Emergency Use Authorization (EUA) for
EVUSHELD (Tixagevimab 150 mg and Cilgavimab 150 mg injection co-packaged for intramuscular use)
Center for Drug Evaluation and Research (CDER) Review

Identifying Information

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number(s)[1]	EUA 000104
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	AstraZeneca Pharmaceuticals LP Stacey Cromer Berman, PhD Senior Regulatory Affairs, Director and Team Lead One MedImmune Way Gaithersburg, MD 20878 Phone: (b) (6) Email: (b) (6)
Manufacturer, if different from Sponsor	
Submission Date(s)	September 30, 2021
Receipt Date(s)	September 30, 2021
OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Reviewer Name(s)/Discipline(s)	Andrea George, Ph.D., Product Quality Reviewer Yun Wu, Ph.D., Product Quality Microbiology and Facilities Reviewer Max Van Tassell, Ph.D., Product Quality Microbiology Team Lead Zhong Li, Ph.D., Facilities Team Lead Riley Myers, Ph.D., Application Technical Lead Joanna Zhou, Ph.D., OBP/DBRRI Review Chief Thuy Thanh Nguyen, Pharm.D., OPMA/DBM Branch Chief Derek Smith, Ph.D, OPMA, Deputy Director Shamika Brooks, PharmD, MHA, BCPS, OPQ RBPM

[1] If a Pre-EUA is in existence at the time of the EUA request submission and has been assigned an EUA number, the EUA request should use the same EUA number and electronic archive file.

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Integrated Review Completion Date	December 8, 2021
Proprietary Name	EVUSHELD
Established Name/Other names used during development	AZD7442 (tixagevimab, AZD8895) injection; (cilgavimab, AZD1061) injection, co-packaged for intramuscular use
Dosage Forms/Strengths	Tixagevimab 150 mg/1.5 mL (100 mg/mL) IM Cilgavimab 150 mg/1.5 mL (100 mg/mL) IM
Therapeutic Class	SARS-CoV-2 spike protein-directed attachment inhibitor
Intended Use or Need for EUA	Pre-exposure prophylaxis of COVID-19

Intended Population(s)	Pre-exposure prophylaxis of COVID-19 in adults and pediatric individuals (12 years of age and older weighing at least 40 kg):
	• Who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 **and**
	  • Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments **and** may not mount an adequate immune response to COVID-19 vaccination **or**
	  • For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19

	vaccine(s) and/or COVID-19 vaccine component(s).
Product in the Strategic National Stockpile (SNS)	No
Distributor, if other than Sponsor	

I. EUA Determination/Declaration

On February 4, 2020, Secretary of Health and Human Services determined pursuant to section 564 of the Federal Food, Drug and Cosmetic (FD&C) Act that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad and that involves a novel (new) coronavirus (nCoV) first detected in Wuhan City, Hubei Province, China in 2019 (2019-nCoV). The virus is now named SARS-CoV-2, which causes the illness COVID-19.

On the basis of this determination, the Secretary of Health and Human Services declared that circumstances exist justifying the authorization of emergency use of drugs and biologics during the COVID-19 outbreak, pursuant to section 564 of the FD&C Act, subject to the terms of any authorization issued under that section.

II. Recommendations

A. Recommend EUA Issuance

The Division of Antivirals, Office of Infectious Diseases, Office of New Drugs, CDER recommends EUA issuance.

The EUA will authorize EVUSHELD (tixagevimab co-packaged with cilgavimab) for emergency use as pre-exposure prophylaxis of COVID-19 in adults and pediatric individuals (12 years of age and older weighing at least 40 kg):

- Who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 **and**
  - Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments **and** may not mount an adequate immune response to COVID-19 vaccination[2] **or**
  - For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s).

B. Eligibility of the Product for an EUA

[2] For additional information please see https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html. Healthcare providers should consider the benefit-risk for an individual patient.

