EU RMP	
Drug Substance	tixagevimab and cilgavimab
Version Number	5
Succession Number	2
Data lock point	22 February 2023
Date of final sign off	See e-signature page

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) for EVUSHELD™ (tixagevimab and cilgavimab)

QPPV Name: Magnus Ysander

QPPV oversight declaration: The content of this EU RMP has been reviewed and approved by the marketing authorisation holder´s QPPV in the EU, Magnus Ysander. The electronic signature is available on file.

ADMINISTRATIVE INFORMATION

This EU RMP (Version 5 succession 2) has been created by consolidating EU RMP V4 S2 and V5 S1.

Summary of significant changes in this RMP

Part I	No updates
Part II SI	No updates
Part II SII	No updates
Part II SIII	No updates
Part II SIV	No updates
Part II SV	No updates
Part II SVI	No updates
Part II SVII	Removed planned study in pregnant women
Part II SVIII	No updates
Part III	Removed study D8850R00006 from additional pharmacovigilance activities
Part IV	No updates
Part V	Removed study D8850R00006
Part VI	Removed study D8850R00006

Other RMP versions under evaluation	**Version number:** 5 Succession 1 **Submitted:** 30 June 2023 **Procedure Number:** EMEA/H/C/005788/II/0013
Details of currently approved RMP	**Version number:** 4 Succession **2** **Procedure Number**: EMEA/H/C/005788/II/0009/G **Date of approval:** 12 October 2023

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ANNEXES

Annexes	
Annex 1- EudraVigilance Interface	Not applicable
Annex 2- Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	Not applicable
Annex 3- Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan	Not applicable
Annex 4- Specific adverse drug reaction follow-up forms	Included
Annex 5- Protocols for proposed and ongoing studies in RMP part IV	Not applicable
Annex 6- Details of proposed additional risk minimisation activities	Not applicable
Annex 7- Other supporting data (including referenced material)	Included
Annex 8- Summary of Changes to the Risk Management Plan Over Time	Included

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	Definition/Explanation
ACE2	Angiotensin-converting enzyme 2
ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
ADCD	Antibody-dependent complement deposition
ADCP	Antibody-dependent cellular phagocytosis
ADNKA	Antibody-dependent NK cell activation
ADE	Antibody-dependent enhancement of disease
ADR	Adverse Drug Reaction
AIDS	Acquired immune deficiency syndrome
ARDS	acute respiratory distress syndrome
CDC	Centers for Disease Control and Prevention
C1q	Complement component 1q
COVID-2019	Coronavirus disease 2019
DCO	Data cut-off
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
Fc	Fraction crystallizable
FcγR	Fc gamma receptor
FcRn	Neonatal Fc receptor
GISAID	Global Initiative on Sharing Avian Influenza Data
GLP	Good Laboratory Practice
HIV	Human immunodeficiency virus
ICH	International Council for Harmonisation
ICU	Intensive care unit
Ig	Immunoglobulin
IM	Intramuscular
INN	International non-proprietary name
IV	Intravenous
mAb	Monoclonal antibody
MAH	Marketing authorisation holder

Abbreviation/ Special term	Definition/Explanation
MedDRA	Medical Dictionary for Regulatory Activities
PE	Pulmonary embolism
PI	Prescribing information
PK	Pharmacokinetic
PSUR	Periodic Safety Update Report
RBD	Receptor binding domain
RMP	Risk Management Plan
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SmPC	Summary of Product Characteristics (EU)
SMQ	Standardised MedDRA Query
SOC	System Organ Class
t1/2	Terminal half-life
TCR	Tissue cross-reactivity
TM	L234F/L235E/P331S substitutions in the immunoglobulin heavy chain to reduce Fc receptor and C1q binding
US	United States
WHO	World Health Organisation
YTE	M252Y/S254T/T256E substitutions in the immunoglobulin heavy chain to increase FcRn affinity that results in the increased half life of an antibody

I. PART I: PRODUCT OVERVIEW

Table I-1 Product Overview

Active substance(s) (INN or common name)	Tixagevimab and cilgavimab
Pharmacotherapeutic group(s) (ATC Code)	Immune sera and immunoglobulins, antiviral monoclonal antibodies (J06BD03)
Marketing Authorisation Holder	AstraZeneca AB 15185 Södertälje Sweden
Medicinal products to which this RMP refers	One
Invented name in the EEA	EVUSHELD
Marketing authorisation procedure	Centralized
Brief description of the product	Chemical class: EVUSHELD is comprised of 2 human IgG1κ mAbs (tixagevimab and cilgavimab), which are directed against the receptor binding domain of the SARS-CoV-2 spike protein.
	Summary of mode of action: The mAbs contained in EVUSHELD bind to non-overlapping epitopes on the receptor binding domain protein of the virus and block its interaction with the ACE2 host cellular receptor, resulting in a blockade of virus entry, effectively neutralizing the SARS-CoV-2 virus.
	Important information about its composition: Tixagevimab and cilgavimab are produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. EVUSHELD is a combination comprised of the 2 mAbs (tixagevimab and cilgavimab), each of which neutralizes the virus and blocks binding to its human cellular receptors. The use of 2 mAbs provides redundancy in case of virus mutation and escape. Tixagevimab and cilgavimab mAbs have been engineered with triple amino acid substitutions M252Y/S254T/T256E (YTE) in the Fc region to prolong the $t_{1/2}$, which is expected to provide protection from COVID-19 for a duration of at least 6 months. In addition, the triple amino acid substitutions L234F/L235E/P331S (TM) in the Fc region were engineered for both tixagevimab and cilgavimab to reduce Fc-mediated effector function.
Hyperlink to the Product Information	EVUSHELD, Summary of Product Characteristics

Table I-1 Product Overview

Indication(s) in the EEA	Pre-exposure prophylaxis EVUSHELD is indicated for the pre-exposure prophylaxis of COVID-19 in adults and adolescents aged 12 years older and weighing at least 40 kg. Treatment EVUSHELD is indicated for the treatment of adults and adolescents (aged 12 years and older weighing at least 40 kg) with COVID-19, who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.
Dosage in the EEA	Pre-exposure prophylaxis The recommended dose in adults and adolescents aged 12 years and older weighing at least 40 kg is 150 mg of tixagevimab and 150 mg of cilgavimab, administered as 2 separate sequential IM injections. Treatment The recommended dose in adults and adolescents aged 12 years and older weighing at least 40 kg is 300 mg of tixagevimab and 300 mg of cilgavimab, administered as 2 separate sequential intramuscular injections. EVUSHELD should be given as soon as possible after a positive viral test for SARS-CoV-2 and within 7 days of the onset of symptoms of COVID-19.
Pharmaceutical form(s) and strengths in the EEA	EVUSHELD is a solution for injection supplied in separate vials of tixagevimab and cilgavimab as 150 mg colourless to slightly yellow, clear to opalescent solutions for injection at a concentration of 100 mg/mL.
Will the product be participant to additional monitoring in the EU?	Yes

ACE2, angiotensin-converting enzyme 2; ATC, Anatomical Therapeutic Chemical [code]; COVID-19, coronavirus disease 2019; EEA, European Economic Area; EU, European Union; Fc, fraction crystallizable; Ig, immunoglobulin; IM, intramuscular; INN, International non-proprietary name; mAb, monoclonal antibody; RMP, Risk Management Plan; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; t1/2, terminal half-life.

II. PART II: SAFETY SPECIFICATION

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

Indication

- COVID-19 Prophylaxis
- Treatment of mild to moderate COVID-19

Incidence and prevalence

COVID-19 is an infectious disease caused by a novel (or new) coronavirus not previously seen in humans – severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

To date, there have been over 750 million confirmed cases of COVID-19 worldwide, including over 6.8 million deaths, reported to WHO (WHO 2023a). In Europe, there have been over 273 million confirmed cases including over 2.1 million deaths (WHO 2023a).

Since the first reports of COVID-19, infection has spread worldwide, prompting the World Health Organisation (WHO) to declare a public health emergency in late January 2020 (WHO 2020a) and characterise the novel coronavirus as a pandemic in March 2020 (WHO 2020b).

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

Individuals of any age can acquire SARS-CoV-2 infection, although the risk of severe COVID-19 increases with age. Epidemiological studies suggest that the risk for 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 ICU admission relative to adults (CDC 2020a, ECDC 2023). Patients with COVID-19 infection can experience a wide range of symptoms from mild to critical illness (ECDC 2023). Older adults, males, and persons with chronic medical conditions, including cardiovascular disease, chronic kidney disease, chronic liver disease, cancer, obesity, diabetes, pre-existing hypertension, pulmonary disease, immunosuppression, and sickle cell disease, are at increased risk of severe or critical disease (Gallo Marin et al , Beaney et al 2022, ECDC 2023)

Increasing evidence of disaggregated data from China and Europe suggest that the number of confirmed COVID-19 cases is comparable among men and women; however, men may have more severe illness and higher mortality from COVID-19 than women (Gebhard et al 2020; Beaney et al 2022). Studies from the US have also reported increased mortality with COVID-19 in male relative to female patients (Finelli et al 2021). In the US, non-Hispanic American Indian, Alaska Native, and Black and Hispanic persons have been affected

disproportionally (Tian et al 2020, Williamson et al 2020, Zheng et al 2020). Ethnicity (particularly non-White ethnicity) has been recognised as a predictor for more severe disease, and/or risk of hospitalisation in numerous studies (Gao et al 2021). Recent evidence suggests that racial disparities in COVID-19 risk were more pronounced in the early waves of the pandemic, and that such association is mediated mainly by community-level socioeconomic status, contact with suspected or confirmed COVID-19 cases, and lack of access to clinical care (Lo et al 2021, Magesh et al 2021).

The main existing treatment options

Prophylaxis

Currently, 7 first generation vaccines in the EU and 6 vaccines in the UK have been authorised or approved for active immunisation to prevent COVID-19 in adults, and 3 of these vaccines are indicated for use in children or adolescents (EMA 2023a, NHS 2023). Over 180 candidate vaccines are in clinical development and approximately 200 are in nonclinical investigation (WHO 2023b).

