
European Union Risk Management Plan

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|------------------------|--------------------------------------|
| Drug Substance | ChAdOx1-S (recombinant) (AZD1222) |
| Version Number | 5 |
| Succession number | 2 |
| Data lock point | 03 February 2022 |
| 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 5) has been updated to include:

- Inclusion of data for COVID-19 vaccination booster dose in adults 18 years and older, previously vaccinated with primary series of AZD1222 or another authorised COVID -19 vaccine
- Reactogenicity data updated with homologous or heterologous booster dose information
- Updated data from study D8110C00001 as a result of a new data cut off of 31 July 2021
- Change in frequency of review for data sources utilised for signal detection (Table III-1) including:
 - EudraVigilance Data analysis System (EVDAS) Electronic Reaction Monitoring Report (eRMR) review changed from biweekly to monthly due to dramatic decrease in case volume
 - Batch distribution data review changed from biweekly to monthly due to significant decrease in case volume and no identified lot or manufacturing issues since the beginning of this process
 - Clinical trial AEs from AZ and non-sponsored studies review changed from bi-weekly to monthly due to significant decrease in case volume as a result of pivotal studies currently in the follow-up period
- Discontinuation of Safety Summary Reports (SSRs), previously scheduled bi-monthly, due to significant experience gained following administration of more than 2 billion doses. The PBRERs submitted on a 6 monthly basis and will serve as the tool for discussion of any safety topics as well as other standard pharmacovigilance activities
- Reclassification of the Important identified risk "Anaphylaxis" and removal from the list of safety concerns at the request of EMA.
- Updates to reproductive/developmental toxicity as per latest nonclinical information
- Updates to epidemiology data, PASS study timelines, study status and Adverse Events of Special Interest (AESI) list

References to the SmPC are to the version approved on 03 Feb 2022.

Summary of significant changes in this RMP

| | |
|---------------|--|
| Part I: | No changes |
| Part II SI: | Updated the epidemiology data to reflect the latest information |
| Part II SII: | Updated the reproductive/developmental toxicity data as per latest nonclinical information |
| Part II SIII: | Updated exposure data for AZD1222 booster dose |
| Part II SIV: | No changes |

| | |
|----------------|--|
| Part II SV: | Latest cumulative post-marketing exposure data added (data cut-off date of 31 December 2021) |
| Part II SVI: | No changes |
| Part II SVII: | <ul style="list-style-type: none"> AESI list updated to include Giant Cell Arteritis (GCA), updated PTs for AMN/AMOR/PAMM, Immune-mediated neurological conditions, Myocarditis/Pericarditis, Embolic and thrombotic events (Thrombosis), Pregnancy outcome – Maternal, Pregnancy outcome – Neonates, Acute liver injury, Multisystem inflammatory syndrome in children/adults (MIS-C/A) topics and removed the AESI medical concept Paraesthesia and dysaesthesia Reactogenicity section updated with the homologous or heterologous booster dose of AZD1222 from the D7220C00001 study and the published study conducted in Brazil Updated DCO3 data from the D8110C00001 study Information on reporting rate of TTS after second dose of AZD1222 aligned with the SmPC update. Important identified risk "Anaphylaxis" reclassified and removed from the list of safety concerns at the request of EMA with same changes reflected throughout the document |
| Part II SVIII: | Removal of Important identified risk of Anaphylaxis from the list of safety concerns |
| Part III: | <ul style="list-style-type: none"> Updated review frequency of EudraVigilance Data Analysis System (EVDAS) Electronic Reaction Monitoring Report (eRMR), all Clinical Trial AEs from AZ and non-AZ sponsored studies and batch distribution data from bi-weekly to monthly Updated the information for discontinuation of Summary safety report Updated milestone for the UK effectiveness study (D8111R00007), TTS study (D8111R00010) and COV studies (including COV001, COV002, COV003, COV005) Removed the studies with completed milestones from the Summary Table of Additional Pharmacovigilance Activities (Table III-2) |
| Part IV: | No changes |
| Part V: | <ul style="list-style-type: none"> Updated routine risk minimization measures (Table V-1) and summary of risk minimization measures (Table V-2) to remove Important identified risk of Anaphylaxis. Updated additional PV activities (Table V-2 & Table VI-4) with D8111C00010 study for the important identified and potential risks |
| Part VI: | Updated to reflect changes throughout the EU RMP. |
| Part VII: | Annex 4: Removed Anaphylaxis TSQ |

Other RMP versions under evaluation

| | |
|-------------------|----------------|
| Version number: | Not applicable |
| Submitted: | Not applicable |
| Procedure number: | Not applicable |

Details of currently approved RMP

| | |
|--------------------------|-------------------------|
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TABLE OF CONTENTS

| | | |
|----------|--|----|
| | ADMINISTRATIVE INFORMATION | 2 |
| | TABLE OF CONTENTS..... | 5 |
| | LIST OF TABLES | 6 |
| | LIST OF ANNEXES..... | 9 |
| | LIST OF ABBREVIATIONS AND DEFINITION OF TERMS | 10 |
| I. | PART I: PRODUCT OVERVIEW..... | 13 |
| II. | PART II: SAFETY SPECIFICATION..... | 15 |
| II.1 | MODULE SI: EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION | 15 |
| II.1.1 | Prevention of COVID-19 | 15 |
| II.2 | MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION | 21 |
| II.2.1 | Summary of key findings from non-clinical data..... | 21 |
| II.3 | MODULE SIII: CLINICAL TRIAL EXPOSURE..... | 25 |
| II.4 | MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS.... | 28 |
| II.4.1 | Exclusion Criteria in pivotal clinical studies within the development programme | 28 |
| II.4.2 | Limitations to detect adverse reactions in clinical trial development programmes..... | 30 |
| II.4.3 | Limitations in respect to populations typically under-represented in clinical trial development programmes..... | 30 |
| II.5 | MODULE SV: POST-AUTHORISATION EXPERIENCE | 32 |
| II.5.1 | Method used to calculate exposure..... | 32 |
| II.5.2 | Exposure..... | 32 |
| II.6 | MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION..... | 34 |
| II.7 | MODULE SVII: IDENTIFIED AND POTENTIAL RISKS..... | 35 |
| II.7.1 | Identification of safety concerns in the initial RMP submission..... | 35 |
| II.7.1.1 | Risk not considered important for inclusion in the list of safety concerns in the RMP | 35 |
| II.7.1.2 | Risks considered important for inclusion in the list of safety concerns in the RMP | 36 |
| II.7.1.3 | Adverse Events of Special Interest..... | 38 |
| II.7.1.4 | Further Considerations for COVID-19 Vaccines | 40 |
| II.7.2 | New safety concerns and reclassification with a submission of an updated RMP | 44 |
| II.7.3 | Details of important identified risks, important potential risks and missing information..... | 44 |
| II.7.3.1 | Presentation of important identified risks and important potential risks | 44 |
| II.7.3.2 | Presentation of missing information..... | 52 |
| II.8 | MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS..... | 56 |

| | | |
|-----------|--|-----|
| III. | PART III: PHARMACOVIGILANCE PLAN..... | 57 |
| III.1 | ROUTINE PHARMACOVIGILANCE ACTIVITIES..... | 57 |
| III.1.1 | Signal Detection | 57 |
| III.1.1.1 | Signal Evaluation..... | 60 |
| III.1.2 | ICSR Reporting | 60 |
| III.1.3 | Specific Adverse Reaction Follow-Up Questionnaires | 61 |
| III.1.4 | Summary Safety Reports | 61 |
| III.1.5 | Enhanced Passive Surveillance | 61 |
| III.1.6 | Traceability..... | 61 |
| III.2 | ADDITIONAL PHARMACOVIGILANCE ACTIVITIES | 62 |
| III.2.1 | Post Marketing safety studies..... | 62 |
| III.2.1.1 | Pregnancy Registry..... | 62 |
| III.2.1.2 | Post-marketing safety studies..... | 63 |
| III.2.2 | Ongoing Clinical Studies | 68 |
| III.3 | SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES | 71 |
| IV. | PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES | 81 |
| V. | PART V: RISK MINIMISATION MEASURES..... | 82 |
| V.1 | ROUTINE RISK MINIMISATION MEASURES..... | 82 |
| V.2 | ADDITIONAL RISK MINIMISATION MEASURES | 83 |
| V.3 | SUMMARY OF RISK MINIMISATION MEASURES..... | 83 |
| VI. | PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR AZD1222..... | 88 |
| VI.1 | THE MEDICINE AND WHAT IT IS USED FOR..... | 88 |
| VI.2 | RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS | 88 |
| VI.2.1 | List of important risks and missing information | 89 |
| VI.2.2 | Summary of important risks | 90 |
| VI.2.3 | Post-authorisation development plan..... | 96 |
| VI.2.3.1 | Studies which are conditions of the marketing authorisation | 96 |
| VI.2.3.2 | Other studies in post-authorisation development plan..... | 97 |
| | LIST OF REFERENCES..... | 100 |