[3] On December 3, 2021, FDA expanded the EUA for bamlanivimab and etesevimab administered together to additionally authorize bamlanivimab and etesevimab administered together for use a post-exposure prophylaxis in all adults and pediatric individuals, including neonates, who are at high-risk for progression to severe COVID-19, including hospitalization or death, subject to the terms and conditions of the authorization. At the time of this authorization, REGEN-COV is authorized for emergency use as post-exposure prophylaxis in adults and pediatric individuals (12 years of age and older weighing at least 40 kg), who are at high risk for progression to severe COVID-19, including hospitalization or death, subject to the terms and conditions of the authorization.

- COVID-19 is a serious or life-threatening disease or condition caused by SARS-CoV-2, as specified in the declaration of emergency.
- Tixagevimab and cilgavimab, the active components of EVUSHELD, are neutralizing IgG1 monoclonal antibodies that bind to distinct, non-overlapping epitopes within the receptor binding domain of the spike protein of SARS-CoV-2.
- Based on the totality of the scientific evidence available to FDA, including data from adequate and well-controlled clinical trials, it is reasonable to believe that EVUSHELD (tixagevimab co-packaged with cilgavimab) may be effective for pre-exposure prophylaxis of COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are not currently infected with SARS-CoV-2, have not recently been exposed to an individual infected with SARS-CoV-2, and who either have moderate to severe immune compromise and may not mount an adequate immune response to COVID-19 vaccination or for whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s); and when used under such conditions, the known and potential benefits of EVUSHELD outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the emergency use of EVUSHELD for use as pre-exposure prophylaxis of COVID-19 in individuals who either have moderate to severe immune compromise and may not mount an adequate immune response to COVID-19 vaccination or for whom vaccination with any available COVID-19 vaccine is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine and/or its components.
    - At present, there is one approved COVID-19 vaccine, COMIRNATY (the Pfizer-BioNTech COVID-19 Vaccine), which is indicated as a series of 2 doses for active immunization to prevent COVID-19 in individuals 16 years of age and older. COMIRNATY is an mRNA vaccine that includes within a lipid nanoparticle, a nucleoside-modified messenger RNA that encodes the viral spike glycoprotein of SARS-CoV-2. In addition to the approved use, emergency use of COMIRNATY is authorized for:
        - children 5 through 15 years of age (October 29, 2021 for 5 through 11 years of age and May 10, 2021 for 12 through 15 years of age),
        - a third dose at least 28 days following the second dose in individuals who have undergone solid organ transplantation or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise (on August 12, 2021), and
        - a booster dose at least 6 months after completing the primary series in individuals 18 years of age and older (September 22, 2021 for a limited population and November 19, 2021 for the entire adult population).

- a single booster dose as a heterologous booster dose following completion of primary vaccination with another authorized COVID-19 vaccine (October 20, 2021)

- At present, two additional COVID-19 vaccines are authorized for emergency use to prevent COVID-19: the Moderna vaccine, which is a mRNA vaccine administered as a 2-dose primary series, and the Janssen/Johnson & Johnson vaccine, which contains a replication-incompetent recombinant adenovirus type 26 vector expressing the SARS-CoV-2 spike protein in a stabilized confirmation and is administered intramuscularly as a single dose. The Moderna and Janssen vaccines are authorized for individuals 18 years of age and older. In addition, emergency use was authorized for:
  - a third dose of the Moderna vaccine administered at least 28 days following the second dose in individuals who have undergone solid organ transplantation or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise (August 12, 2021)
  - a booster dose of the Moderna vaccine at least 6 months after completing the primary series in individuals 18 years of age and older (October 20, 2021 for a limited population and November 19, 2021 for the entire adult population)
  - a booster dose of the Janssen vaccine at least 2 months after the primary vaccination in individuals 18 years of age and older (October 20, 2021)
  - a single booster dose of either the Janssen or the Moderna vaccine as a heterologous booster dose following completion of primary vaccination with another authorized COVID-19 vaccine (October 20, 2021)
- At present, there are two SARS-CoV-2 spike protein directed human IgG1 monoclonal antibody combinations, bamlanivimab and etesevimab (Eli Lilly and Company) and casirivimab and imdevimab (Regeneron Pharmaceuticals, Inc.), that are authorized for emergency use for post-exposure prophylaxis of COVID-19 in adults and pediatric individuals[3] who are at high risk for progression to severe COVID-19, including hospitalization or death, and are not fully vaccinated or who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination, and who have been exposed to an individual infected with SARS-CoV-2. Bamlanivimab and etesevimab are administered together as a single intravenous infusion, and casirivimab and