Despite good efficacy of COVID-19 vaccines, breakthrough infections of fully vaccinated individuals are emerging both in the general population (Hacisuleyman et al 2021) and in high-risk populations, such as patients on immunosuppressants (Geisen et al 2021), patients with haematological malignancy (Agha et al 2021), patients who have received a solid organ transplant (Boyarsky et al 2021a, Boyarsky et al 2021b), and dialysis patients (Broseta et al 2021). Data from US and Europe showed that approximately 3% of the population are unable to mount an optimal immune response to COVID-19 vaccines and are not receiving the full benefit of vaccination (Broseta et al 2021;CDC 2021; Deepak et al 2021; Rabinowich et al 2021; Simon et al 2021; Lee et al 2021).

The mAbs EVUSHELD (tixagevimab/cilgavimab) and RONAPREVE (casirivimab/imdevimab) are the only 2 non-vaccine products approved in the EU for prevention of COVID-19 in adults and adolescents aged 12 years and older (EMA 2023b).

Treatment of mild to moderate COVID-19

Patients with SARS-CoV-2 infection can experience a range of clinical manifestations, from no symptoms to critical illness.

Management of COVID-19 is based on best supportive care and emerging standard of care, with protective effects demonstrated in clinical studies for some drugs and interventions, including antivirals, anti-SARS-CoV-2 mAbs, anti-inflammatory drugs, and immunomodulators. Antivirals and mAb therapies are likely to be most effective earlier in the clinical course of disease, when SARS-CoV-2 replication is greatest, or soon after symptom onset. Anti-inflammatory drugs and immunomodulators may be used to combat the hyperinflammatory state seen in severe disease (Cascella et al 2021).

Individuals with mild disease are managed in the ambulatory setting with supportive care and isolation. Close observation over the time course of those with mild disease is advised for the elderly and those at increased risk for more severe disease due to pre-existing conditions. Where authorised, mAb therapies can be considered for outpatients who are at risk of disease progression (Cascella et al 2021).

For the treatment of mild to moderate COVID-19 in patients who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19, 4 mAbs (XEVUDY [sotrovimab], REGKIRONA [regdanvimab], RONAPREVE [casirivimab/imdevimab], EVUSHELD [tixagevimab and cilgavimab]) and 2 anti-viral therapies (VEKLURY [remdesivir], PAXLOVID [PF-07321332/ritonavir]) are authorised in the EU (EMA 2023b).

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

SARS-CoV-2 infection can be classified into 6 distinct types including asymptomatic or presymptomatic infection, as well as mild, moderate, severe, and critical illness. Transmission of SARS-CoV-2 may occur from presymptomatic, asymptomatic or symptomatic individuals (Cascella et al 2021). Early evidence suggested that viral transmission was possible from asymptomatic individuals (CDC 2020b, Lavezzo et al 2020, Oran and Topol 2020). Estimated rates of asymptomatic SARS-CoV-2 infection, however, vary widely with significant heterogeneity between studies, with an interquartile range (IQR) of estimates across 130 studies ranging from 14% to 50% (prediction interval 2% to 90%) (Buitrago-Garcia et al 2022). Symptomatic patients can experience a range of symptoms from mild to critical illness, with shifts in patterns of reported symptoms relative to dominant variants throughout the pandemic (Schulze and Bayer 2022).

Based on a large cohort study, which included > 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 et al 2021). It is worth noting that patterns of clinical outcomes have been changing throughout the pandemic, along with the changing landscape of dominant Variants of Concern, the widespread use of COVID-19 vaccines, and the improvement in both early detection and management of symptomatic cases. For example, recent research

suggested a shift towards atypical but less severe clinical presentation with Omicron vs Delta variants (Menni et al 2022).

Overall, among Chinese patients who developed severe illness, the median time to dyspnoea ranged from 5 to 8 days, the median time to ARDS ranged from 8 to 12 days, and the median time to ICU admission ranged from 10 to 12 days (Huang et al 2020, Wang et al 2020, Yang et al 2020, Zhou et al 2020). Based on early reports from China, among all hospitalised patients, a range of 26% to 32% of patients were admitted to the ICU. Among all infected 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 et al 2021), with much higher mortality observed among patients admitted to the ICU (39% to 72% depending on the study, with improvements seen in ICU mortality over the course of the pandemic (Dennis et al 2021). The median length of hospitalisation among survivors was 10 to 13 days (Chen et al 2020, Geisen et al 2021, Huang et al 2020, Wang et al 2020, Wu et al 2020, Yang et al 2020).

Data from the SEMI-COVID registry in Spain (a retrospective, multicentre national cohort study) demonstrated that immunosuppressed patients admitted to hospital with COVID-19 had statistically ($p < 0.001$) longer hospital stays than those without immunocompromise (median 10 days vs 9 days) (Suárez-García et al 2021). Immune impairment in this study was also associated with 60% higher rates of COVID-19-associated mortality compared to patients without immunocompromise, 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 (Agha et al 2021, Chen et al 2020, Wang et al 2020).
- Acute myocardial infarction is a potential risk in patients with severe systemic inflammation and hypercoagulability due to COVID-19 (Long et al 2020).
- Thromboembolic complications, including PE 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 et al 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 neutrophilia are a hallmark of severe disease (Coopersmith et al 2021). Hypercoagulability in COVID-19 is well known. Although the exact mechanisms are unclear, it is thought to be linked to cytokine-induced inflammatory response (Abou-Ismail et al, 2020).
- Laboratory evidence of 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), meningoencephalitis (Moriguchi et al 2020), acute disseminated encephalomyelitis (Paterson et al 2020), and acute necrotising encephalopathy (Poyiadji et al 2020).
  - Neurologic complications, in particular encephalopathy manifesting with agitated delirium, was common in patients with critical illness.
  - Delirium/encephalopathy was reported in approximately two thirds of patients with COVID-19-related ARDS (Helms et al 2020).
- A multisystem inflammatory syndrome with clinical features similar to those of Kawasaki disease and toxic shock syndrome has been described in children with COVID-19 (Licciardi et al 2020, Kabeerdoss et al 2021). A similar syndrome has also been reported in adults following COVID-19 (Morris et al 2020).
- Secondary infections, bacterial or fungal coinfections were reported in 8% of patients (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 coronavirus 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 et al 2021).

- Long-term complications of COVID-19 (post-acute sequelae) can develop following infection of any severity, affecting up to 1 in 5 people following acute illness from COVID-19. Although sequalae are chronic and often debilitating, long COVID remains poorly characterised in current COVID-19 prevention and treatment strategies (Iqbal et al 2021). Multiple organ systems can be affected, including respiratory, cardiovascular, nervous system, musculoskeletal, cutaneous, and neuropsychiatric manifestations (Ballering et al 2022).

The typical recovery time from COVID-19 is thought to be approximately 2 to 6 weeks for severe and critical illness (WHO 2021). However, the duration of disease is highly variable, with recovery time dependent on risk factors (including age) and comorbidities (Mizrahi et al 2020). Duration of symptoms may be higher in individuals with suboptimal immune responses (Dreyer et al 2021).

Important comorbidities

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

The risk for severe illness from COVID-19 increases with age, particularly in adults aged 70 years and older (Wu and McGoogan 2020). In addition, proposed comorbidities associated with COVID-19 severity and mortality include cardiovascular disease, chronic kidney disease, obesity, diabetes, pulmonary disease, immunosuppression (immunosuppressive disease, immunosuppressive medications), immunocompromised state (from solid organ transplant, blood or bone marrow transplant, immune deficiencies, HIV), sickle cell disease (ACEP 2020, Gallo Marin et al 2021), chronic liver disease, hypertension, and cancer.

II.2 MODULE SII: NONCLINICAL PART OF THE SAFETY SPECIFICATION

II.2.1 Summary of key findings from nonclinical data

Pharmacology

EVUSHELD is a combination of 2 monoclonal antibodies (tixagevimab and cilgavimab) that bind to the RBD of the SARS-CoV-2 spike protein. Tixagevimab and cilgavimab bind to non-overlapping epitopes on the spike protein to block its interaction with the ACE2 host cellular receptor, resulting in a blockade of virus entry to effectively neutralise SARS-CoV-2(Dong et al 2021). Tixagevimab and cilgavimab are derived from B cells of convalescent patients (Zost et al 2020). In vitro, EVUSHELD has been shown to neutralise a majority of known SARS-CoV-2 variants, including Variants of Concern (eg, Alpha, Beta, Gamma, Delta, and many Omicron variants). AstraZeneca continues to survey and monitor emergent variants and assess the in vitro neutralisation activity of EVUSHELD against them. In non-human primates, prophylactic administration of EVUSHELD prevented SARS-CoV-2 infection in a dose-

dependent manner; therapeutic administration of EVUSHELD accelerated SARS-CoV-2 clearance from the lungs and nasal mucosae of infected animals. EVUSHELD administration protected non-human primates against virus-induced lung injury and inflammation in either setting (Loo et al 2022).

The typical half-life of a human IgG is approximately 10 to 21 days, participant to recycling by FcRn (Bonilla 2008). Tixagevimab and cilgavimab were designed with the AstraZeneca proprietary technology to extend mAb t1/2 in humans (YTE; M252Y/S254T/T256E, Dall'Acqua et al 2006). The YTE substitutions have been demonstrated to safely extend mAb t1/2 to 85 to 117 days in healthy human adults in the Phase I study of nirsevimab (Griffin et al 2017) and is used in several AstraZeneca mAbs that have been studied in the clinic. Pharmacokinetic data from the completed Phase I study (D8850C00001) demonstrated a t1/2 of both tixagevimab and cilgavimab of approximately 90 days (see D8850C00001 Clinical Study Report) confirming a more than 4-fold increase in half-life relative to the 10 to 21 days normally observed for non-modified IgG1 antibodies in humans.