LIST OF TABLES

| | | |
|------------|--|----|
| Table I-1 | Product Overview | 13 |
| Table II-1 | Clinical Trial Exposure to AZD1222 (US Study D8110C00001 and Pooled Oxford Studies - Safety Analysis Set) | 25 |
| Table II-2 | Clinical Trial Exposure to AZD1222 by Age Group and Sex (US Study D8110C00001 Pooled Oxford Studies - Safety Analysis Set)..... | 25 |

| | | |
|-------------|--|----|
| Table II-3 | Clinical Trial Exposure to AZD1222 by Race (US Study D8110C00001 and Pooled Oxford Studies – Safety Analysis Set) | 26 |
| Table II-4 | Clinical trial exposure to AZD1222 booster dose (Safety Analysis Set - D7220C00001) for previously vaccinated cohorts): | 27 |
| Table II-5 | Clinical trial exposure to AZD1222 booster dose by Age group, Sex and Race (Safety analysis set - D7220C00001)..... | 27 |
| Table II-6 | Exposure of Special Populations Included or not Included in the Clinical Development Programme | 30 |
| Table II-7 | VAXZEVRIA cumulative exposure (based on doses distributed) from IBD to 31 December 2021, by Region/Country/Collaboration..... | 32 |
| Table II-8 | VAXZEVRIA cumulative exposure (by doses administered), by Region/Country | 33 |
| Table II-9 | List of AZD1222 AESIs | 39 |
| Table II-10 | Summary of Safety Concerns..... | 56 |
| Table III-1 | Data sources for signal detection and frequency of review | 57 |
| Table III-2 | Ongoing and planned additional pharmacovigilance activities..... | 72 |
| Table V-1 | Description of routine risk minimisation measures by safety concern..... | 82 |
| Table V-2 | Summary table of pharmacovigilance activities and risk minimisation activities by safety concern | 83 |
| Table VI-1 | List of important risks and missing information | 89 |
| Table VI-2 | Important identified risk: Thrombosis with thrombocytopenia syndrome . | 90 |
| Table VI-3 | Important identified risk: Thrombocytopenia, including immune thrombocytopenia | 91 |
| Table VI-4 | Important identified risk: Guillain-Barré syndrome..... | 91 |
| Table VI-6 | Important potential risk: Thrombosis | 92 |
| Table VI-7 | Important potential risk: Nervous system disorders, including immune-mediated neurological conditions..... | 93 |
| Table VI-8 | Important potential risk: Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)..... | 93 |
| Table VI-9 | Missing information: Use during pregnancy and while breastfeeding..... | 94 |
| Table VI-10 | Missing information: Use in immunocompromised patients | 94 |
| Table VI-11 | Missing information: Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) | 95 |
| Table VI-12 | Missing information: Use in patients with autoimmune or inflammatory disorders | 95 |

| | | |
|-------------|---|----|
| Table VI-13 | Missing information: Interactions with other vaccines | 95 |
| Table VI-14 | Missing information: Long-term safety | 95 |

LIST OF ANNEXES

| Annexes |
|---------|
|---------|

Annex 4- Specific adverse drug reaction follow-up forms

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 I-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 |
| | <u>Chemical class:</u> Recombinant replication-deficient viral vector vaccine |
| Brief description of the product | <u>Summary of mode of action:</u> 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. |
| | <u>Important information about its composition:</u> VAXZEVRIA is produced in genetically modified human embryonic kidney (HEK) 293 cells and by recombinant DNA technology. <u>List of excipients:</u> 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 | <u>Current:</u> 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 | <u>Current:</u> The VAXZEVRIA 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. |

Table I-1 Product Overview

| | |
|---|---|
| Pharmaceutical form(s) and strengths | <u>Current:</u> 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 in 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 18 December 2021, over 271 million confirmed cases of COVID-19 infection have been diagnosed globally with more than 5.3 million deaths (WHO 2021a). By 17 December 2021, there had been over 28 million confirmed cases of COVID-19 infection and over 332 thousand deaths in the EU/European Economic Area (ECDC 2021).

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. Epidemiological studies suggest that acute COVID-19 occurs at a lower frequency in patients < 18 years old than in adults (CDC 2020a, Livingston and Bucher 2020, Wu and McGoogan 2020), with a smaller percentage of children with COVID-19 requiring hospitalisation or intensive care unit admission relative to adults (CDC 2020a, ECDC 2020). Patients with COVID-19 can experience a wide range of symptoms from mild to critical illness (CDC 2020b, ECDC 2020). Older adults and persons with medical conditions, including cardiovascular disease, chronic kidney disease, 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).

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). 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 disproportionately 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; however, the role of socio-economic status and comorbidities in confounding those associations remains to be clarified (Gao 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 07 October 2021, at least 13 different vaccines, utilizing 4 platforms, have been administered globally (WHO 2021a). As of October 2021, 136 candidate vaccines are in clinical development and 194 are in nonclinical investigation (WHO 2021a).

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 2021).

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 2021). As of December 2021, CHMP has granted marketing authorizations for 3 mAbs [XEVDY (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 [molnupiravir]), and dexamethasone (Cascella et al 2021).

Four anti-SARS-CoV-2 mAb products have received Emergency Use Authorizations (EUAs) from the Food and Drug Administration (FDA). Bamlanivimab plus etesevimab, casirivimab plus imdevimab (REGEN-COV), and sotrovimab 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

COVID-19 can be classified into 5 distinct types including asymptomatic or 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 2021). Estimated rates of asymptomatic SARS-CoV-2 infection are approximately 40% to 45%, with viral transmission possible from asymptomatic individuals (CDC 2020b, Lavezzo et al 2020, Oran and Topol 2020). Symptomatic patients can experience a range of symptoms from mild to critical illness. Based on the largest cohort study to date of > 44000 persons with confirmed COVID-19 from China, the majority of patients experienced mild to moderate illness (Wu and McGoogan 2020):

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

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).

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-Ismaïl 2020).

- Laboratory evidence of an increased levels of proinflammatory cytokines, similar to cytokine release syndrome, with persistent fevers, elevated inflammatory markers (eg, D dimer, ferritin), and elevated proinflammatory cytokines have been associated with critical and fatal illnesses (Huang et al 2020, Mehta et al 2020).
- Central and peripheral nervous system complications including Guillain-Barré syndrome (Paterson et al 2020, Toscano et al 2020), encephalopathy (Helms et al 2020), meningo encephalitis (Moriguchi et al 2020), acute disseminated encephalomyelitis (Paterson et al 2020), and acute necrotizing encephalopathy (Poyiadji et al 2020).
 - Neurologic complications, in particular encephalopathy manifesting with agitated delirium, was common in patients with critical illness.
 - Delirium/encephalopathy was reported in approximately two thirds of patients with COVID-19-related ARDS (Helms et al 2020).
- 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 sequelae 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)

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 2021a). 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 III: CLINICAL TRIAL EXPOSURE

Primary vaccination course with AZD1222

Table II-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 AZD1222 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 II-2) and race (Table II-3) are also provided.

Table II-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 | 12282 ^b | 33869 |
| Received a standard dose as the first dose (Dose 1 SD) | 21587 | 10317 | 31904 |

^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 II-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 = 12282) | Total AZD1222 (N = 33869) |
| Age group at screening (years) | | | |
| 18 - 64 | 16760 (77.6) | 11026 (89.8) | 27786 (82.0) |
| ≥ 65 | 4827 (22.4) | 1256 (10.2) | 6083 (18.0) |
| Sex | | | |
| Female | 9575 (44.4) | 6850 (55.8) | 16425 (48.5) |

Table II-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 = 12282) | Total AZD1222 (N = 33869) |
| Age group at screening (years) | | | |
| Male | 12012 (55.6) | 5432 (44.2) | 17444 (51.5) |

Table II-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 = 12282) | Total AZD1222 (N = 33869) |
| White | 17061 (79.0) | 9275 (75.5) | 26336 (77.8) |
| Asian | 947 (4.4) | 449 (3.7) | 1396 (4.1) |
| Black or African American | 1794 (8.3) | 1201 (9.8) | - |
| 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 | - | 1 (< 0.1) | 1 (< 0.1) |
| Not reported | 262 (1.2) | - | 262 (0.8) |

Booster dose (third dose) with AZD1222

Table II-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 II-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 II-5:

Table II-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 or any other demyelinating condition (only excluded from US study D8110C00001)

Reasons for exclusion: Patients with Guillain-Barré syndrome 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. 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 II-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 II-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 2021, global post-marketing exposure (by doses distributed) to VAXZEVRIA was estimated to be 2.46 billion doses. Cumulative regional data are presented in Table II-7.

Table II-7 VAXZEVRIA cumulative exposure (based on doses distributed) from IBD to 31 December 2021, by Region/Country/Collaboration

| Region ^a | Exposure by doses distributed |
|--|-------------------------------|
| Europe | 218687400 |
| International | 557239620 |
| North America | 8953500 |
| Japan | 53338170 |
| Serum Institute of India (licensing partner) | 1466804570 |
| Fiocruz (licensing partner) | 148614150 |
| R-Pharm (licensing partner) | 10358700 |
| Global | 2463996110 |

^a 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' Data from Serum Institute of India, Fiocruz and from R-Pharm are as of 31 December 2021.

Vaccine doses administered is a subset of doses distributed. Cumulative up to 31 December 2021, global post-marketing exposure (by doses administered) to Vaxzevria was estimated to be 1.6 billion doses and are summarised in Table II-8.