[3] On December 3, 2021, FDA expanded the EUA for bamlanivimab and etesevimab administered together to additionally authorize bamlanivimab and etesevimab administered together for use a post-exposure prophylaxis in all adults and pediatric individuals, including neonates, who are at high-risk for progression to severe COVID-19, including hospitalization or death, subject to the terms and conditions of the authorization. At the time of this authorization, REGEN-COV is authorized for emergency use as post-exposure prophylaxis in adults and pediatric individuals (12 years of age and older weighing at least 40 kg), who are at high risk for progression to severe COVID-19, including hospitalization or death, subject to the terms and conditions of the authorization.

imdevimab are administered together as either a single subcutaneous injection or as a single intravenous infusion.

III. Proposed Use and Dosing of the Product Under the EUA

Proposed Use under EUA

The Division recommends the following for inclusion in the EUA:

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of the unapproved product EVUSHELD (tixagevimab co-packaged with cilgavimab) for the pre-exposure prophylaxis of COVID-19 in adults and pediatric individuals (12 years of age and older weighing at least 40 kg):

- Who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 **and**
  - Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments **and** may not mount an adequate immune response to COVID-19 vaccination[4] **or**
  - For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s).

EVUSHELD has been authorized by FDA for the emergency use described above. EVUSHELD is not FDA-approved for any use, including use for pre-exposure prophylaxis of COVID-19.

Medical conditions or treatments that may result in moderate to severe immunocompromise and an inadequate immune response to COVID-19 vaccination include but are not limited to:

- Active treatment for solid tumor and hematologic malignancies
- Receipt of solid-organ transplant and taking immunosuppressive therapy
- Receipt of chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)
- Moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Advanced or untreated HIV infection (people with HIV and CD4 cell counts <200/mm^3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV)
- Active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents,

[4] For additional information please see https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html. Healthcare providers should consider the benefit-risk for an individual patient.
[5] AZD7442 is used in Section VIII to refer to tixagevimab and cilgavimab

antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory (e.g., B-cell depleting agents)

Limitations Of Authorized Use

- EVUSHELD is not authorized for use in individuals:
  - For treatment of COVID-19, or
  - For post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2.
- Pre-exposure prophylaxis with EVUSHELD is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended. Individuals for whom COVID-19 vaccination is recommended, including individuals with moderate to severe immune compromise who may derive benefit from COVID-19 vaccination, should receive COVID-19 vaccination.
- In individuals who have received a COVID-19 vaccine, EVUSHELD should be administered at least two weeks after vaccination.

Authorized Dosage under EUA

The recommended dosage of EVUSHELD in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) is 150 mg of tixagevimab and 150 mg of cilgavimab administered as two separate consecutive intramuscular (IM) injections.

Repeat Dosing

While SARS-CoV-2 remains in circulation, individuals who qualify for EVUSHELD per the conditions of the EUA can be redosed every 6 months.

Pregnant or Lactating Patients

No dosage adjustment is recommended in pregnant or lactating women. EVUSHELD has not been studied in pregnant or lactating women. EVUSHELD should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

Other Specific Populations

No dosage adjustment is recommended in geriatric patients. Clinical trials of EVUSHELD have included patients 65 years or older (23% of subjects in the pooled pharmacokinetic (PK) analysis), and patients 75 years or older (3.3% of the subjects in the pooled PK analysis). There was no clinically meaningful difference in the PK of tixagevimab and cilgavimab in geriatric subjects compared to younger subjects.