To reduce the theoretical risk of ADE, the 2 antibodies were engineered with amino acid substitutions (TM; L234F/L235E/P331S) in the Fc region that reduces IgG binding to FcγR and complement proteins (Oganesyan et al 2008). The TM substitutions have been used in a number of other AstraZeneca mAb programs in oncology and autoimmune diseases that have been studied in the clinic; all have shown an acceptable safety profile (Antonia et al 2018, Furie et al 2019, Imfinzi USPI, Morand et al 2020). At physiological serum concentrations, tixagevimab and cilgavimab show reduced or no binding to FcγR and C1q complement protein, and reduced or no effector function (including ADCC, ADCP, ADCD, and ADNKA). Tixagevimab and cilgavimab do not mediate any antibody-dependent infection of immune cells that do not express the ACE2 receptor. In SARS-CoV-2 challenge studies, non-human primates that received sub-neutralising concentrations of EVUSHELD showed similar viral load and lung pathology as animals that received the isotype control antibody (Loo et al 2022), supporting that EVUSHELD poses minimal risk for ADE.

The impact of EVUSHELD on vaccine-elicited immune responses were separately evaluated in a mouse and a non-human primate model. In these studies, animals were administered isotype control mAb or EVUSHELD, followed by a single IM administration of AZD1222 (the Oxford-AstraZeneca adenovirus-based COVID-19 vaccine), or 2 AZD1222 immunisations 4 weeks apart. Regardless of whether animals were immunised once or twice, those with prior EVUSHELD administration showed vaccine-elicited spike-specific T cell responses that were similar to control animals that received isotype mAb. Similarly, all vaccinated animals demonstrated similar vaccine-elicited spike- or RBD-specific antibodies, regardless of whether they received isotype control mAb or EVUSHELD prior to the immunisation. The results demonstrate that EVUSHELD administration minimally alters the cellular or the humoral immune responses that are elicited by subsequent COVID-19

vaccinations in nonclinical models. Based on these results, EVUSHELD is not anticipated to interfere with vaccine efficacy.

Toxicity

Both of the antibodies that make up EVUSHELD (tixagevimab and cilgavimab) are directed against viral targets, specifically, epitopes on the RBD of the SARS-CoV-2 spike protein. These targets are not endogenously expressed in healthy animal or human tissues. Therefore, and in accordance with ICH S6 (R1), a nonclinical safety programme, including 2 GLP TCR studies, (one in adult human and cynomolgus monkey tissues and one in foetal human tissues) and a single dose GLP toxicology study in cynomolgus monkeys, has been completed. In the first TCR study, potential target and off-target binding of each of the individual antibodies and the combination to the full panel of 32 different human and cynomolgus monkey adult tissues from 3 individual donors was assessed. In the second TCR study (Study 20282218), binding of each of the individual antibodies and the combination to a panel of human foetal tissues was assessed. In these TCR studies, no binding to any human or cynomolgus monkey adult tissues or human foetal tissues was observed.

Since both antibody components of EVUSHELD are directed at foreign targets that are not endogenously expressed in animals or humans, the rationale for species selection for the single dose toxicity study was not based on target-binding considerations. Rather, the rationale for selection of the cynomolgus monkey as the species for nonclinical safety evaluation is based on binding of these antibodies to the neonatal Fc receptor (FcRn) in the cynomolgus monkey.

<u>Key issues identified from acute or repeat-dose toxicity studies</u>

Single dose toxicity: Single dose administration of EVUSHELD via IV infusion was well tolerated in cynomolgus monkeys at single IV and IM doses of 600 mg/kg (combination of 300 mg/kg of tixagevimab and 300 mg/kg of cilgavimab) and 150 mg/kg (75 mg/kg of each antibody) respectively (Study 20249158). There were no EVUSHELD-related adverse changes in any endpoint examined. EVUSHELD-related changes were confined to mildly increased globulins on Day 2 resulting in minimal increases in the total protein and decreases in the albumin: globulin ratio. These changes were considered not to be adverse and to be related to the administration of 600 mg/kg of EVUSHELD resulting in a rise of globulin concentrations. There were no EVUSHELD-related findings in any of the other endpoints assessed in the study.

Repeated dose toxicity: No repeated dose toxicity studies have been conducted with EVUSHELD. The YTE substitutions and the resulting long half-life of both components (tixagevimab and cilgavimab) of EVUSHELD resulted in high exposure during the full 57 days of follow-up in the single dose toxicology study (Study 20249158). Therefore, additional short-term toxicity with repeated dosing was not conducted with EVUSHELD.

Reproductive/developmental toxicity

In accordance with ICH S6 (R1), no studies were conducted and no studies are planned to evaluate the effects of EVUSHELD on fertility or embryo-foetal and pre/postnatal development because EVUSHELD binds a virus-specific target that is not expressed in nonclinical animal models or in humans. Further, EVUSHELD did not bind any of the evaluated human reproductive tissues (including placenta) or human foetal tissues in TCR studies.

Genotoxicity

No genotoxicity studies have been conducted with EVUSHELD. In accordance with ICH S6 (R1), genotoxicity testing has not been conducted, and is not planned, because it is not applicable to biotechnology-derived large protein products. EVUSHELD, a combination of 2 large protein molecules, is not expected to cross the nuclear or mitochondrial membranes to interact directly with DNA or other chromosomal materials.

Carcinogenicity

In accordance with ICH S6 (R1), carcinogenicity studies have not been conducted with EVUSHELD and are not planned given that the target for this product is a virus-specific target, which is not expressed in nonclinical animal models or in humans.

Safety pharmacology

No dedicated safety pharmacology study has been conducted or is planned for EVUSHELD.

Cardiovascular safety pharmacology (electrocardiograms, heart rate, body temperature, and blood pressure), respiratory safety pharmacology (respiratory rate), and neurological safety pharmacology (neurological observational battery), were assessed as part of the single-dose toxicology study in cynomolgus monkeys. A single IV dose of 600 mg/kg of EVUSHELD did not induce any safety pharmacology effects.

II.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

Treatment of mild to moderate COVID-19

A total of 452 adult participants with mild to moderate symptomatic COVID-19 were exposed to EVUSHELD in the Phase III Study (TACKLE).

Study D8851C00001 (TACKLE) was a Phase III, randomised (1:1), double-blind, placebo-controlled clinical trial studying EVUSHELD for the treatment of adult participants with mild to moderate COVID-19. The study enrolled individuals who were not hospitalised for COVID-19 treatment and had at least one or more COVID-19 symptom that was at least mild in severity. Treatment was initiated within 3 days of obtaining the sample for a positive SARS-CoV-2 viral infection and within ≤ 7 days of COVID-19 symptom onset. Participants received standard of care treatment and either 300 mg of tixagevimab and 300 mg of

cilgavimab (N = 413) or placebo (N = 421), administered as 2 separate intramuscular injections. Participants were stratified by time from symptom onset (≤ 5 days vs > 5 days) and risk of progression to severe COVID-19 (high risk vs low risk).

The duration of follow-up ranged from 6 to 571 days post-dose, with a median duration of follow-up of 458.5 days.

Exposure data are summarised by age group and gender (Table II-1) and ethnicity (Table II-2).

Table II-1 Exposure to EVUSHELD by age group and gender - TACKLE treatment study, full analysis set

Age group	M	F
Adults (18-64 years)	185	208
Elderly		
65-74 years	17	21
75-84 years	11	10
85+ years	0	0
Totals	213	239

F, female; M, male.

Table II-2 Exposure to EVUSHELD by ethnicity -TACKLE treatment study, full analysis set

Ethnicity	Participants (%)
Hispanic or Latino	230 (50.9)
Not Hispanic or Latino	222 (49.1)
Total	452

COVID-19 prophylaxis

In the COVID-19 prophylaxis studies (D8850C00002 [PROVENT] and D8850C00003 [STORM CHASER]), a total of 4210 participants were exposed to EVUSHELD.

PROVENT was a Phase III, randomised (2:1), double-blind, placebo-controlled clinical trial studying EVUSHELD for the pre-exposure prophylaxis of COVID-19 in adults ≥ 18 years of age. All participants were individuals considered to be at increased risk for inadequate response to active immunisation (due to age ≥ 60 years, co-morbidity, pre-existing chronic illness, immunocompromised, or intolerant of vaccination) or at increased risk of SARS-CoV-2 infection (due to their location or circumstances at time of enrolment). Participants received either a single dose (administered as 2 intramuscular injections) of EVUSHELD 300 mg (150 mg of tixagevimab and 150 mg of cilgavimab administered

separately) or placebo. The study excluded participants with a history of laboratory-confirmed SARS-CoV-2 infection or SARS-CoV-2 antibody positivity at screening.

STORM CHASER was a Phase III randomised (2:1), double-blind, placebo-controlled clinical trial of EVUSHELD for the post-exposure prophylaxis of COVID-19 in adults ≥ 18 years of age. Enrolled participants were at appreciable risk of imminently developing COVID-19 following potential exposure (within 8 days) to an identified individual with a laboratory-confirmed SARS-CoV-2 infection (symptomatic or asymptomatic). Participants received a single dose (administered as 2 intramuscular injections) of EVUSHELD 300 mg (150 mg of tixagevimab and 150 mg of cilgavimab administered separately) or placebo. The study excluded participants with a history of laboratory-confirmed SARS-CoV-2 infection or SARS-CoV-2 antibody positivity at screening.

The duration of follow-up ranged from 1 to 605 days post-dose, with a median duration of follow-up of 456 days in the PROVENT study and 455 days in the STORM CHASER study.

Exposure data are summarised by age group and gender (Table II-3) and ethnicity (Table II-4).

Table II-3 Exposure to EVUSHELD by age group and gender - pooled prophylaxis clinical studies, safety analysis set

	Participants	
Age group	**M**	**F**
Adults (18-64 years)	1773	1529
Elderly		
65-74 years	386	351
75-84 years	75	78
85+ years	6	12
Totals	2240	1970

F, female; M, male.