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

| Region/Country ^a | Exposure by doses administered | |
|-----------------------------|--------------------------------|----------|
| | Dose 1 | Dose 2 |
| European Union | 39111582 | 29825433 |
| United Kingdom | 24803571 | 24166444 |
| Australia | 6873833 | 6740025 |
| Argentina | 9949751 | 9551025 |
| Bangladesh | 14305313 | 7371670 |
| Guatemala | 1730474 | 1125665 |
| Malaysia | 2043338 | 2022371 |
| Philippines | 14192014 | |
| Canada | 2803871 | |
| India | 1264211249 | |
| Brazil | 115043755 | |
| Chile | 545440 | |
| Lebanon | 688878 | |
| New Zealand | 2458 | |
| South Korea | 20443988 | |
| Uruguay | 88924 | |
| Grand Total | 1597641072 | |

^a Administration data is not available for all countries where VAXZEVRIA is distributed

The data cut off for Brazil is 09 December 2021 and that of New Zealand is 14 December 2021.

The data cut off for Australia is 19 December 2021.

The data cut off for EU, UK, Chile, Philippines, South Korea, Uruguay is 26 December 2021.

The data cut off for Bangladesh, Guatemala, India, Lebanon, Malaysia is 27 December 2021.

The data cut off for Argentina is 28 December 2021 and that of Canada is 31 December 2021

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 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. This risk was subsequently re-categorised as an important identified risk in EU RMP Version 3.

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 II-10. 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 II-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 |
| | 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 |

Table II-9 List of AZD1222 AESIs

| Body System/Classification | AESI |
|-----------------------------|--------------------------------------|
| 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 07 December 2020 in the pooled Oxford studies, solicited local and systemic adverse events (AEs) were reported by 73.5% and 73.1% of evaluated participants in the pooled Dose 1 SD safety dataset (N = 10317), 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 48.3% and 60.2% 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 = 12282) as of 07 December 2020 indicates that early discontinuation from the study for any reason was very low in the AZD1222 arm (n = 92 participants [0.7%]). 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 II.7.3.2).

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

Anaphylaxis previously considered as an ‘important identified risk’ in the EU RMP is reclassified as ‘non-important identified risk’ hence removed from the list of safety concerns at the request of EMA through email dated 04 March 2022.

Use of AZD1222 in individuals with history of hypersensitivity to the active substances or to any of the excipients contained in the vaccine is contraindicated (SmPC Section 4.3 & 6.1). Furthermore, SmPC Section 4.4 provides, additional warnings and precautions regarding the management of anaphylactic event following AZD1222 administration.

Cumulative data from post-authorisation setting demonstrate the adherence to the risk mitigation activities included in the AZD1222 Product Information and that anaphylactic events are managed appropriately in clinical practice. The risk is considered fully characterised. There are no additional risk minimization activities ongoing or planned, no specific clinical measures or further evaluation planned for this risk as part of the pharmacovigilance plan. As such, this risk of Anaphylaxis is not considered to impact the benefit risk balance of AZD1222 and is no longer considered “Important” in the EU RMP.

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

II.7.3.1 Presentation of important identified risks and important potential risks **Important 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.

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 ($< 0.1\%$) 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, 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.

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.

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% (7/12,282 participants) in the AZD1222 group and 0.2% (18/11,962 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.

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

Potential mechanisms

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

Evidence source(s) and strength of evidence

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

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 07 December 2020, neurologic or neuroinflammatory AESIs were reported in 0.7% (81/12,282 participants) in the AZD1222 group and 0.8% (90/11,963 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 7 participants (0.1%) in the AZD1222 group and 4 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 3 SAEs of demyelinating events: 2 cases in the AZD1222 group (1 case of transverse myelitis, and 1 case of multiple sclerosis in a participant with pre-existing, but previously unrecognised, multiple sclerosis), and 1 case of myelitis in the control group. 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 nervous system disorders, including immune-mediated neurological conditions, following vaccination.

Preventability

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

Impact on the risk-benefit balance of the product

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

Public health impact

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

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

Potential mechanisms

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

Evidence source(s) and strength of evidence

There is a theoretical concern that vaccination against SARS-CoV-2 may be associated with enhanced severity of COVID-19 episodes which would manifest as VAED/VAERD. Vaccine-associated enhanced disease was observed in children given formalin-inactivated whole-virus vaccines against respiratory syncytial virus and measles virus (Haynes et al 2020), and findings from experimental models of SARS-CoV and MERS-CoV infection suggest that VAED/VAERD may be possible in certain conditions (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-19¹ occurred in the control group than among AZD1222 recipients. In the pooled Oxford studies as of 07 December 2020, COVID-related AESIs were reported in

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

0.1% (15/12,282 participants) in the AZD1222 group and 0.3% (36/11,963 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 July 2021) 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 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.

II.7.3.2 Presentation of missing information

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).

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, a metanalytic post-marketing safety study using existing secondary health data sources in patients receiving immunosuppressant medication or with primary immunodeficiency, and an interventional study in immunocompromised adults; see Section III.2.1 for further details), and in ongoing clinical study COV005 (see Section III.2.2).

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).

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).

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.

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.7.3.1. 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 II-11.

Table II-10 Summary of Safety Concerns

| | |
|----------------------------|--|
| Important identified risks | <ul style="list-style-type: none">• Thrombosis with thrombocytopenia syndrome• Thrombocytopenia, including immune thrombocytopenia• Guillain-Barré syndrome |
| Important potential risks | <ul style="list-style-type: none">• Thrombosis• Nervous system disorders, including immune-mediated neurological conditions• Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) |
| Missing information | <ul style="list-style-type: none">• 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 III-1.

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

| Data Source | Frequency of review |
|---|---------------------|
| AstraZeneca global safety database (SAPPHIRE), which includes Clinical Trial SAEs and all Post Marketing case reports received by AstraZeneca and License Partners (including special situation reports and case reports from the MHRA and EU [EudraVigilance]) | Weekly |
| EudraVigilance Data Analysis System (EVDAS) Electronic Reaction Monitoring Report (eRMR) | Monthly |
| US Vaccine Adverse Event Reporting System (VAERS) | Weekly |
| Literature (Embase and Insight Meme) | Weekly |
| All Clinical Trial AEs from AZ and non-AZ sponsored studies | 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 weekly 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 ($\text{RoR} > 1.0$), 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 weekly as part of routine surveillance activities. In addition, daily reports may be produced for cases not yet closed on the safety database to allow for early identification of any potential safety issue. Reports 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 a gamma-Poisson shrinker model to identify batches with a higher proportion of AE reporting. 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 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), SAPHIRE 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 Failure² 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

On 11 January 2022, EMA recommended discontinuation of the Summary Safety Reports (SSRs) for AZD1222. This is based upon the rationale provided by PRAC as received in the Assessment Report for the 8th SSR (review period: 01 October 2021 – 30 November 2021) dated 14 December 2021, which was the last AZD1222 SSR produced by AstraZeneca. PSURs submitted on a 6-monthly basis, will serve as the tool for discussion of any safety topics as well as other standard pharmacovigilance activities.

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 permitted by National Competent Authorities.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

In order to obtain data to aid the further characterisation of the safety concerns described in Section II.7.3, 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; Registry-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, placental 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: | <ul style="list-style-type: none"> 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 Subsequent Quarterly update - period 1 (period of 1 Jun to 31 Aug): Oct 2022/ Oct 2023/ Oct 2024/ Oct 2025 Semi-annual report - period 2 (period of 1 Jun to 30 Nov each year): Jan 2022/ Jan 2023/ Jan 2024/ Jan 2025/ Jan 2026 Quarterly update - period 3 (period of 1 Dec to 28th Feb following year): Apr 2022/ Apr 2023/ Apr 2024/ Apr 2025/ Apr 2026 Annual update report – period 4 (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 (D8110R00002 [US] 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 in individuals who have not received any vaccination for COVID-19, overall and in subpopulations of interest. The study objective is to evaluate the incidence and relative risk of safety concerns and AESIs. |
| Study design: | This is a retrospective, longitudinal cohort study using population-based automated health care data to ascertain vaccination details, patient characteristics, and outcomes of interest. |

| | |
|-------------------|---|
| | The study observation period starts on the date of the first AZD1222 vaccination (index date) and will end at 2 years after the index date, or earlier if other censoring rules apply (eg, death, leaving database). A minimum prior period of one year of database history will be required to collect information on patient characteristics and prior risks. |
| Study population: | All patients exposed to AZD1222 with a date of vaccination (preferably batch date) and a minimum of 12 months of prior history in the database. |
| Milestones: | The milestones below are only for the D8111R00006 study: <ul style="list-style-type: none"> • 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 • Interim report 2: Oct 2022 • Interim report 3: Apr 2023 • Final report of study results: Oct 2023 |