No dosage adjustment is recommended in individuals with renal impairment. No clinical trials have been conducted to evaluate the effects of renal impairment on the PK of tixagevimab and cilgavimab. However, neither antibody is eliminated

intact in the urine, nor catabolized by the kidney since mAbs with molecular weight >69 kDa cannot undergo glomerular filtration thus renal impairment is not expected to affect the exposure of tixagevimab or cilgavimab.

No clinical trials have been conducted to evaluate the effects of hepatic impairment on the PK of tixagevimab and cilgavimab. The impact of hepatic impairment on the PK of tixagevimab and cilgavimab is unknown.

Rationale for Dose

The pre-exposure prophylaxis dose is the same regimen that was evaluated in the randomized, double-blinded, placebo-controlled PROVENT trial in adults. Analysis of data from the PROVENT trial showed a statistically significant reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness for participants who had received a single 300 mg (150 mg tixagevimab and 150 mg cilgavimab) EVUSHELD IM dose compared to placebo at a median follow-up time of 196 days. There was no trend of decreased efficacy at Day 183. Please refer to *Section XIII Nonclinical Data to Support Efficacy* and *Section XI Human Clinical Pharmacology* for data to support adequate antiviral activity in vivo against SARS-CoV-2 viral variants at the proposed 300 mg (150 mg tixagevimab and 150 mg cilgavimab) EVUSHELD IM dosing regimen.

Rationale for Redosing (repeat dose prophylaxis)

The authorized repeat dosing regimen for pre-exposure prophylaxis is 300 mg (150 mg tixagevimab and 150 mg cilgavimab) EVUSHELD IM administered once every 6 months. Although clinical data were limited after Day 183, the available data suggest that prophylactic protection of SARS-CoV-2 RT-PCR-positive symptomatic illness persists through 6 months but may not persist beyond 6 months (Day 183; see *Section VIII Human Efficacy Data*). Additional PROVENT clinical data to inform the duration of protection are unlikely to be collected given the high rate of unblinding for vaccination by the August 2021 data cut-off (55%). The authorized repeat dosing regimen is expected to produce C_{trough} values greater than or equal to Day 183 concentrations in the PROVENT trial following a single EVUSHELD IM dose, which are close to the timepoint where the efficacy of pre-exposure prophylaxis has been demonstrated. Of note, PK and safety profile of the repeat dosing regimen has not been empirically studied. However, the totality of the clinical and clinical pharmacology evidence available supports a prospect of benefit and it is reasonable to believe the known and potential benefits outweigh the known and potential risks in certain individuals who remain at risk of infection to SARS-CoV-2 and COVID-19 disease.

IV. Product Information (Dose Preparation and Administration)

Dosage Forms And Strengths

The recommended dosage of EVUSHELD for emergency use is 150 mg of tixagevimab (dark grey vial cap) and 150 mg of cilgavimab (white vial cap) administered as two separate consecutive intramuscular injections.

Injection:

- tixagevimab 150 mg/1.5 mL (100 mg/mL) in a single-dose vial.
- cilgavimab 150 mg/1.5 mL (100 mg/mL) in a single-dose vial.

Preparation

Each EVUSHELD carton contains two vials: one of each antibody. Each vial contains an overfill to allow the withdrawal of 150 mg (1.5 mL).

- Tixagevimab and cilgavimab must be prepared by a qualified healthcare provider.
- Tixagevimab and cilgavimab are each supplied in individual single-dose vials. Do not shake the vials.
- Visually inspect the vials for particulate matter and discoloration. Tixagevimab and cilgavimab are clear to opalescent, colorless to slightly yellow solutions. Discard the vials if the solution is cloudy, discolored, or visible particles are observed.
- Withdraw 1.5 mL of cilgavimab solution and 1.5 mL of tixagevimab solution into TWO separate syringes.
- This product is preservative-free and therefore, the prepared syringes should be administered immediately. If immediate administration is not possible, and the prepared tixagevimab and cilgavimab syringes need to be stored, the total time from vial puncture to administration must not exceed 4 hours:
    - in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF), or
    - at room temperature up to 25ºC (77ºF).