Table II-4 Exposure to EVUSHELD by ethnicity - pooled prophylaxis clinical studies, safety analysis set

Ethnicity	Participants (%)
Hispanic or Latino	974 (23.1)
Not Hispanic or Latino	3031 (72.0)
Not reported [a]	127 (3.0)
Unknown	78 (1.9)
Total	4210

[a] Participants with missing data.

Exposure in the paediatric population

As per the DCO of 04 November 2022, a total of 30 paediatric participants have been exposed to EVUSHELD in the ongoing Phase I Study (D8850C00006 [TRUST]).

Exposure data are summarised below by age group and gender (Table II-5), and ethnicity (Table II-6).

Table II-5 Exposure to EVUSHELD by age group and gender – D8850C00006 (TRUST) study, safety analysis set

Age group	Participants	
	Male	Female
≥ 12 years to < 18 years	8	10
≥ 1 years to < 12 years	4	8
Total	12	18

Table II-6 Exposure to EVUSHELD by ethnicity – D8850C00006 (TRUST) study, safety analysis set

Ethnicity	Participants (%)
Hispanic or Latino	8 (26.7)
Not Hispanic or Latino	22 (73.3)

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

II.4.1 Exclusion Criteria in pivotal clinical studies within the development programme

Pregnant women

Reason for exclusion: Women who were pregnant were excluded from the clinical studies to avoid potential harm to the unborn foetus.

Is it considered to be included as missing information: Yes

Paediatric and adolescent patients < 18 years of age

Reason for exclusion: This population was excluded from the pivotal clinical studies based on the general principle that paediatric patients are not 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. A Phase I paediatric study (TRUST) is now ongoing, with 30 paediatric participants recruited to date.

Is it considered to be included as missing information: No

Rationale: The safety profile of EVUSHELD is not expected to be different in the indicated population of adolescents > 12 years and older weighing ≥ 40 kg from the population studied in the clinical trials as EVUSHELD is not hepatically or renally excreted. A study on paediatric population (≥ 29 weeks gestational age to less than 18 years) is ongoing (TRUST study).

History of allergy to any component of the mAbs

Reason for exclusion: Patients with known allergy/hypersensitivity to the active ingredient of the investigational medicinal product or excipients, were excluded from the clinical studies because these individuals may have a higher risk of severe hypersensitivity (anaphylactic reaction).

Is it considered to be included as missing information: No

Rationale: EVUSHELD is contraindicated in patients with known hypersensitivity to active substance or excipients; therefore, this population is not relevant to the approved indication.

Clinically significant bleeding disorder (eg, factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venipuncture

Reason for exclusion: As EVUSHELD is administered as an IM injection, patients with history of bleeding disorders were excluded from the clinical studies because they have an increased risk of injection haemorrhage or bruising following IM injection.

Is it considered to be included as missing information: No

Rationale: Prevention and management of injection site bleeding after IM injection is fully integrated into standard immunisation practice. Therefore, this population/utilisation is not relevant for consideration as missing information.

Any prior receipt of investigational or licensed vaccine or other mAb/biologic indicated for the prevention of SARS-CoV-2 or COVID-19

Reason for exclusion: Patients were excluded in order to avoid factors that may confound a complete understanding of the efficacy data of EVUSHELD and ensure interpretability of data.

Is it considered to be included as missing information: No

Rationale: This population was not excluded on the basis of safety and there is no scientific rationale to suspect that the safety profile of EVUSHELD observed in the general population

would be impacted by COVID-19 vaccination or prior treatment with a mAb/biologic indicated for the prevention of SARS-CoV-2.

EVUSHELD specifically binds to the RBD of the SARS-CoV-2 spike protein to neutralise viral entry and replication. As EVUSHELD binds to the exogenous SARS-CoV-2 target, it is not expected that there will be any impact on the safety profile for EVUSHELD in patients who have received prior treatment with a mAb that has endogenous targets. The presence of another mAb is unlikely to impact EVUSHELD PK parameters including clearance and elimination. In addition, mAbs are cleared via high capacity nonspecific endocytosis followed by lysosomal degradation. Therefore, it is unlikely that mAbs will demonstrate any PK interaction at therapeutic concentrations. Any ADAs resulting from another mAb are unlikely to affect the safety of EVUSHELD. Anti-drug-antibodies against another commercial mAb or EVUSHELD are unlikely to cross-react since mAb ADAs are typically against the highly specific target-binding epitope.

It is expected that COVID-19 vaccine may be given either before or after administration of EVUSHELD. Data from animal studies reported that 1 to 3 days prior to EVUSHELD administration did not alter the cellular or the humoral immune responses elicited by subsequent COVID-19 vaccinations (Study MCBS7442-0012). The available clinical safety data do not reveal any additional safety concerns for participants who were exposed to EVUSHELD in PROVENT and STORM CHASER and who then subsequently received COVID-19 vaccines. Based on these results, EVUSHELD is not anticipated to interfere with vaccine safety or efficacy. Although there are no clinical data available on the use of EVUSHELD following COVID-19 vaccination, there is no evidence that prior vaccination for other diseases (eg, rabies and hepatitis) impacts the safety or efficacy of subsequent immunoglobulin treatment. Therefore, the use of EVUSHELD, either prior to or following vaccination, is not relevant for consideration as missing information, and further characterisation of this population is not required.

History of infection with severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS)

Reason for exclusion: Patients were excluded to avoid factors that may confound a complete understanding of the efficacy data of EVUSHELD and ensure interpretability of data.

Is it considered to be included as missing information: No

Rationale: This population was not excluded on the basis of safety, and there is no scientific rationale to suspect that the safety profile in this population is different to that of the general target population. Further characterisation of this population is neither feasible nor warranted.

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 adverse reactions or adverse reactions with a long latency.

II.4.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Exposure of special populations included or not in the Treatment clinical trial are summarised in Table II-7 and in the Prophylaxis clinical trials are summarised in Table II-8.

Table II-7 Exposure of special populations included or not in Treatment clinical trial development programs

Type of special population	Number of participants exposed (%)
Pregnant women	Not included in the clinical development programme
Breastfeeding women	Not included in the clinical development programme
Patient with relevant comorbidities:	
Cancer	19 (4.2)
Chronic lung disease/asthma	58 (12.8)
Obesity-- those with a BMI greater than 30	195 (43.1)
Hypertension	137 (30.3)
Cardiovascular disease	42 (9.3)
Diabetes	53 (11.7)
Chronic kidney disease	10 (2.2)
Immunocompromised state	22 (4.9)
Chronic Liver Disease	7 (1.5)
Sickle cell disease	0
Smoking	180 (39.8)

BMI, Body mass index.

Table II-8 Exposure of special populations included or not in Prophylaxis clinical trial development programs

Type of special population	Number of participants exposed (%)
Pregnant women	Not included in the clinical development programme
Breastfeeding women	Not included in the clinical development programme
Patients with relevant comorbidities:	
Chronic kidney disease	214 (5.1)
Chronic obstructive pulmonary disease	192 (4.6)
Asthma	436 (10.4)

Table II-8 Exposure of special populations included or not in Prophylaxis clinical trial development programs

Type of special population	Number of participants exposed (%)
Scarring in the lungs (pulmonary fibrosis)	6 (0.1)
Type 1 diabetes	25 (0.6)
Type 2 diabetes	559 (13.3)
Sickle cell disease	2 (0.0)
Serious heart conditions	295 (7.0)
Thalassaemia (a blood disorder)	5 (0.1)
High blood pressure	1430 (34.0)
Cerebrovascular diseases	98 (2.3)
Obesity -- those with a BMI greater than 30	1765 (41.9)
Lower immune health because of a solid organ transplant	19 (0.5)
Dementia	10 (0.2)
Liver disease	203 (4.8)

BMI, Body mass index.

II.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

EVUSHELD was first authorised for emergency use in Bahrain on 14 November 2021 for pre-exposure prophylaxis indication, and has since received marketed authorisation approval in several countries, including the EU, as well as multiple early access authorisations globally.

II.5.1 Method used to calculate exposure

The global post-authorisation/marketing exposure data (including available early access) are presented by number of units distributed. It is estimated based on EVUSHELD's monthly actual ex-factory sales volume from each local marketing company.

II.5.2 Exposure

The cumulative global post-authorisation/marketing distribution data for EVUSHELD, from the first authorisation date of 14 November 2021 to 30 November 2022 has been estimated to be approximately 2621679 units.

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

Potential for misuse for illegal purposes

In view of the mechanism of action of EVUSHELD, no potential for misuse for illegal purposes exists.

II.7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

II.7.1 Identification of safety concerns in the initial RMP submission

This section describes the safety concerns at the time of RMP Version 1 approval.

II.7.1.1 Risk not considered important for inclusion in the list of safety concerns in the RMP Version 1

Reasons for not including an identified or potential risk in the list of safety concerns in the RMP

Potential risks that require no further characterisation

Serious hypersensitivity reactions including anaphylaxis: Hypersensitivity including anaphylaxis are acute serious allergic reactions with multi-organ-system involvement that can present as, or rapidly progress to, a severe life-threatening reaction requiring immediate medical attention. Acute allergic reactions may include hypotension, dyspnoea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, and unresponsiveness (including shock). Monoclonal antibodies have the potential to cause anaphylaxis and other serious hypersensitivity reactions, including immune complex disease, which could induce the development of ADA. The occurrence of such ADA could result in immune complex disease (with manifestations such as arthralgias, serum sickness, nephritis, and vasculitis) or altered EVUSHELD levels or activity.

There were no related SAEs of anaphylaxis or serious hypersensitivity reactions reported in the EVUSHELD clinical programme.

Healthcare professionals are familiar with this risk, and the management of this risk is integrated into routine medical practice when administering protein-based infusion/injection therapies. Therefore, the risk of serious hypersensitivity reactions is considered to be a potential risk not categorised as important for inclusion in the RMP. The potential risk of serious hypersensitivity, including anaphylaxis are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and risk minimisation messages in the product information are expected to be adhered to by prescribers (see Section 4.4 SmPC).