Metanalytic post-marketing safety study in patients receiving immunosuppressant medication or with primary immunodeficiency using existing secondary health data sources

| | |
|---------------------------------|--|
| Study name and title: | Metanalytic post-marketing safety study in patients receiving immunosuppressant medication or with primary immunodeficiency using existing secondary health data sources (<i>study name/code to be confirmed</i>). |
| Rationale and study objectives: | To evaluate the safety profile of AZD1222 in patients receiving immunosuppressant medication(s) or with primary immunodeficiency, in order to provide additional data to support the characterisation of the area of missing information of ‘ <i>Use in immunocompromised patients</i> ’. This study will aggregate results using a metanalytical approach across multiple datasets from the UK, EU and US, with the aim of aggregating a sufficient sample size in order to discharge the risk of an event rate less than or equal to 1 in 10000. |
| Study design: | Under development. |
| Study population: | To be determined. |
| Milestones: | <ul style="list-style-type: none"> • Submission of study protocol: Q3 2022. |

Interventional study in immunocompromised adults

| | |
|---------------------------------|---|
| Study name and title: | Immunogenicity and Safety Study of AZD1222 Vaccine in Immunocompromised Adults (D8111C00010). |
| Rationale and study objectives: | The purpose of this study is to evaluate the immunogenicity and safety profile of AZD1222 for prevention of COVID-19 in seronegative immunocompromised adults receiving stable doses of immunosuppressant medication(s) or with stable primary immunodeficiency, to provide data that supports the use of AZD1222 in this population. |

| | |
|-------------------|---|
| | <p>The primary study objective is to characterise the immunogenicity of a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in SARS-CoV-2 naïve immunocompromised adults ≥ 18 years.</p> <p>The secondary safety objective is to characterize the reactogenicity and safety of a 3-dose primary vaccination series with AZD1222, with a 4-week dosing interval, in SARS-CoV-2 naïve immunocompromised adults ≥ 18 years.</p> |
| Study design: | <p>This is a Phase IV, open-label, non-randomized, multi-cohort, multi-center study of the immunogenicity and safety of AZD1222 for the prevention of COVID-19 in previously unvaccinated immunocompromised adults ≥ 18 years. Immunocompromised participants will receive primary vaccination with 3 IM doses of AZD1222 separated by 4 weeks and will continue to be followed to the end of the study. Immunocompetent participants will receive a third dose booster 6 months after dose 1 and will continue to be followed to the end of the study.</p> |
| Study population: | <p>Adults >18 years of age who have stable immunocompromising conditions or on stable doses of immunocompromising therapeutics.</p> |
| Milestones: | <ul style="list-style-type: none"> • Submission of study design concept: 28 Feb 2021 • Submission of study protocol: 24 Apr 2021 • Submission of primary clinical study report: 28 Feb 2023 • Submission of final report: 30 Nov 2023 |

In vitro interaction with PF4 and/or platelets

| | |
|---------------------------------|--|
| Study name and title: | <p>In vitro interaction of AZD1222 or spike protein with PF4 and/or platelets (MS1222-0001)/ (MS1222-0004)/ (MS1222-0005).</p> |
| Rationale and study objectives: | <p>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.</p> |
| Study design: | <p>Computational prediction of spike interaction with PF4: Modelling possible interaction of spike protein with PF4 as a potential mechanism.</p> <p>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.</p> |
| Study population: | <p>In vitro assay involving sera from Covid/Vaccine naïve individuals and AZD1222 vaccinated individuals. Platelets will be sourced from healthy donors.</p> |
| Milestones: | <ul style="list-style-type: none"> • 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: | <p>Are HIT antibodies increased in the sera of vaccinated individuals MS1222-0003</p> |
|-----------------------|---|

| | |
|---------------------------------|---|
| 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: | <ul style="list-style-type: none"> 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: | <ul style="list-style-type: none"> 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: | <ul style="list-style-type: none"> 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 (D8110R00003 [US] and D8111R00005/ D8111R00017 [EU/UK]). |
| Rationale and study objectives: | <p>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).</p> <p>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.</p> |
| 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: | <ul style="list-style-type: none"> • 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: Q1 2024 |

Thrombotic thrombocytopenia syndrome (D8111R00010)

The following study is considered to be voluntary post authorisation safety study and is included in the pharmacovigilance plan for transparency.

| | |
|---------------------------------|--|
| 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: | Submission of final study report: Q1 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: | <ul style="list-style-type: none"> Final study report due: 31 Dec 2022. |

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: | <p>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.</p> <p>This study comprises 11 separate investigational groups of participants, with each group investigating a specific dosing regimen and age group.</p> <p>All participants will be followed up for 12 months from last vaccination visit. This study is being conducted in the UK.</p> |
| Study population: | Adult volunteers aged at least 18 years. |
| Milestones: | <ul style="list-style-type: none"> Final study report due: 31 Dec 2022 |

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: | <p>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.</p> <p>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.</p> |
| Milestones: | <ul style="list-style-type: none"> Final study report due: 31 Dec 2022 |

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: | <ul style="list-style-type: none"> Final study report due: 31 Dec 2022 |

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: | <p>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.</p> <p>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.</p> |
| 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: | <ul style="list-style-type: none"> Final study report due: 31 Dec 2022 |

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: | <ul style="list-style-type: none"> • 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: | <ul style="list-style-type: none"> • Interim analysis: Q1 2021 • Primary analysis: Q2 2021. |

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

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

Table III-2 Ongoing and planned additional pharmacovigilance activities

| Study name / title Status | Study code | Summary of activity objectives | Safety concerns addressed | Milestones | Due dates |
|--|-------------|---|---|---------------------------------|-------------|
| Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation | | | | | |
| Immunogenicity and Safety Study of AZD1222 Vaccine in Immunocompromised Adults <u>Status:</u> Ongoing | D8111C00010 | To characterise the immunogenicity of a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in SARS-CoV-2 naïve immunocompromised adults. | <ul style="list-style-type: none">• Use in immunocompromised patients• Thrombosis with thrombocytopenia syndrome• Thrombosis• Thrombocytopenia, including immune thrombocytopenia• Guillain-Barré syndrome• Nervous system disorders, including immune-mediated neurological conditions• Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)• Long term safety | Study design concept submission | 28 Feb 2021 |
| | | | | Study protocol submission | 24 Apr 2021 |
| | | | | Primary report submission | 28 Feb 2023 |
| | | | | Final report submission | 30 Nov 2023 |
| Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances | | | | | |
| Study COV001 A Phase I/II Study to Determine Efficacy, Safety, and Immunogenicity of the Candidate Coronavirus Disease (COVID-19) Vaccine ChAdOx1 | COV001 | To assess the efficacy and safety of AZD1222 against COVID-19 | <ul style="list-style-type: none">• Thrombosis with thrombocytopenia syndrome• Thrombosis• Thrombocytopenia, including immune thrombocytopenia• Guillain-Barré syndrome• Nervous system disorders, including immune-mediated neurological conditions | Final report | 31 Dec 2022 |

Table III-2 Ongoing and planned additional pharmacovigilance activities

| Study name / title Status | Study code | Summary of activity objectives | Safety concerns addressed | Milestones | Due dates |
|---|------------|---|---|--------------|-------------|
| nCoV-19 in UK Healthy Adult Volunteers <u>Status</u> : Ongoing | | | <ul style="list-style-type: none"> Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Long-term safety | | |
| 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 <u>Status</u> : Ongoing | COV002 | To assess the efficacy and safety of AZD1222 against COVID-19 in adults aged 18 years and older in the UK | <ul style="list-style-type: none"> Thrombosis with thrombocytopenia syndrome Thrombosis Thrombocytopenia, including immune thrombocytopenia Guillain-Barré syndrome Nervous system disorders, including immune-mediated neurological conditions Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Long-term safety | Final report | 31 Dec 2022 |
| Study COV003 A Randomised, Controlled, Phase III Study to Determine the Safety, Efficacy, and Immunogenicity of the Non-Replicating ChAdOx1 nCoV-19 Vaccine | COV003 | To evaluate the efficacy of AZD1222 vaccine against COVID-19 disease confirmed with PCR | <ul style="list-style-type: none"> Thrombosis with thrombocytopenia syndrome Thrombosis Thrombocytopenia, including immune thrombocytopenia Guillain-Barré syndrome Nervous system disorders, including immune-mediated neurological conditions | Final report | 31 Dec 2022 |

Table III-2 Ongoing and planned additional pharmacovigilance activities

| Study name / title Status | Study code | Summary of activity objectives | Safety concerns addressed | Milestones | Due dates |
|--|-------------|---|--|---------------------------|-------------|
| <u>Status</u> : Ongoing | | | <ul style="list-style-type: none"> Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Long-term safety | | |
| 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 <u>Status</u> : Ongoing | COV005 | <p>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.</p> <p>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.</p> | <ul style="list-style-type: none"> Thrombosis with thrombocytopenia syndrome Thrombosis Thrombocytopenia, including immune thrombocytopenia Guillain-Barré syndrome Nervous system disorders, including immune-mediated neurological conditions Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Use in immunocompromised patients Long-term safety | Final report | 31 Dec 2022 |
| D8110C00001 A Phase III Randomized, Double-blind, Placebo-controlled Multicentre Study in Adults to | 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 | <ul style="list-style-type: none"> Thrombosis with thrombocytopenia syndrome Thrombosis | Primary efficacy analysis | Q2 2021 |
| | | | | Final report | Q4 2023 |

