

9. Laboratory Results- Before/During/After Treatment- Please provide details of the following relevant lab tests (attach 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 (Respiratory) Disease (VAED/VAERD)/ Anosmia/Ageusia

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 #:
Reporter's Address:	Reporter's Signature:	Date *(DD/MM/YY):*

2. Patient's Details

Initials:

Gender at birth: ☐ Male ☐ Female
For female, currently Pregnant ?:
☐ No ☐ Yes

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

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

Haematopoietic 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 (Respiratory) Disease (VAED/VAERD)/ Anosmia/Ageusia

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)
	☐ Ageusia	☐ 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

Dose 1 received: ☐ No ☐ Yes Date and time of vaccination (DD/MM/YY / hh:mm): Batch/Lot #:

Is this covid-19 vaccine AstraZeneca: ☐ No ☐ Yes If no, name of the vaccine (vaccine brand name or manufacturer):

Dose 2 received: ☐ No ☐ Yes Date and time of vaccination (DD/MM/YY / hh:mm): Batch/Lot #:

Is this covid-19 vaccine AstraZeneca : ☐ No ☐ Yes If no, name of the vaccine (vaccine brand name or manufacturer):
:

Any other additional dose of COVID-19 vaccine received after 1 dose or 2 dose series of COVID 19 vaccine: ☐ No ☐ Yes
Date and time of vaccination (DD/MM/YY / hh:mm): Batch/Lot #:
Name of the vaccine (vaccine brand name or manufacturer):

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 causally 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) reoccur after reintroduction?
☐ No ☐ Yes ☐ Not applicable, If applicable, please provide Date Drug was Reintroduced *(DD/MM/YY)*: _____

7. Concomitant Drugs/ Concomitant Vaccines *(Non Covid Vaccines administered in the last 4 weeks) 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. (attach a list if available).*

Concomitant Drug / Concomitant Vaccine Name	Indication	For vaccines please enter Batch/Lot #	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 (Respiratory) Disease (VAED/VAERD)/ Anosmia/ Ageusia

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

							☐ 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

Were there any adverse events experienced with the previous Covid -19 vaccines, if yes, please provide the details (including date of vaccination, date of event, treatment and outcome of the event):

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], haemoglobin, 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.