Administration

- Tixagevimab and cilgavimab must be administered by a qualified healthcare provider.
- Administer the two components of EVUSHELD consecutively.
- Administer the IM injections at different injection sites, preferably one in each of the gluteal muscles, one after the other.
- Clinically monitor individuals after injections and observe for at least 1 hour.

Storage

- Store unopened vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Discard any unused portion.
- DO NOT FREEZE. DO NOT SHAKE.

V. Background Information on the Disease/Condition and Available Therapeutic Alternatives

Background Information on the Condition

The 2019 novel coronavirus, first identified in Wuhan China, and now identified as SARS-CoV-2, causes the disease named coronavirus disease 2019 (COVID-19). COVID-19 is a serious and life-threatening illness which can result in pneumonia, respiratory failure, multi-organ failure, and death.

On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic. According to the WHO, more than 257 million confirmed cases of COVID-19 caused by the 2019 novel coronavirus (SARS-CoV-2) have been reported globally as of November 23, 2021, including an estimated 5.2 million deaths. As of November 23, 2021, approximately 48 million cases of COVID-19, with more than 770,000 deaths, have been reported in the United States according to CDC.

SARS-CoV-2 variants have emerged over time and continue to emerge. According to the CDC's national surveillance report, in early January 2021 <10% of SARS-CoV-2 variants circulating in the US were variants of concern or interest. However, by the end of March 2021, approximately two thirds of SARS-CoV-2 variants circulating in the US were variants of concern or interest, with B.1.1.7 (Alpha) comprising 44% of circulating variants at the time. B.1.1.7 was supplanted as the most prevalent variant in the US in June 2021 by the Delta variant (B.1.617.2 and AY lineages), which accounted for 97% of circulating SARS-CoV-2 in the US, as well as most SARS-CoV-2 globally, by August 2021. In November 2021, the Omicron (B.1.1.529) variant was detected in South Africa and has spread globally; characteristics of this variant, including its susceptibility to currently authorized treatments, are still being discovered.

Patients with symptomatic SARS-CoV-2 infection (i.e., COVID-19) can experience a wide range of clinical manifestations, with disease severity ranging from mild to severe. Severe illness is defined as hospitalization, admission to the intensive care unit, mechanical ventilation, or death. The progression of SARS-CoV-2 infection to severe COVID-19 can occur in adults of any age, but the risk increases with age. Per the CDC, over 80% of COVID-19 deaths occur in adults aged 65 years and older, and more than 95% of COVID-19 deaths occur in adults aged 45 years and older. Irrespective of age, certain underlying comorbidities or conditions, such as cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity, type 2 diabetes, pregnancy, and immunocompromised states, increase the risk of progression to severe COVID-19. People who have experienced long-standing systemic health and social inequities, such as many racial and ethnic minorities and those with disabilities, are also at increased risk of worse outcomes (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html).

The respiratory presentation in adolescents has been similar to that in adults. The disease is typically milder in children, but a small proportion have experienced severe disease that requires treatment in an ICU and prolonged mechanical ventilation (Götzinger et al., 2020).

Prevention Alternatives

There is no adequate, approved, and available alternative to the emergency use of tixagevimab and cilgavimab administered as pre-exposure prophylaxis of COVID-19 as described in Section II of this memorandum.

On August 2, 2021, the Pfizer-BioNTech COVID-19 vaccine (also known as COMIRNATY) was approved for use by FDA. It is indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. This vaccine, originally authorized for emergency use on December 11, 2020, contains nucleoside-modified messenger RNA encoding the spike glycoprotein of SARS-CoV-2 and is administered intramuscularly as a series of two doses 3 weeks apart. Since the original EUA, the Pfizer-BioNTech COVID-19 vaccine EUA has been expanded to include children 5 through 15 years of age, and a booster dose administered at least 6 months after the primary series in individuals 18 years of age and older (see Section IIC above). Information on the EUAs for COVID-19 vaccines is available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#vaccines.