Table III-2 Ongoing and planned additional pharmacovigilance activities

| Study name / title Status | Study code | Summary of activity objectives | Safety concerns addressed | Milestones | Due dates |
|--|--------------------------------------|---|--|---|-------------------------------------|
| Determine the Safety, Efficacy, and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19 <u>Status</u> : Ongoing | | To assess the safety and tolerability of 2 IM doses of AZD1222 compared to placebo in adults ≥ 18 years of age To assess the reactogenicity of 2 IM doses of AZD1222 compared to placebo in adults ≥ 18 years of age (Substudy only) | <ul style="list-style-type: none"> Thrombocytopenia, including immune thrombocytopenia Guillain-Barré syndrome Nervous system disorders, including immune-mediated neurological conditions Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) Long-term safety | | |
| Category 3 – Required additional pharmacovigilance activities | | | | | |
| Pregnancy Registry Pregnancy Registry of Women Exposed to AZD1222 Immediately Before or During Pregnancy as Part of the C-VIPER Registry Consortium. <u>Status</u> : Ongoing | D8110C00003 (Pregistry-sponsored) | To estimate the risk of the most common obstetric outcomes (pregnancy losses, placental 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 | <ul style="list-style-type: none"> Use during pregnancy and while breastfeeding | 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 |
| | | | | SAP | 15 Jan 2022 |
| | | | | Quarterly update - Period 1 | Oct 2022/Oct 2023/Oct 2024/Oct 2025 |

Table III-2 Ongoing and planned additional pharmacovigilance activities

| Study name / title Status | Study code | Summary of activity objectives | Safety concerns addressed | Milestones | Due dates |
|--|--|---|---|--------------------------------------|--|
| | | of the LMP to end of pregnancy and their offspring relative to a matched unexposed reference group. | | Semi-annual report -period 2 | Jan 2022/ Jan 2023/ Jan2024/ Jan2025/ Jan 2026 |
| | | | | Quarterly update – period 3 | Apr 2022/Apr 2023/Apr 2024/Apr 2025/Apr 2026 |
| | | | | Annual Update – Period 4 | Jul 2022/Jul 2023/Jul 2024/Jul 2025 |
| | | | | Final report | Jul 2026 |
| Post-marketing observational study using existing secondary health data sources A post-authorisation/post-marketing observational study to evaluate the association between exposure to AZD1222 and safety concerns | D81110R00002 (US) D8111R00006 (EU/UK) | To evaluate the incidence and relative risk of safety concerns and AESIs. | <ul style="list-style-type: none"> • Thrombosis with thrombocytopenia syndrome • Thrombosis • Thrombocytopenia, including immune thrombocytopenia • Guillain-Barré syndrome • Nervous system disorders, including immune-mediated neurological conditions • Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) | Study Design Concept submission | 18 Dec 2020 |
| | | | | Protocol submission | 01 Apr 2021 |
| | | | | Final protocol submission | 15 July 2021 |
| | | | | Statistical analysis plan submission | Nov 2021 |
| | | | | Progress report | Oct 2021 |

Table III-2 Ongoing and planned additional pharmacovigilance activities

| Study name / title Status | Study code | Summary of activity objectives | Safety concerns addressed | Milestones | Due dates |
|--|-----------------------------------|--|---|-------------------------------|-----------|
| using existing secondary health data sources. <u>Status:</u> Ongoing | | | <ul style="list-style-type: none"> • 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 | Interim report 1 | Apr 2022 |
| | | | | Interim report 2 | Oct 2022 |
| | | | | Interim report 3 | Apr 2023 |
| | | | | Final report of study results | Oct 2023 |
| Metanalytic post-marketing safety study in patients receiving immunosuppressant medication or with primary immunodeficiency using existing secondary health data sources <u>Status:</u> Planned | <i>Study code to be confirmed</i> | To evaluate the safety profile of AZD1222 in patients receiving immunosuppressant medication(s) or with primary immunodeficiency | <ul style="list-style-type: none"> • Use in immunocompromised patients | Protocol submission | Q3 2022 |

Table III-2 Ongoing and planned additional pharmacovigilance activities

| Study name / title Status | Study code | Summary of activity objectives | Safety concerns addressed | Milestones | Due dates |
|---|--|--|---|--|--------------|
| Are HIT antibodies increased in the sera of vaccinated individuals <u>Status:</u> Ongoing | MS1222-0003 | To 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. | <ul style="list-style-type: none"> Thrombosis with thrombocytopenia syndrome | Final report | 01 Aug 2021* |
| Post-marketing effectiveness study Post-authorisation/ Post-marketing retrospective cohort study to evaluate the effectiveness of the AZD1222 vaccine to prevent serious COVID-19 infection in conditions of usual care through public-private partnership with COVIDRIVE utilizing primary data collected prospectively through the COVIDRIVE platform. <u>Status:</u> Ongoing | D8110R00003 (US) 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. | <i>Not applicable</i> | 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 |
| | | | | First interim report (D8111R00017) | Q2 2022 |

Table III-2 Ongoing and planned additional pharmacovigilance activities

| Study name / title Status | Study code | Summary of activity objectives | Safety concerns addressed | Milestones | Due dates |
|--|------------|--|---|--|-------------|
| | | | | Second interim report (D8111R00017) | Q4 2022 |
| | | | | Third interim report (D8111R00017) | Q2 2023 |
| | | | | Final report (D8111R00017) | Q1 2024 |
| <p>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</p> <p><u>Status:</u> Ongoing</p> | COV004 | <p>To assess the safety, tolerability and reactogenicity profile of the candidate vaccine ChAdOx1 nCoV-19</p> <p>To assess immunogenicity of ChAdOx1 nCoV-19</p> | <ul style="list-style-type: none"> • Thrombosis with thrombocytopenia syndrome • Thrombosis • Thrombocytopenia, including immune thrombocytopenia • Guillain-Barré syndrome • Nervous system disorders, including immune-mediated neurological conditions • Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) • Long-term safety | Final report | 31 Dec 2022 |

Table III-2 Ongoing and planned additional pharmacovigilance activities

| Study name / title Status | Study code | Summary of activity objectives | Safety concerns addressed | Milestones | Due dates |
|---|-------------|---|--|--------------------|-----------|
| D8111R00007 Real-world effectiveness of the Oxford/AstraZeneca COVID-19 vaccine in England <u>Status:</u> Ongoing | D8111R00007 | To evaluate the effectiveness of the AZD1222 in England | <ul style="list-style-type: none"> Not applicable | Final Study report | Q1 2023 |
| Voluntary PASS | | | | | |
| D8111R00010 An assessment of a relationship between the exposure to COVID-19 vaccines and risk of thrombotic thrombocytopenia syndrome <u>Status:</u> Ongoing | D8111R00010 | To evaluate an association between COVID-19 vaccine exposure and thromboembolic events occurring with thrombocytopenia (thrombotic thrombocytopenia syndrome; TTS). | <ul style="list-style-type: none"> Thrombosis with thrombocytopenia syndrome; | Final Study report | Q1 2023 |

* ongoing review at time of RMP update which may impact future 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 V-1.

Table V-1 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: <ul style="list-style-type: none"> SmPC Section 4.3, 4.4 and 4.8 PL Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: <ul style="list-style-type: none"> SmPC Sections 4.3 and 4.4 PL Section 2 and 4 |
| Thrombocytopenia, including immune thrombocytopenia | Routine risk communication: <ul style="list-style-type: none"> SmPC Section 4.8 PL Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: <ul style="list-style-type: none"> SmPC Section 4.4 PL Section 2 |
| Guillain-Barré syndrome | Routine risk communication: <ul style="list-style-type: none"> SmPC Section 4.8 PL Section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: <ul style="list-style-type: none"> SmPC Section 4.4 PL Section 2 |
| Important Potential Risks | |
| Thrombosis | Routine risk minimisation activities recommending specific clinical measures to address the risk: <ul style="list-style-type: none"> SmPC Section 4.4 |
| Nervous system disorders, including immune-mediated neurological conditions | Routine risk minimisation activities recommending specific clinical measures to address the risk: <ul style="list-style-type: none"> SmPC section 4.4 PL Section 2 |
| Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) | None |
| Missing Information | |

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

| Safety concern | Routine risk minimisation activities |
|---|--|
| Use during pregnancy and while breastfeeding | Routine risk communication: <ul style="list-style-type: none"> SmPC Section 4.6 PL Section 2 |
| Use in immunocompromised patients | Routine risk communication: <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> SmPC Section 4.5 PL Section 2 |
| Long-term safety | None |

V.2 ADDITIONAL RISK MINIMISATION MEASURES

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

V.3 SUMMARY OF RISK MINIMISATION MEASURES

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

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|--|
| Important Identified Risks | | |
| Thrombosis with thrombocytopenia syndrome | Routine risk minimisation measures: <ul style="list-style-type: none"> SmPC Sections 4.3, 4.4 and 4.8 PL Sections 2 and 4 | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: <ul style="list-style-type: none"> Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: <ul style="list-style-type: none"> Interventional study in immunocompromised adults (D8111C00010) Biodistribution study (1169DM) In vitro expression of Spike protein (MS1222-0002) HIT antibodies in vaccinated sera (MS1222-0003) |