Potential risks also not considered important

Antibody-dependent enhancement of disease (ADE): ADE is a theoretical risk for all mAbs used for prevention of COVID-19. One of the syndromes of ADE involves increased binding efficiency of virus-antibody complexes to Fc receptor bearing cells, which trigger virus entry. The mAbs in EVUSHELD have been designed with a modification to prevent binding to cellular Fc receptors, so the risk of ADE occurring via this mechanism should range from very low to none. Several non~~pre~~clinical studies have been conducted to assess the potential risk of ADE following administration of EVUSHELD. The data are consistent with that from other mAbs with TM substitutions in their Fc region that reduce antibody effector function and support that EVUSHELD, and the 2 mAbs that comprise it, pose minimal theoretical risk for mediating ADE. Potential clinical outcomes resulting from ADE include lack of therapeutic effect progressing to unanticipated worsening of COVID-19, which has not been observed in the clinical trials to date. An impact on therapeutic effectiveness due to ADE is unlikely given the design of EVUSHELD. For these reasons ADE is not considered to impact the benefit-risk profile of EVUSHELD.

Cardiac and thromboembolic events: In Study D8850C00002 (PROVENT), at the DCO of 29 August 2021, there was a small numerical imbalance in SAEs in the Cardiac disorders SOC between the treatment groups (23 [0.7%] in the EVUSHELD group and 5 [0.3%] in the placebo group). There were no reports of Cardiac disorders SAEs in Study D8850C00003 (STORM CHASER) (19 August 2021 DCO). In Study D8851C00001 (TACKLE), at DCO 21 August 2021 there were 2 (0.4%) SAEs in the Cardiac disorders SOC in the EVUSHELD and 1 (0.2%) in the placebo group. None of the Cardiac disorder SAEs in the EVUSHELD group were considered related to the investigational product by the investigator. All participants who experienced cardiac disorder SAEs had cardiac-related risk factors and/or a prior history of cardiovascular disease at baseline. There was no clear temporal pattern, and a causal relationship between EVUSHELD and these events has not been established. The SAEs from SMQ Embolic and thrombotic events were also reviewed from these 2 studies (PROVENT and STORM CHASER), there is no clinically meaningful imbalance in thromboembolic events between participants who received EVUSHELD and those who received placebo. Across the cases, many participants had confounding cardiac-related medical histories and risk factors present at baseline. The cardiac and thromboembolic events will continue to be closely monitored as part of routine pharmacovigilance activities. For these reasons, cardiac and thromboembolic events are not considered to impact the benefit-risk profile of EVUSHELD and routine pharmacovigilance activities are considered sufficient to monitor these events. A specific adverse reaction follow-up targeted questionnaire for cardiac SAEs will be implemented. There are no additional pharmacovigilance activities, clinical measures, or additional risk minimisation measures in place and cardiac and thromboembolic events are not considered important.

Identified risks not considered important:

Identified risks based on class effect and route of administration that do not impact the risk benefit profile are listed below:

Injection site reactions: Injection site reactions may be observed with administration of EVUSHELD. They may manifest as local inflammation, redness, itching, pain, bruising, infection, or excessive bleeding at the site of injection. These reactions are managed according to standard clinical practice and product labelling (see Section 4.8 SmPC).

Hypersensitivity including rash and urticaria: Non-serious hypersensitivity reactions can occur with use of mAbs. These reactions are managed according to standard clinical practice and product labelling (see Section 4.8 SmPC).

II.7.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks

There are no important identified risks for EVUSHELD.

Important Potential Risks

There are no important potential risks for EVUSHELD.

Missing Information: Use in pregnant women

Pregnant women are at an increased risk for severe illness from COVID-19 compared to nonpregnant women. Therefore, it is important to further evaluate the impact of EVUSHELD in pregnant women as exposure is anticipated, and EVUSHELD is not contraindicated in this population.

Pregnant women were excluded from the clinical studies.

Risk benefit impact:

There are insufficient data to determine the safety profile in pregnant women. Nonclinical reproductive toxicity studies have not been conducted with EVUSHELD. However, a foetal TCR study demonstrated no binding to foetal tissues. Human IgG1 antibodies are known to cross the placental barrier; therefore, EVUSHELD has the potential to be transferred from the mother to the developing foetus. It is unknown whether the potential transfer of EVUSHELD provides any benefit or risk to the foetus (see Section 4.6 SmPC, “EVUSHELD should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the foetus”).

II.7.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

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

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

Important Identified Risks:

There are no important identified risks for EVUSHELD.

Important Potential Risks:

There are no important potential risks for EVUSHELD.

II.7.3.2 Presentation of missing information

Missing information: Use in Pregnant women

Evidence source: There is a limited amount of data for the use of EVUSHELD in pregnant and/or lactating women, or from women who became pregnant after receiving EVUSHELD. While nonclinical safety studies have not indicated any concerns, the effect of EVUSHELD on the foetus is unknown, as data are currently insufficient to inform on any associated risk.

Population in need of further characterisation: Use of EVUSHELD in pregnant women will be monitored via routine safety surveillance activities.

II.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

II.8.1 Summary of the safety concerns

Table II-9 summarised the safety concerns.

Table II-9 Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	Use in pregnant women

III. PART III: PHARMACOVIGILANCE PLAN

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine Pharmacovigilance Activities

AstraZeneca undertakes routine pharmacovigilance activities consistent with the International Council for 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 EVUSHELD 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.

Specific adverse reaction follow-up questionnaires for safety concerns:

There are no follow-up questionnaires for safety concerns for EVUSHELD. However, there are follow-up questionnaires in place for lack of efficacy (refer to Other forms of routine pharmacovigilance activities below) and cardiac events (refer to Section II.7.1.1).

Other forms of routine pharmacovigilance activities:

Continuous and thorough reviews of genomic databases such as GISAID for emerging Variants of Interest and Variants of Concern will be conducted. Phenotypic evaluation of specific variants that are prevalent or becoming prevalent with substitutions in or near the target epitopes of the antibodies that make up EVUSHELD will follow when appropriate. Cumulative data from these reviews will be summarised in the PSUR under the section of "Lack of efficacy from post-marketing". This PSUR section also summarises the lack of efficacy cases reported during post-authorisation use cumulatively and for the reporting interval.

A follow-up questionnaire was implemented for lack of efficacy cases from post-authorisation use.

As part of the enhanced signal detection activities for the duration of the COVID-19 pandemic, AstraZeneca will monitor data on treatment failure due to emerging variants from all available data sources, including but not limited to:

- Spontaneous cases (via targeted follow-up questionnaire for lack of efficacy including fields to request information on the variant)
- Clinical trial data from MAH and development partners
- Literature
- Studies conducted by public health authorities

If the review of the data leads to an impact on the benefit risk of the product, AstraZeneca will submit the data to EMA, including a benefit-risk discussion and any warranted product information updates within 1 month via appropriate variation procedure.

Periodic and cumulative data on the use in pregnancy will be presented in PSUR. AstraZeneca will present a tabular format for reporting numbers of individual case safety reports in the PSUR in line with the EMA draft guideline EMA/653036/2019.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable

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

This section is not applicable as no post-authorisation efficacy studies are planned.

V. PART V: RISK MINIMISATION MEASURES

V.1 ROUTINE RISK MINIMISATION MEASURES

Routine risk minimisation measures by safety concern are summarised 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	None (as there are no Important identified risks)
Important potential risks	None (as there are no Important potential risks)
Missing information	
Use in pregnant women	Routine risk communication: see Section 4.6 SmPC and Section 2 Package Leaflet Routine risk minimisation activities recommending specific clinical measures to address the risk: None

SmPC, Summary of Product Characteristics.

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

Pharmacovigilance activities and risk minimisation activities by safety concern are summarised in Table V-2.

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		
None	NA	NA
Important potential risks		
None	NA	NA
Missing information		
Use in pregnant-women	Routine Risk Minimization Measures: SmPC Section 4.6 and Package Leaflet Section 2	NA

NA, not applicable; SmPC, Summary of Product Characteristics.

VI. PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR EVUSHELD (TIXAGEVIMAB AND CILGAVIMAB)

This is a summary of the RMP for EVUSHELD. The RMP details important risks of EVUSHELD, how these risks can be minimised, and how more information will be obtained about the risks and uncertainties for EVUSHELD (missing information).

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

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

VI.1 THE MEDICINE AND WHAT IT IS USED FOR

EVUSHELD is indicated for the pre-exposure prophylaxis and treatment of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg (see SmPC for the full indication). It contains tixagevimab and cilgavimab as the active substances, and it is given by IM administration.

Further information about the evaluation of EVUSHELD’s benefits can be found in EVUSHELD’s EPAR, including in its plain-language summary, available on the EMA

website, under the medicine's webpage (https://www.ema.europa.eu/en/medicines/human/EPAR/evusheld).

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

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

VI.2.1 List of important risks and missing information

Important risks of EVUSHELD are risks that need special risk management activities to further investigate or minimise the risk (see Table VI-1 and Table VI-2), 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 EVUSHELD. 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 and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table VI-1 List of important risks and missing information

Important identified risks	None
Important potential risks	None
Missing Information	Use in pregnant women

VI.2.2 Summary of important risks

Table VI-2 Missing information: Use in pregnant women

Risk minimisation measures	Routine risk communication: SmPC Section 4.6, and Package Leaflet Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

SmPC, Summary of Product Characteristics.

VI.2.3 Post-authorisation development plan

VI.2.3.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligations of EVUSHELD.

VI.2.3.2 Other studies in post-authorisation development plan

Not applicable

LIST OF REFERENCES

Abou-Ismail et al, 2020
Abou-Ismail MY, Diamond A, Kapoor S, Arafah Y, Nayak L. The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. Thromb Res. 2020 Oct;194:101-15.

ACEP 2020
ACEP (American College of Emergency Physicians). Emergency department COVID-19 severity classification. 2020 [19 October 2020]. Available at: https://www.acep.org/globalassets/sites/acep/media/covid-19-main/acep_evidencecare_covid19severitytool.pdf. Accessed on 19 October 2020.