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

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|--|---|
| | | <ul style="list-style-type: none"> 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 (D8110R00002 [US], D8111R00006 [EU]) Study COV001 Study COV002 Study COV003 Study COV004 Study COV005 Study D8110C00001 Study D8111C00002 |
| Thrombocytopenia, including immune thrombocytopenia | Routine risk minimisation measures: <ul style="list-style-type: none"> SmPC Sections 4.4 and 4.8 PL Sections 2 and 4 | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: <ul style="list-style-type: none"> Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: <ul style="list-style-type: none"> Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) Interventional study in immunocompromised adults (D8111C00010) Study COV001 Study COV002 Study COV003 Study COV004 Study COV005 Study D8110C00001 Study D8111C00002 |
| Guillain-Barré syndrome | Routine risk minimisation measures: <ul style="list-style-type: none"> SmPC Sections 4.4 and 4.8 PL Sections 2 and 4 | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: <ul style="list-style-type: none"> Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: <ul style="list-style-type: none"> Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) Interventional study in immunocompromised adults (D8111C00010) Study COV001 |

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

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|--|
| | | <ul style="list-style-type: none"> Study COV002 Study COV003 Study COV004 Study COV005 Study D8110C00001 Study D8111C00002 |
| Important Potential Risks | | |
| Thrombosis | Routine risk minimisation measures: <ul style="list-style-type: none"> SmPC Sections 4.4 | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: <ul style="list-style-type: none"> Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: <ul style="list-style-type: none"> Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) Interventional study in immunocompromised adults (D8111C00010) Study COV001 Study COV002 Study COV003 Study COV004 Study COV005 Study D8110C00001 Study D8111C00002 |
| Nervous system disorders, including immune-mediated neurological conditions | Routine risk minimisation measures: <ul style="list-style-type: none"> SmPC Sections 4.4 and 4.8 PL Section 2 and 4 | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: <ul style="list-style-type: none"> Specific adverse reaction follow-up questionnaire (<i>to be issued for immune-mediated neurological conditions only</i>) Additional pharmacovigilance activities: <ul style="list-style-type: none"> Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) Interventional study in immunocompromised adults (D8111C00010) Study COV001 Study COV002 Study COV003 Study COV004 Study COV005 Study D8110C00001 Study D8111C00002 |

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

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) | None | <p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <ul style="list-style-type: none"> Specific adverse reaction follow-up questionnaire <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) Interventional study in immunocompromised adults (D8111C00010) Study COV001 Study COV002 Study COV003 Study COV004 Study COV005 Study D8110C00001 Study D8111C00002 |
| Missing Information | | |
| Use during pregnancy and while breastfeeding | <p>Routine risk minimisation measures:</p> <ul style="list-style-type: none"> SmPC Section 4.6 PL Section 2 | <p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <ul style="list-style-type: none"> None <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> Pregnancy Registry (D8110C00003) Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) |
| Use in immunocompromised patients | <p>Routine risk minimisation measures:</p> <ul style="list-style-type: none"> SmPC Section 4.4 PL Section 2 | <p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <ul style="list-style-type: none"> None <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) Metanalytic post-marketing safety study in patients receiving immunosuppressant medication or with primary immunodeficiency using existing secondary health data sources Interventional study in immunocompromised adults (D8111C00010) Study COV005 |

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

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|--|--|
| Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) | None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: <ul style="list-style-type: none"> None Additional pharmacovigilance activities: <ul style="list-style-type: none"> Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) |
| Use in patients with autoimmune or inflammatory disorder | None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: <ul style="list-style-type: none"> None Additional pharmacovigilance activities: <ul style="list-style-type: none"> Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) |
| Interactions with other vaccines | Routine risk minimisation measures: <ul style="list-style-type: none"> SmPC Section 4.5 PL Section 2 | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: <ul style="list-style-type: none"> None Additional pharmacovigilance activities: <ul style="list-style-type: none"> Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) |
| Long-term safety | None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: <ul style="list-style-type: none"> None Additional pharmacovigilance activities: <ul style="list-style-type: none"> Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) Interventional study in immunocompromised adults (D8111C00010) 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 VI-1 List of important risks and missing information

| | |
|----------------------------|--|
| Important identified risks | <ul style="list-style-type: none">• Thrombosis with thrombocytopenia syndrome• Thrombocytopenia, including immune thrombocytopenia• Guillain-Barré syndrome |
| Important potential risks | <ul style="list-style-type: none">• Thrombosis• Nervous system disorders, including immune-mediated neurological conditions• Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD) |

Table VI-1 List of important risks and missing information

| | |
|---------------------|---|
| Missing Information | <ul style="list-style-type: none"> • Use during pregnancy and while breastfeeding • Use in immunocompromised patients • Use in frail patients with co-morbidities (eg, chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disorders) • Use in patients with autoimmune or inflammatory disorders • Interactions with other vaccines • Long-term safety |
|---------------------|---|

VI.2.2 Summary of important risks

Table VI-2 Important 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 | <p>Routine risk minimisation measures:</p> <ul style="list-style-type: none"> • SmPC Sections 4.3, 4.4 and 4.8 • PL Sections 2 and 4 |
| Additional pharmacovigilance activities | <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • Interventional study in immunocompromised adults (D8111C00010) • 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 (D8110R00002 [US], D8111R00006 [EU]) • Study COV001 • Study COV002 • Study COV003 • Study COV004 • Study COV005 • Study D8110C00001 • Study D8111C00002 <p>See Section VI.2.3 of this summary for an overview of the post-authorisation development plan.</p> |

Table VI-3 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: <ul style="list-style-type: none"> • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities: <ul style="list-style-type: none"> • Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) • Interventional study in immunocompromised adults (D8111C00010) • Study COV001 • Study COV002 • Study COV003 • Study COV004 • Study COV005 • Study D8110C00001 • Study D8111C00002 See Section VI.2.3 of this summary for an overview of the post-authorisation development plan. |

Table VI-4 Important 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 <i>Campylobacter jejuni</i> 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: |

Table VI-4 Important identified risk: Guillain-Barré syndrome

| | |
|---|--|
| | <ul style="list-style-type: none"> SmPC Sections 4.4 and 4.8 PL Sections 2 and 4 |
| Additional pharmacovigilance activities | <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) Interventional study in immunocompromised adults (D8111C00010) Study COV001 Study COV002 Study COV003 Study COV004 Study COV005 Study D8110C00001 Study D8111C00002 <p>See Section VI.2.3 of this summary for an overview of the post-authorisation development plan.</p> |

Table VI-5 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 | <p>Routine risk minimisation measures:</p> <ul style="list-style-type: none"> SmPC Sections 4.4 |
| Additional pharmacovigilance activities | <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) Interventional study in immunocompromised adults (D8111C00010) Study COV001 Study COV002 Study COV003 Study COV004 Study COV005 Study D8110C00001 Study D8111C00002 <p>See Section VI.2.3 of this summary for an overview of the post-authorisation development plan.</p> |

Table VI-6 Important potential risk: Nervous system disorders, including immune-mediated neurological conditions

| | |
|---|--|
| Evidence for linking the risk to the medicine | <p>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.</p> <p>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.</p> <p>Very rare events of immune-mediated neurological conditions have been observed following vaccination with AZD1222 during post-authorisation use.</p> |
| 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 | <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) • Interventional study in immunocompromised adults (D8111C00010) • Study COV001 • Study COV002 • Study COV003 • Study COV004 • Study COV005 • Study D8110C00001 • Study D8111C00002 <p>See Section VI.2.3 of this summary for an overview of the post-authorisation development plan.</p> |

Table VI-7 Important potential risk: Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)

| | |
|---|---|
| Evidence for linking the risk to the medicine | <p>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</p> |
|---|---|

Table VI-7 Important potential risk: Vaccine-associated enhanced disease (VAED), including vaccine-associated enhanced respiratory disease (VAERD)

| | |
|---|--|
| | <p>MERS-CoV infection suggest that VAED/VAERD may be possible in certain conditions.</p> <p>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.</p> <p>There have been no confirmed post-marketing reports of VAED/VAERD.</p> |
| Risk factors and risk groups | There are no known risk factors identified for VAED/VAERD. |
| Risk minimisation measures | None |
| Additional pharmacovigilance activities | <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) • Interventional study in immunocompromised adults (D8111C00010) • Study COV001 • Study COV002 • Study COV003 • Study COV004 • Study COV005 • Study D8110C00001 • Study D8111C00002 <p>See Section VI.2.3 of this summary for an overview of the post-authorisation development plan.</p> |

Table VI-8 Missing information: Use during pregnancy and while breastfeeding

| | |
|---|--|
| Risk minimisation measures | <p>Routine risk minimisation measures</p> <ul style="list-style-type: none"> • SmPC Section 4.6 • PL Section 2 |
| Additional pharmacovigilance activities | <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • Pregnancy Registry (D8110C00003) • Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) <p>See Section VI.2.3 of this summary for an overview of the post-authorisation development plan.</p> |

Table VI-9 Missing information: Use in immunocompromised patients

| | |
|----------------------------|--|
| Risk minimisation measures | <p>Routine risk minimisation measures</p> <ul style="list-style-type: none"> • SmPC Section 4.4 • PL Section 2 |
|----------------------------|--|

Table VI-9 Missing information: Use in immunocompromised patients

| | |
|---|--|
| Additional pharmacovigilance activities | <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) • Metanalytic post-marketing safety study in patients receiving immunosuppressant medication or with primary immunodeficiency using existing secondary health data sources • Interventional study in immunocompromised patients (D8111C00010) • Study COV005 <p>See Section VI.2.3 of this summary for an overview of the post-authorisation development plan.</p> |
|---|--|

Table VI-10 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 | <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) <p>See Section VI.2.3 of this summary for an overview of the post-authorisation development plan.</p> |

Table VI-11 Missing information: Use in patients with autoimmune or inflammatory disorders

| | |
|---|--|
| Risk minimisation measures | None |
| Additional pharmacovigilance activities | <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) <p>See Section VI.2.3 of this summary for an overview of the post-authorisation development plan.</p> |

Table VI-12 Missing information: Interactions with other vaccines

| | |
|---|--|
| Risk minimisation measures | <p>Routine risk minimisation measures</p> <ul style="list-style-type: none"> • SmPC Section 4.5 • PL Section 2 |
| Additional pharmacovigilance activities | <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) <p>See Section VI.2.3 of this summary for an overview of the post-authorisation development plan.</p> |

Table VI-13 Missing information: Long-term safety

| | |
|----------------------------|------|
| Risk minimisation measures | None |
|----------------------------|------|

Table VI-13 Missing information: Long-term safety

| | |
|---|--|
| Additional pharmacovigilance activities | <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • Post-marketing observational study using existing secondary health data sources (D8110R00002 [US], D8111R00006 [EU]) • Interventional study in immunocompromised adults (D8111C00010) • Study COV001 • Study COV002 • Study COV003 • Study COV004 • Study COV005 • Study D8110C00001 • Study D8111C00002 <p>See Section VI.2.3 of this summary for an overview of the post-authorisation development plan.</p> |
|---|--|

VI.2.3 Post-authorisation development plan

VI.2.3.1 Studies which are conditions of the marketing authorisation

The following studies are conditions / specific obligations of the marketing authorisation:

Study D8111C00010 - Immunogenicity and Safety Study of AZD1222 Vaccine in Immunocompromised Adults

Purpose of the study: To characterise the immunogenicity of a 2-dose primary vaccination with AZD1222 with a 4-week dosing interval in SARS-CoV-2 naïve immunocompromised adults.

In vitro expression of spike protein following transduction by AZD1222

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

Purpose of the study: This study was initiated as the first-in-human study employing candidate vaccine AZD1222 (ChAdOx1 nCoV-19). The primary objectives of this study are to assess the efficacy and safety of AZD1222 against COVID-19.

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

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

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

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

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

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

VI.2.3.2 Other studies in post-authorisation development plan

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

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] / D81110R00002 [US])

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).

Metanalytic post-marketing safety study in patients receiving immunosuppressant medication or with primary immunodeficiency using existing secondary health data sources

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

Are HIT antibodies increased in the sera of vaccinated individuals

Purpose of the study: To 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.

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] / D8110R00003 [US])

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.

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

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

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WHO (World Health Organization). Coronavirus disease (COVID-19): Vaccines. Available at: [https://www.who.int/news-room/q-a-detail/coronavirus-disease-\(covid-19\)-vaccines?adgroupsurvey={adgroupsurvey}&gclid=Cj0KCQiAst2BBhDJARIsAGo2ldUVPhI8S9Zu5CnRbk5rXQ5SclKWoTqOmkoJv2mDCH5kNY0XSQhLi_caAhNjEALw_wcB](https://www.who.int/news-room/q-a-detail/coronavirus-disease-(covid-19)-vaccines?adgroupsurvey={adgroupsurvey}&gclid=Cj0KCQiAst2BBhDJARIsAGo2ldUVPhI8S9Zu5CnRbk5rXQ5SclKWoTqOmkoJv2mDCH5kNY0XSQhLi_caAhNjEALw_wcB). Accessed 25 February 2021.

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Wu et al 2020a

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Wu et al 2020b

Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13):1239–1242.

Wu and McGoogan 2020

Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;10.1001/jama.2020.2648; Online ahead of print.

Yang et al 2020

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Zhang et al 2020

Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W et al. Coagulopathy and antiphospholipid antibodies in patients with COVID-19. *N Engl J Med*. 2020;382(17):e38.

Zheng et al 2020

Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. *J Infect*. 2020;81(2):e16-25.

Zhou et al 2020

Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-62.

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

| | |
|--|---|
| TABLE OF CONTENTS | 2 |
| 1. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS..... | 3 |

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

1. Reporter's Information

| | | |
|---------------------|---|------------------|
| Reporter's Name: | Is Reporter a healthcare professional? <input type="checkbox"/> No <input type="checkbox"/> 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: <input type="checkbox"/> Male <input type="checkbox"/> Female For female, currently Pregnant ?: <input type="checkbox"/> No <input type="checkbox"/> Yes | Date of Birth (DD/MM/YYYY): | Age (years): |
| Race: <input type="checkbox"/> White <input type="checkbox"/> Black or African American <input type="checkbox"/> Native American <input type="checkbox"/> Alaska Native <input type="checkbox"/> Native Hawaiian <input type="checkbox"/> Asian <input type="checkbox"/> Other <input type="checkbox"/> Refused or Unknown Ethnic Group: <input type="checkbox"/> Hispanic or Latino <input type="checkbox"/> Not Hispanic or Latino <input type="checkbox"/> Unknown | | | |

3. Adverse Event Details

| Adverse Event(s) | Start Date (DD/MM/YY) | Stop Date (DD/MM/YY) | Outcome |
|------------------|-----------------------|----------------------|--|
| | | | <input type="checkbox"/> Recovered <input type="checkbox"/> Event ongoing <input type="checkbox"/> Recovered with sequelae. If yes, please specify: <input type="checkbox"/> Patient died <input type="checkbox"/> Unknown |
| | | | <input type="checkbox"/> Recovered <input type="checkbox"/> Event ongoing <input type="checkbox"/> Recovered with sequelae If yes, please specify: <input type="checkbox"/> Patient died <input type="checkbox"/> 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/MM/YY):
☐ Thrombosis (Date DD/MM/YY):
☐ Thrombocytopenia (platelet count <150 X 10⁹/L) (Date DD/MM/YY):

How was thrombosis diagnosed?

| | |
|---|--|
| Imaging study: <input type="checkbox"/> Ultrasound -Doppler <input type="checkbox"/> Computed Tomography (CT scan) <input type="checkbox"/> Magnetic resonance venography/arteriography (MRV/MRA) <input type="checkbox"/> Echocardiogram <input type="checkbox"/> Perfusion V/Q scan <input type="checkbox"/> Conventional angiography/Digital subtraction angiography Others, please specify the details | <input type="checkbox"/> Surgical (Procedure that confirms the presence of a thrombus (e.g. Thrombectomy): Please specify the details: _____ <input type="checkbox"/> 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

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: <input type="checkbox"/> Headache <input type="checkbox"/> Seizures If seizures, please specify type _____ No of episodes: _____ Duration of longest seizure episode: _____ <input type="checkbox"/> Photophobia <input type="checkbox"/> blurred vision <input type="checkbox"/> double vision <input type="checkbox"/> sudden visual loss <input type="checkbox"/> temporary loss of vision in one eye <input type="checkbox"/> Unconsciousness <input type="checkbox"/> Altered mental status | Cardiovascular/Respiratory: <input type="checkbox"/> Chest pain/discomfort <input type="checkbox"/> Palpitations <input type="checkbox"/> <u>Dyspnoea</u> <input type="checkbox"/> Cough <input type="checkbox"/> Cyanosis <input type="checkbox"/> Respiratory failure | Gastrointestinal and hepatic system <input type="checkbox"/> Abdominal pain | Muscular: <input type="checkbox"/> pain in legs <input type="checkbox"/> difficulty walking <input type="checkbox"/> instability <input type="checkbox"/> paralysis with weak muscles <input type="checkbox"/> problems with coordination <input type="checkbox"/> paralysis of one side of the body Speech: <input type="checkbox"/> difficulty speaking <input type="checkbox"/> slurred speech | General: <input type="checkbox"/> fatigue <input type="checkbox"/> lightheadedness Sensory <input type="checkbox"/> pins and needles <input type="checkbox"/> reduced sensation of touch <input type="checkbox"/> 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: | <input type="checkbox"/> No <input type="checkbox"/> Yes | Date and time of vaccination (DD/MM/YY / hh:mm): | Batch/Lot #: |
| Is this covid-19 vaccine AstraZeneca: <input type="checkbox"/> No <input type="checkbox"/> Yes If no, name of the vaccine (vaccine brand name or manufacturer): | | | |
| Dose 2 received: | <input type="checkbox"/> No <input type="checkbox"/> Yes | Date and time of vaccination (DD/MM/YY / hh:mm): | Batch/Lot #: |
| Is this covid-19 vaccine AstraZeneca : <input type="checkbox"/> No <input type="checkbox"/> 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: <input type="checkbox"/> No <input type="checkbox"/> Yes | | | |
| Date and time of vaccination (DD/MM/YY / hh:mm): | | Batch/Lot #: | |
| Name of the vaccine (vaccine brand name or manufacturer): | | | |