Agha et al 2021
Agha ME, Blake M, Chilleo C, Wells A, Haidar G. Suboptimal Response to Coronavirus Disease 2019 Messenger RNA Vaccines in Patients With Hematologic Malignancies: A Need for Vigilance in the Postmasking Era. Open Forum Infect Diseases. 2021 Jun 30;8(7): ofab353.

Antonia et al 2018
Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R et al. Overall survival with durvalumab after chemoradiotherapy in Stage III NSCLC. N Engl J Med. 2018;379(24):2342-50.

Ballering et al 2022
Ballering AV, van Zon SKR, Hartman TCO, Rosmalen JGM. Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study. Lancet 2022;400:452-61.

Buitrago-Garcia et al 2022
Buitrago-Garcia D, Ipekci AM, Heron L, Imeri H, Araujo-Chaveron L, Arevalo-Rodriguez I, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: Update of a living systematic review and meta-analysis. PLoS Med. 2022;19(5):e1003987. doi: 10.1371/journal.pmed.1003987.

Beaney et al 2022
Beaney, T, Neves AL, Alboksmaty A, Ashrafian H, Flott K, Fowler A, et al. Trends and associated factors for Covid-19 hospitalisation and fatality risk in 2.3 million adults in England. Nat Commun. 2022;13(1):2356. https://doi.org/10.1038/s41467-022-29880-7.

Bonilla 2008
Bonilla FA. Pharmacokinetics of immunoglobulin administered via intravenous or subcutaneous routes. Immunol Allergy Clin North Am. 2008;28(4):803-19.

Boyarsky et al 2021a
Boyarsky BJ, Chiang TP-Y, Ou MT, Werbel WA, Massie AB, Segev DL, Garonzik-Wang JM. Antibody Response to the Janssen COVID-19 Vaccine in Solid Organ Transplant Recipients. Transplantation. 2021 Aug 1;105(8):e82-e83. doi: 10.1097/TP.0000000000003850.

Boyarsky et al 2021b
Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, et al. Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients. JAMA. 2021 Jun 1;325(21):2204-06. doi: 10.1001/jama.2021.7489.

Broseta et al 2021
Broseta JJ, Rodríguez-Espinosa D, Rodríguez N, Mosquera MDM, Marcos MÁ, Egri N, et al. Humoral and Cellular Responses to mRNA-1273 and BNT162b2 SARS-CoV-2 Vaccines Administered to Hemodialysis Patients. Am J Kidney Dis. 2021 Oct;78(4):571-81.

Cascella et al 2021
Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, Evaluation, and Treatment of Coronavirus (COVID-19) [Updated 2021 Sep 2]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554776/. Accessed 5 November 2021.

CDC 2020a
CDC Covid-19 Response Team. Coronavirus Disease 2019 in Children - United States, February 12 - April 2, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(14):422-6.

CDC 2020b
CDC. COVID-19 pandemic planning scenarios. Updated 10 September 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html. Accessed 19 October 2020.

CDC 2021
CDC. Altered Immunocompetence. General Best Practice Guideline for Immunization: Best Practices Guidance of the Advisory Committee on Immunization Practices. [Online]. Available at: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html. Accessed 23 September, 2021.

Chen et al 2020
Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-13.

Coopersmith et al 2021
Coopersmith CM, Antonelli M, Bauer SR, Deutschman CS, Evans LE, Ferrer R, et al. The Surviving Sepsis Campaign: Research Priorities for Coronavirus Disease 2019 in Critical Illness. Crit Care Med. 2021 Apr 01;49(4):598-622.

Dall'Acqua et al 2006
Dall'Acqua WF, Kiener PA, Wu H. Properties of human IgG1s engineered for enhanced binding to the neonatal Fc receptor (FcRn). J Biol Chem. 2006;281(33):23514-24.

Danzi et al 2020
Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association? Eur Heart J. 2020;41(19):1858.

Deepak et al 2021
Deepak P, Kim W, Paley MA, Yang M, Carvidi AB, El-Qunni AA, et al. Glucocorticoids and B Cell Depleting Agents Substantially Impair Immunogenicity of mRNA Vaccines to SARS-CoV-2. medRxiv [Preprint]. 2021 Apr 9;2021.04.05.21254656. doi: 10.1101/2021.04.05.21254656.

Dennis et al 2021
Dennis JM, McGovern AP, Vollmer SJ, Mateen BA. Improving survival of critical care patients with coronavirus disease 2019 in England: a National cohort study, March to June 2020. Crit Care Med 2021;49:209–14.

Dong et al 2021
Dong, J., Zost, S.J., Greaney, A.J. et al. Genetic and structural basis for SARS-CoV-2 variant neutralization by a two-antibody cocktail. Nat Microbiol. 2021;6:1233–44.

Dreyer et al 2021
Dreyer N, Petruski-Ivleva N, Albert L, Mohamed D, Brinkley E, Reynolds M, et al. Identification of a Vulnerable Group for Post-Acute Sequelae of SARS-CoV-2 (PASC): People with Autoimmune Diseases Recover More Slowly from COVID-19. Int J Gen Med. 2021;14:3941-3949.

ECDC 2023
ECDC (European Centre for Disease Prevention and Control). Latest evidence on COVID-19. https://www.ecdc.europa.eu/en/covid-19/latest-evidence. Accessed 27 March 2023.

EMA 2023a
EMA. COVID-19 vaccines. Available from: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines. Accessed 13 March 2023.

EMA 2023b
EMA. COVID-19 treatments. Available from: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-treatments. Accessed 13 March 2023.

Finelli et al 2021
Finelli L, Gupta V, Petigara T, Yu K, Bauer KA, Puzniak LA. Mortality Among US Patients Hospitalized With SARS-CoV-2 Infection in 2020. JAMA Netw Open. 2021 Apr 01;4(4):e216556.

Furie et al 2019
Furie RA, Morand EF, Bruce IN, Manzi S, Kalunian KC, Vital EM, et al. Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trial. Lancet Rheum. 2019;1(4):e208-e19.

Gao et al 2021
Gao YD, Ding M, Dong X, Zhang J-J, Kursat Azkur A, Azkur D, et al. Risk factors for severe and critically ill COVID-19 patients: A review. Allergy. 2021 Feb;76(2):428-55. doi: 10.1111/all.14657. Epub 2020 Dec 4.

Gallo Marin et al 2021
Gallo Marin B, Aghagoli G, Lavine K, Yang L, Siff EJ, Chiang SS, et al. Predictors of COVID-19 severity: A literature review. Rev Med Virol. 2021 31:1-10. Epub 2020 Jul 30.

Gebhard et al 2020
Gebhard C, Regitz-Zagrosek V, Neuhauser HK, Morgan R, Klein SL. Impact of sex and gender on COVID-19 outcomes in Europe. Biol Sex Differ. 2020;11(1):29.

Geisen et al 2021
Geisen UM, Berner DK, Tran F, Sümbül M, Vullriede L, Ciripoi M, et al. Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort. Ann Rheum Dis. 2021 Oct;80(10):1306-11.

Griffin et al 2017
Griffin MP, Khan AA, Esser MT, Jensen K, Takas T, Kankam MK, et al. Safety, tolerability, and pharmacokinetics of MEDI8897, the respiratory syncytial virus prefusion F-targeting monoclonal antibody with an extended half-life, in healthy adults. Antimicrob Agents Chemother. 2017;61(3):e01714-16

Hacisuleyman et al 2021
Hacisuleyman E, Hale C, Saito Y, Blachere NE, Bergh M, Conlon EG, et al. Vaccine Breakthrough Infections with SARS-CoV-2 Variants. N Engl J Med. 2021 Jun 10;384(23):2212-18

Helms et al 2020
Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic Features in Severe SARS-CoV-2 Infection. N Engl J Med 2020; 382:2268-227.

Huang et al 2020
Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.

Imfinzi USPI
IMFINZI (durvalumab injection, for intravenous use). US Prescribing Information. AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA; Approval 2017. Revised 2022. Available at: https://www.azpicentral.com/imfinzi/imfinzi.pdf.

Iqbal et al 2021
Iqbal FM, Lam K, Sounderajah V, Elkin S, Ashrafian H, Darzi A. Understanding the survivorship burden of long COVID. EClinicalMedicine. 2021;33:100767. doi.org/10.1016/j.eclinm.2021.100767.

Kabeerdoss et al 2021
Kabeerdoss J, Pilania RK, Karkhele R, Kumar TS, Danda D, Singh S. Severe COVID-19, multisystem inflammatory syndrome in children, and Kawasaki disease: immunological mechanisms, clinical manifestations and management. Rheumatol Int. 2021;41:19–32. doi.org/10.1007/s00296-020-04749-4.

Klok et al 2020
Klok FA, Kripa MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020;191:145-7.

Koehler et al 2020
Koehler P, Cornely OA, Böttiger BW, Dusse F, Eichenauer DA, Fuchs F, et al. COVID-19 associated pulmonary aspergillosis. Mycoses. 2020;63(6):528-34.

Kollias et al 2021
Kollias A, Kyriakoulis KG, Lagou S, Kontopantelis E, Stergiou GS, Syrigos K. Venous thromboembolism in COVID-19: A systematic review and meta-analysis. Vasc Med. 2021 Aug;26(4):415-25. doi: 10.1177/1358863X21995566. Epub 2021 Apr 4.

Lavezzo et al 2020
Lavezzo E, Franchin E, Ciavarella C, Cuomo-Dannenburg G, Barzon L, Del Vecchio C, et al. Suppression of a SARS-CoV-2 outbreak in the Italian municipality of Vo'. Nature. 2020;584(7821):425-9.

Lee et al 2021
Lee ARYB, Wong SY, Chai LYA, Lee SC, Lee M, Muthiah MD, et al. Efficacy of COVID-19 vaccines in immunocompromised patients: A systematic review and meta-analysis. medRxiv. 2021 [Preprint].2021.09.28.21264126. Available from: https://doi.org/10.1101/2021.09.28.21264126.