**Questionnaire for Thrombosis in combination with thrombocytopenia,
Thrombosis with thrombocytopenia syndrome (TTS)**

/Embotic 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? |
|-------------------|------------|--------------|-------|-----------------------|----------------------|--|
| | | | | | | <input type="checkbox"/> No <input type="checkbox"/> Yes |
| | | | | | | <input type="checkbox"/> No <input type="checkbox"/> Yes |
| | | | | | | <input type="checkbox"/> No <input type="checkbox"/> 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? |
|---|------------|---|--------------|-------|-----------------------|----------------------|--|
| | | | | | | | <input type="checkbox"/> No <input type="checkbox"/> Yes |
| | | | | | | | <input type="checkbox"/> No <input type="checkbox"/> Yes |
| | | | | | | | <input type="checkbox"/> No <input type="checkbox"/> 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 | <input type="checkbox"/> No <input type="checkbox"/> Yes | | |
| History of Covid-19 (please provide the date of diagnosis) | <input type="checkbox"/> No <input type="checkbox"/> Yes | | |
| CNS tumor/metastases | <input type="checkbox"/> No <input type="checkbox"/> Yes | | |
| Haemophilia/other coagulation disorders | <input type="checkbox"/> No <input type="checkbox"/> Yes | | |
| History of Heparin induced Thrombocytopenia | <input type="checkbox"/> No <input type="checkbox"/> Yes | | |
| History of Primary immune thrombocytopenia/ Thrombocytopenia | <input type="checkbox"/> No <input type="checkbox"/> Yes | | |
| History of Drug induced immune thrombocytopenia | <input type="checkbox"/> No <input type="checkbox"/> Yes | | |
| Anticoagulation / previous heparin use | <input type="checkbox"/> No <input type="checkbox"/> Yes | | |
| Therapeutic thrombolysis | <input type="checkbox"/> No <input type="checkbox"/> Yes | | |
| Sickle cell disease | <input type="checkbox"/> No <input type="checkbox"/> Yes | | |
| Disseminated intravascular coagulation | <input type="checkbox"/> No <input type="checkbox"/> Yes | | |

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

**Questionnaire for Thrombosis in combination with thrombocytopenia,
Thrombosis with thrombocytopenia syndrome (TTS)**

/Embotic 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.

1. Reporter's Information

| | | |
|---------------------|---|------------------|
| Reporter's Name: | Is Reporter a healthcare professional? <input type="checkbox"/> No <input type="checkbox"/> 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 Date of Birth (DD/MM/YYYY): _____ Age (years): _____
For female, currently Pregnant?: ☐ No ☐ Yes

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 |
|------------------|-----------------------|----------------------|--|
| | | | <input type="checkbox"/> Recovered <input type="checkbox"/> Event ongoing <input type="checkbox"/> Recovered with sequelae <input type="checkbox"/> Patient died <input type="checkbox"/> Unknown |
| | | | <input type="checkbox"/> Recovered <input type="checkbox"/> Event ongoing <input type="checkbox"/> Recovered with sequelae <input type="checkbox"/> Patient died <input type="checkbox"/> Unknown |
| | | | <input type="checkbox"/> Recovered <input type="checkbox"/> Event ongoing <input type="checkbox"/> Recovered with sequelae <input type="checkbox"/> Patient died <input type="checkbox"/> 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?

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

Were there any complications caused by the above event(s)? ☐ No ☐ Yes

If 'Yes', please provide a brief statement of complications from the event(s): _____

4. COVID-19 Vaccine

| | | | |
|--|--|--|--------------|
| Dose 1 received: | <input type="checkbox"/> No <input type="checkbox"/> Yes | Date and time of vaccination (DD/MM/YY / hh:mm): | Batch/Lot #: |
| Is this covid-19 vaccine AstraZeneca: | <input type="checkbox"/> No <input type="checkbox"/> Yes | If no, name of the vaccine (vaccine brand name or manufacturer): | |
| Dose 2 received: | <input type="checkbox"/> No <input type="checkbox"/> Yes | Date and time of vaccination (DD/MM/YY / hh:mm): | Batch/Lot #: |
| Is this covid-19 vaccine AstraZeneca : | <input type="checkbox"/> No <input type="checkbox"/> 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?

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? |
|-------------------|------------|--------------|-------|-----------------------|----------------------|--|
| | | | | | | <input type="checkbox"/> No <input type="checkbox"/> Yes |
| | | | | | | <input type="checkbox"/> No <input type="checkbox"/> Yes |
| | | | | | | <input type="checkbox"/> No <input type="checkbox"/> 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? |
|---|------------|---------------------------------------|--------------|-------|-----------------------|----------------------|--|
| | | | | | | | <input type="checkbox"/> No <input type="checkbox"/> Yes |
| | | | | | | | <input type="checkbox"/> No <input type="checkbox"/> Yes |
| | | | | | | | <input type="checkbox"/> No <input type="checkbox"/> Yes |
| | | | | | | | <input type="checkbox"/> No <input type="checkbox"/> Yes |
| | | | | | | | <input type="checkbox"/> No <input type="checkbox"/> Yes |

8. Relevant Medical History/Concurrent Diseases

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

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 Date of Birth (DD/MM/YYYY): _____ Age (years): _____

For female, currently Pregnant?: ☐ No ☐ Yes

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 |
|------------------|--------------------------|-------------------------|--|
| | | | <input type="checkbox"/> Recovered <input type="checkbox"/> Event ongoing <input type="checkbox"/> Recovered with sequelae <input type="checkbox"/> Patient died <input type="checkbox"/> Unknown |
| | | | <input type="checkbox"/> Recovered <input type="checkbox"/> Event ongoing <input type="checkbox"/> Recovered with sequelae <input type="checkbox"/> Patient died <input type="checkbox"/> Unknown |
| | | | <input type="checkbox"/> Recovered <input type="checkbox"/> Event ongoing <input type="checkbox"/> Recovered with sequelae <input type="checkbox"/> Patient died <input type="checkbox"/> 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

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| Renal system | Gastrointestinal and hepatic system | Central Nervous System | Other System |
|---|---|--|---|
| <input type="checkbox"/> Renal dysfunction <input type="checkbox"/> Acute kidney injury <input type="checkbox"/> Others | <input type="checkbox"/> Vomiting <input type="checkbox"/> Diarrhea <input type="checkbox"/> Jaundice <input type="checkbox"/> Acute liver injury <input type="checkbox"/> Ageusia <input type="checkbox"/> Others | <input type="checkbox"/> Altered mental status <input type="checkbox"/> Convulsions/seizures <input type="checkbox"/> Cranial nerve involvement <input type="checkbox"/> Unconsciousness <input type="checkbox"/> Others | <input type="checkbox"/> Acute arthritis <input type="checkbox"/> Dermatological <input type="checkbox"/> Multisystem inflammatory syndrome [MIS] <input type="checkbox"/> Multiorgan failure (please specify which organ systems were affected) <input type="checkbox"/> 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 |
|---|-----------------------|----------------------|---------------------------------|
| <input type="checkbox"/> Remdesivir | | | |
| <input type="checkbox"/> Hydroxychloroquine/chloroquine | | | |
| <input type="checkbox"/> Azithromycin | | | |
| <input type="checkbox"/> Corticosteroids | | | |
| <input type="checkbox"/> Plasmapheresis | | | |
| <input type="checkbox"/> 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? |
|-------------------|------------|--------------|-------|-----------------------|----------------------|--|
| | | | | | | <input type="checkbox"/> No <input type="checkbox"/> Yes |
| | | | | | | <input type="checkbox"/> No <input type="checkbox"/> Yes |
| | | | | | | <input type="checkbox"/> No <input type="checkbox"/> 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? |
|---|------------|---------------------------------------|--------------|-------|-----------------------|----------------------|--|
| | | | | | | | <input type="checkbox"/> No <input type="checkbox"/> Yes |
| | | | | | | | <input type="checkbox"/> No <input type="checkbox"/> Yes |

Questionnaire for

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 <input type="checkbox"/> No <input type="checkbox"/> Yes | | |
| Recent immunization <input type="checkbox"/> No <input type="checkbox"/> Yes | | |
| Lymphoma <input type="checkbox"/> No <input type="checkbox"/> Yes | | |
| HIV positive <input type="checkbox"/> No <input type="checkbox"/> Yes | | |
| Systemic lupus erythematosus <input type="checkbox"/> No <input type="checkbox"/> Yes | | |
| Vasculitis <input type="checkbox"/> No <input type="checkbox"/> Yes | | |
| Other autoimmune disorders <input type="checkbox"/> No <input type="checkbox"/> Yes | | |
| Hypertension <input type="checkbox"/> No <input type="checkbox"/> Yes | | |
| Diabetes <input type="checkbox"/> No <input type="checkbox"/> Yes | | |
| Heart Disease (please specify) <input type="checkbox"/> No <input type="checkbox"/> Yes | | |
| Lung Disease (please specify) <input type="checkbox"/> No <input type="checkbox"/> Yes | | |
| Kidney disease (please specify) <input type="checkbox"/> No <input type="checkbox"/> Yes | | |
| Obesity <input type="checkbox"/> No <input type="checkbox"/> Yes | | |
| Current or Former Smoker <input type="checkbox"/> No <input type="checkbox"/> Yes If Yes, please provide details | | |
| Other, please specify: | | |

☐ 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.