Li et al 2021
Li J, Huang DQ, Zou B, Yang H, Hui WZ, Rui F, et al. Epidemiology of COVID-19: A systematic review and meta-analysis of clinical characteristics, risk factors, and outcomes. J Med Virol. 2021;93(3):1449-58. doi:10.1002/jmv.26424

Licciardi et al 2020
Licciardi F, Pruccoli G, Denina M, Parodi E, Taglietto M, Rosati S, et al. SARS-CoV-2-Induced Kawasaki-Like Hyperinflammatory Syndrome: A Novel COVID Phenotype in Children. Pediatrics. 2020;146:e20201711.

Livingston and Bucher 2020
Livingston E, Bucher K. Coronavirus disease 2019 (COVID-19) in Italy. JAMA. 2020;323(14):1335.

Lo et al 2021
Lo C-H, Nguyen LH, Drew DA, Warner ET, Joshi AD, Graham MS, et al. Race, ethnicity, community-level socioeconomic factors, and risk of COVID-19 in the United States and the United Kingdom. EClinicalMedicine. 2021;38:101029. doi:10.1016/j.eclinm.2021.101029.

Long et al 2020
Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. Am J Emerg Med. 2020 Jul;38(7):1504-7.

Loo et al 2022
Loo Y-M, McTamney PM, Arends RH, Abram ME, Aksyuk AA, Diallo S, et al. The SARS-CoV-2 monoclonal antibody combination, AZD7442, is protective in nonhuman primates and has an extended half-life in humans. Sci Transl Med. 2022 Mar 9;14(635):eabl8124. doi: 10.1126/scitranslmed.abl8124. Epub 2022.

Magesh et al 2021
Magesh S, John D, Li WT, Li Y, Mattingly-App A, Jain S, et al. Disparities in COVID-19 outcomes by race, ethnicity, and socioeconomic status: A systematic-review and meta-analysis. JAMA Netw Open. 2021;4(11):e2134147. doi:10.1001/jamanetworkopen.2021.34147.

Mao et al 2020
Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA neurology. 2020;77(6):683-90.

Mehta et al 2020
Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-4.

Menni et al 2022
Menni C, Valdes AM, Polidori L, Antonelli M, Penamakuri S, Nogal A, et al. Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-CoV-2 during periods of omicron and delta variant dominance: a prospective observational study from the ZOE COVID Study. Lancet 2022;399:1618-24. https://doi.org/10.1016/S0140-6736(22)00327-0.

Mizrahi et al 2020
Mizrahi B, Shilo S, Rossman H, Kalkstein N, Marcus K, Barer Y, et al. Longitudinal symptom dynamics of COVID-19 infection. Nat Commun. 2020;6208. doi.org/10.1038/s41467-020-20053-y

Morand et al 2020
Morand EF, Furie R, Tanaka Y, Bruce IN, Askanase AD, Richez C, et al. Trial of anifrolumab in active systemic lupus erythematosus. N Engl J Med. 2020;382(3):211-21.

Moriguchi et al 2020
Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis. 2020;94:55-8.

Morris et al 2020
Morris SB, Schwartz NG, Patel P, Abbo L, Beauchamps L, Balan S, et al. Case Series of Multisystem Inflammatory Syndrome in Adults Associated with SARS-CoV-2 Infection – United Kingdom and United States, March-August 2020. MMWR Morb Mortal Wkly Rep. 2020;69:1450–6.

Nannoni et al 2021
Nannoni S, de Groot R, Bell S, Markus HS. Stroke in COVID-19: A systematic review and meta-analysis. Int J Stroke. 2021 Feb;16(2):137-49.

NHS 2023
National Health Service (NHS). About COVID-19 vaccination. Available from: https://www.nhs.uk/conditions/coronavirus-covid-19/coronavirus-vaccination/coronavirus-vaccine. Accessed on 13 March 2023.

Oganesyan et al 2008
Oganesyan V, Gao C, Shirinian L, Wu H, Dall'Acqua WF. Structural characterization of a human Fc fragment engineered for lack of effector functions. Acta Crystallogr D Biol Crystallogr. 2008;64(Pt 6):700-4.

Oran and Topol 2020
Oran DP, Topol EJ. Prevalence of asymptomatic SARS-CoV-2 infection: A narrative review. Ann Intern Med. 2020;173(5):362-7.

Oxley et al 2020
Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. N Engl J Med. 2020;382(20):e60.

Paterson et al 2020
Paterson RW, Brown RL, Benjamin L, Nortley R, Wiethoff S, Bharucha T, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain. 2020 Oct 1;143(10):3104-20. Doi: 10.1093/brain/awaa240.

Parra et al 2020
Parra A, Juanes A, Losada CP, Álvarez-Sesmero S, Santana VD, Martí I, et al. Psychotic symptoms in COVID-19 patients. A retrospective descriptive study. Psychiatry Res. 2020;291:113254.

Petrilli et al 2020
Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ. 2020;369:m1966.

Poyiadji et al 2020
Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: imaging features. Radiology. 2020;296(2):E119-20.

Rabinowich et al 2021
Rabinowich L, Grupper A, Baruch R, Ben-Yehoyada M, Halperin T, Turner D, et al. Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients. J Hepatol. 2021;75(2):435-8.

Rawson et al 2020
Rawson TM, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, et al. Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis. 2020;71(9):2459-68. doi.10.1093/cid/ciaa530.

Richardson et al 2020
Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020;323(20):2052-9.

Rogers et al 2020
Rogers JP, Chesney E, Oliver D, Pollak TA, McGuire P, Fusar-Poli P, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatry. 2020;7(7):611-27.

Rutsaert et al 2020
Rutsaert L, Steinfort N, Van Hunsel T, Bomans P, Naesens R, Mertes H, et al. COVID-19-associated invasive pulmonary aspergillosis. Ann Intensive Care. 2020;10(1):71.

Schulze and Bayer 2022
Schulze H and Bayer W. Changes in symptoms experienced by SARS-CoV-2-infected individuals – From the first wave to the Omicron variant. Front. Virol. 2022;2:880707. doi: 10.3389/fviro.2022.880707.

Simon et al 2021
Simon D, Tascilar K, Fagni F, Krönke G, Kleyer A, Meder C, et al. SARS-CoV-2 vaccination responses in untreated, conventionally treated and anticytokine-treated patients with immune-mediated inflammatory diseases. Ann Rheum Dis. 2021;80(10):1312-6.

Suárez-García et al 2021
Suárez-García I, Perales-Fraile I, González-García A, Muñoz-Blanco A, Manzano L, Fabregate M, et al. In-hospital mortality among immunosuppressed patients with COVID-19: Analysis from a national cohort in Spain. PLoS One. 2021;16(8):e0255524.

Taquet et al 2021
Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry. 2021 May;8(5):416-27. doi: 10.1016/S2215-0366(21)00084-5. Epub 2021 Apr 6.

Tian et al 2020
Tian J, Yuan X, Xiao J, Zhong Q, Yang C, Liu B, et al. Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study. Lancet Oncol. 2020;21(7):893-903.

Toscano et al 2020
Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, et al. Guillain-Barré Syndrome associated with SARS-CoV-2. N Engl J Med. 2020;382(26):2574-6.

Varatharaj et al 2020
Varatharaj A, Thomas N, Ellul MA, Davies NWS, Pollak TA, Tenorio EL, et al. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. Lancet Psychiatry. 2020;7(10):875-82.

Wang et al 2020
Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9.

WHO 2020a
WHO (World Health Organization). Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). 30 January 2020. Available at: https://www.who.int/news/item/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov). Accessed on 20 December 2020.

WHO 2020b
WHO. WHO announces COVID-19 outbreak a pandemic. 12 March 2020. Available at: https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/3/who-announces-covid-19-outbreak-a-pandemic. Accessed on 20 December 2020.

WHO 2021
WHO (World Health Organization). Post COVID-19 condition (Long COVID). 16 October 2021. https://www.who.int/srilanka/news/detail/16-10-2021-post-covid-19-condition. Accessed 27 March 2023.

WHO 2023a
WHO (World Health Organization). WHO Coronavirus (COVID-19) dashboard. Available from: https://covid19.who.int. Accessed 13 March 2023.

WHO 2023b
WHO (World Health Organization). COVID-19 – Landscape of novel coronavirus candidate vaccine development worldwide – 10 March 2023. Available at: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines. Accessed 13 March 2023.

Williamson et al 2020
Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430-6.

Wu et al 2020
Wu C, Chen X, Cai Y, Xia Ja, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934-43.

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;323(13):1239-42. doi: 10.1001/jama.2020.2648; Online ahead of print.

Yang et al 2020
Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475-81.

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.

Zost et al 2020
Zost SJ, Gilchuk P, Case JP, Binshtein E, Chen RE, Nkolola JP, et al. Potently neutralizing and protective human antibodies against SARS-CoV-2. Nature. 2020;584(7821):443-9.

EU RMP Part VII Annex 4

Drug Substance	AZD7442 (tixagevimab and cilgavimab)

EU RISK MANAGEMENT PLAN (RMP) for AZD7442 (comprising tixagevimab and cilgavimab)

Part VII Annex 4 - specific adverse drug reaction follow-up forms

TABLE OF CONTENTS

1. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

The following specific adverse reaction follow-up questionnaires will be used to collect further information.

Questionnaire for Emergence of viral variants/ Lack of efficacy/ Antibody-dependent enhancement of disease (ADE)

Questionnaire for Embolic and Thrombotic Events

Questionnaire for Adverse Event of close monitoring Cardiac Disorders (All SAEs in Cardiac Disorder SOC)

AstraZeneca

Questionnaire for Lack of efficacy/ Antibody-dependent enhancement of disease (ADE)

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:	Sex: ☐ Male ☐ Female For female, currently Pregnant ?: ☐ No ☐ Yes	Date of Birth (*DD/MM/YYYY*):	Age (*years*):

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

3. Details of event

Date (*DD/MM/YYYY*) of first COVID-19 symptom onset and details of the symptoms with outcome:	Date (*DD/MM/YYYY*) Details of symptoms: Outcome: ☐ Recovered ☐ Recovering ☐ No improvement
SARS-CoV-2 test performed: ☐ Yes ☐ No ☐ Unknown	If Yes,please provide Date (*DD/MM/YYYY*) of SARS-CoV-2 test: Result of SARS-CoV-2 test:
Details of SARS-CoV-2 test performed:	☐ SARS-CoV-2 RT-PCR test Was the virology sample sequenced? ☐ Yes ☐ No If yes, please specify strain identified: ☐ SARS-CoV-2 antigen test: ☐ Other, please specify:
Date of diagnosis of lack of effect: (*DD/MM/YYYY*):	

Additional SARS-CoV-2 test performed: (**please attach additional COVID-19 test information such as test date, result, test type etc. if applicable**)

4. EVUSHELD administration

Indication:	Dose received choose the dose Injection: 150 mg/1.5 mL (100 mg/mL) of tixagevimab ☐ No ☐ Yes Injection: 150 mg/1.5 mL (100 mg/mL) of cilgavimab ☐ No ☐ Yes Date of EVUSHELD administration *(DD/MM/YY)*: Batch/Lot #:
	Dose received choose the dose Injection: 300 mg/3 mL (100 mg/mL) of tixagevimab ☐ No ☐ Yes Injection: 300 mg/3 mL (100 mg/mL) of cilgavimab ☐ No ☐ Yes Date of EVUSHELD administration *(DD/MM/YY)*: Batch/Lot #:

5. COVID-19 Vaccine

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

6. 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**

AstraZeneca

Questionnaire for
Lack of efficacy/
Antibody-dependent enhancement of disease (ADE)

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

☐ Remdesivir
☐ Molnupiravir
☐ Hydroxychloroquine/chloroquine
☐ Azithromycin
☐ Corticosteroids
☐ Plasmapheresis
☐ Other (Please Specify)

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

8. Relevant Medical History/Concurrent Diseases

Medical History		Start Date*(DD/MM/YY)*	Stop Date*(DD/MM/YY)*
Primary Immunodeficiency	☐ No ☐ Yes		
Secondary Immunodeficiency	☐ No ☐ Yes		
Lymphoma	☐ No ☐ Yes		
HIV positive	☐ No ☐ Yes		
Systemic lupus erythematosus	☐ No ☐ Yes		
Vasculitis	☐ No ☐ Yes		
Other autoimmune disorders	☐ No ☐ Yes		
Current or Former Smoker If Yes, please provide details	☐ No ☐ Yes		
Other, please specify:			

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

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

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

Test	Date	Results
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)		
Please provide and attach results of any relevant laboratory and diagnostic procedures performed to diagnose antibody-dependent enhancement of SARS-CoV-2 if available		
Other, please specify:		

Thank you for completing this form.

AstraZeneca

Questionnaire for Embolic and Thrombotic Events

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

1. Reporter's Information

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

2. Patient's Details

Initials: Gender at Birth: ☐ Male ☐ Female For female, currently Pregnant ?: ☐ No ☐ Yes Date of Birth (*DD/MM/YYYY*): Age (*years*):

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

3. Adverse Event Details

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

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

Please tick appropriate diagnosis; If yes, please could you provide the following further information, if available:
☐ Thrombosis with thrombocytopenia syndrome (Date DD/MMM/YYYY):
☐ Thrombosis (Date DD/MMM/YYYY):
☐ Thromocytopenia (platelet count <150 X 109/L) (Date DD/MMM/YYYY):

How was thrombosis diagnosed?

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

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

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

Please provide details about the site of Thrombosis (please check all that is applicable also provide the date of diagnosis)
☐ Arterial thrombosis
☐ Venous thrombosis
☐ Small vessels thrombosis
☐ Cerebral thrombosis
☐ Cerebrovascular venous sinus thrombosis
☐ Splanchnic vein thrombosis
☐ Coronary thrombosis
☐ Pulmonary thrombosis (emboli or thrombosis)
☐ Leg extremities thrombosis
☐ Hepatic thrombosis
☐ Renal thrombosis|
☐ Ocular thrombosis
☐ Adrenal thrombosis

AstraZeneca

Questionnaire for Embolic and Thrombotic Events

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

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

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

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

4. EVUSHELD

Indication:	Dose received choose the dose Injection: 150 mg/1.5 mL (100 mg/mL) of tixagevimab ☐ No ☐ Yes Injection: 150 mg/1.5 mL (100 mg/mL) of cilgavimab ☐ No ☐ Yes Date of EVUSHELD administration *(DD/MM/YY)*: Batch/Lot #:
	Dose received choose the dose Injection: 300 mg/3 mL (100 mg/mL) of tixagevimab ☐ No ☐ Yes Injection: 300 mg/3 mL (100 mg/mL) of cilgavimab ☐ No ☐ Yes Date of EVUSHELD administration *(DD/MM/YY)*: Batch/Lot #:

5. COVID-19 Vaccine

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

AstraZeneca

Questionnaire for
Embolic and Thrombotic Events

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

Booster	Dose received ☐ No ☐ Yes Date of Vaccination *(DD/MM/YY)*: Batch/Lot #: Manufacturer:

6. 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: _____

7. Other Suspect Drugs

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

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

If any of the above drugs were stopped, did the event(s) improve after stopping?

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

Did the event(s) recur after reintroduction?

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

8. Concomitant Drugs/ Vaccines

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

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

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

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

AstraZeneca

Questionnaire for
Embolic and Thrombotic Events

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

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

9. Laboratory Results- Before/During/After Treatment Please provide details of the relevant lab tests as applicable (attached 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)		
Heparin-induced Thrombocytopenia (HIT) PF4 Antibody ELISA		
PF4-serotonin release assay		

AstraZeneca

Questionnaire for
Embolic and Thrombotic Events

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

D-dimers, fibrinogen levels		
Serum anti-platelet antibodies		
Partial thromboplastin time (PTT)		
INR		
Total cholesterol		
Anticardiolipin (ELISA) IgM		
Anticardiolipin (ELISA) IgG		
Anti-beta 2 glycoprotein I		
Anti-prothrombin		
H pylori, HIV, HCV		
Random / Fasted blood glucose		
Ultrasound (e.g. carotid, cardiac)		
ECG		
MRI		
CT		
Cerebral angiography		
Other, please specify: Please provide and attach results of any relevant laboratory and diagnostic procedures performed, if available		

Thank you for completing this form.

AstraZeneca

Questionnaire for Adverse Event of close monitoring
Cardiac Disorders (All SAEs in Cardiac Disorder SOC)

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*):

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

3. Adverse Event Details

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

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

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

Provide the date of onset of symptoms
What was the diagnosis and date of diagnosis?

What signs and symptoms did the patient experience?

☐ Dyspnoea / Breathlessness
☐ Chest pain/discomfort
☐ Palpitations
☐ Fatigue
☐ Orthopnoea/paroxysmal nocturnal dyspnea

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

Was CPR required? ☐ Yes ☐ No

4. EVUSHELD administration

Indication:	Dose received choose the dose Injection: 150 mg/1.5 mL (100 mg/mL) of tixagevimab ☐ No ☐ Yes Injection: 150 mg/1.5 mL (100 mg/mL) of cilgavimab ☐ No ☐ Yes Date of EVUSHELD administration *(DD/MM/YY)*: Batch/Lot #:
	Dose received choose the dose Injection: 300 mg/3 mL (100 mg/mL) of tixagevimab ☐ No ☐ Yes Injection: 300 mg/3 mL (100 mg/mL) of cilgavimab ☐ No ☐ Yes Date of EVUSHELD administration *(DD/MM/YY)*: Batch/Lot #:

5. COVID-19 Vaccine status

Indication:	Dose1 received ☐ No ☐ Yes Date of Vaccination *(DD/MM/YY)*: Batch/Lot #: Manufacturer:
	Dose2 received ☐ No ☐ Yes Date of Vaccination *(DD/MM/YY)*: Batch/Lot #: Manufacturer:

AstraZeneca

Questionnaire for Adverse Event of Special Interest (AESI)

Myocardial Infarction/ Acute cardiac injury including microangiopathy, cardiogenic shock, heart failure, stress cardiomyopathy

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

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

6. How was the patient treated?

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

☐ Treatment details - ***please specify:*** _____

7. Other Suspect Drugs

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

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

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)*: _____

8. Concomitant Drugs/Concomitant Vaccines

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

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

9. Relevant Medical History/Concurrent Diseases

Medical History		**Start Date** *(DD/MM/YY)*	**Stop Date** *(DD/MM/YY)*
Previously known ischemic heart disease/ heart failure/ Valvular heart disease	☐ No ☐ Yes		
Pulmonary oedema	☐ No ☐ Yes		
Any thrombosis or embolism	☐ No ☐ Yes		
Hypertension	☐ No ☐ Yes		
Hyperlipidemia	☐ No ☐ Yes		
Diabetes mellitus	☐ No ☐ Yes		
Concomitant disease: (liver, renal, infectious, respiratory, immunological, neoplasm, etc.)	☐ No ☐ Yes		
Obesity	☐ No ☐ Yes		
Smoking	☐ No ☐ Yes		
Family medical history of cardiac diseases? Please specify	☐ No ☐ Yes		

Other, please specify:

9. Laboratory Results- Before/During/After Treatment

Please provide details of the relevant lab tests as applicable (attach test results if available).

Test	**Was the test performed?**	**Test Date (DD/MM/YY)**	**Result**

AstraZeneca

Questionnaire for Adverse Event of Special Interest (AESI)

Myocardial Infarction/ Acute cardiac injury including microangiopathy, cardiogenic shock, heart failure, stress cardiomyopathy

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

Electrocardiography (ECG)	☐ No ☐ Yes		
Echocardiography	☐ No ☐ Yes		
Coronary angiography	☐ No ☐ Yes		
Arterial Blood Gases	☐ No ☐ Yes		
Cardiac enzymes: CK-MB/ Troponin T/ Troponin N	☐ No ☐ Yes		
Blood glucose levels/ HbA1C	☐ No ☐ Yes		
Details of diagnostic test performed : Please provide details below.			

Thank you for completing this form.