There are currently two additional vaccines against COVID-19 that are authorized for emergency use in adults 18 years of age and older:

- The Moderna COVID-19 vaccine, which contains nucleoside-modified messenger RNA encoding the pre-fusion stabilized spike glycoprotein of SARS-CoV-2.
- The Janssen COVID-19 vaccine which contains a recombinant, replication-incompetent human adenovirus type 26 vector that expresses the spike protein in a stabilized confirmation.

COVID-19 vaccination is recommended for everyone 5 years and older for the prevention of COVID-19 in the US (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html). The Advisory Committee on Immunization Practices (ACIP) has recommended the FDA-approved or authorized COVID-19 vaccines, consistent with their approval or authorizations.

The CDC considers a history of the following to be a contraindication to vaccination with COVID-19 vaccines:

- Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a component of the COVID-19 vaccine
- Immediate allergic reaction of any severity to a previous dose or known (diagnosed) allergy to a component of the vaccine.

In addition, the CDC recommends that persons with a history of myocarditis or pericarditis after a dose of an mRNA COVID-19 vaccine should defer receiving a subsequent dose.

Individuals with certain immunocompromising conditions, like solid organ transplant recipients, are less likely to mount a detectable antibody response to

COVID-19 vaccination compared to immunocompetent individuals. Several small studies found that only 20-40% of solid organ transplant recipients and 38-89% of individuals on hemodialysis have an antibody response after the two dose mRNA COVID-19 vaccines; a third dose led to an antibody response in 33-50% of individuals who had no detectable antibody response to the initial series (https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-13/02-COVID-Dooling-508.pdf). On August 12, 2021, the FDA amended the EUAs for the Pfizer-BioNTech and Moderna COVID-19 vaccines to allow for the use of an additional dose for certain immunocompromised individuals. The CDC now recommends that people with moderately to severely compromised immune systems receive an additional dose of mRNA COVID-19 vaccine at least 28 days after the initial 2 doses.

Based on the safety and efficacy demonstrated and the widespread availability of COVID-19 vaccines in the US, a Limitation of Authorized Use stating that administration of EVUSHELD is not a substitute for vaccination against COVID-19 will be included in the Fact Sheet for Healthcare Providers. In addition, recommendations on the timing of EVUSHELD in relation to vaccine receipt for immunocompromised individuals will be included in the Fact Sheet for Healthcare Providers. Similar messaging will be included in the Fact Sheet for Patients, Parents and Caregivers.

VI. Related Regulatory Submission(s)

EVUSHELD (tixagevimab co-packaged with cilgavimab), has been studied under IND 150712 in a Phase 1 dose-ranging trial (both IV and IM administration), two Phase 3 prophylaxis trials using 300 mg IM, and one Phase 2/3 treatment trial in non-hospitalized adults using 600 mg IM (Sponsor: AstraZeneca Pharmaceuticals LP). EVUSHELD has also been studied under two separate INDs in the Phase 2/3 master platform trials:

- ACTIV-2 in non-hospitalized adults with COVID-19 (IND 151193, Sponsor: NIAID/NIH)
- ACTIV-3 in patients hospitalized with COVID-19 (IND 151543, Sponsor: NIAID/NIH)

In addition to the above-mentioned cross-referenced submissions, the following related Master Files are referenced for EVUSHELD:

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- (b) (4)
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VII. Summary of Clinical Data

The data to support the authorization of EVUSHELD were generated from the primary analysis from the ongoing Phase 3 trial PROVENT. Additional data from the Phase 1 trial D8850C00001 and a subgroup analysis of the Phase 3 trial STORM CHASER were also reviewed (***Table 1***). The Applicant initially requested authorization for prevention of COVID-19 to include both pre- and post-exposure prophylaxis, which is why an assessment of EVUSHELD for post-exposure prophylaxis is included in this review.

Tixagevimab and cilgavimab are also being studied in four ongoing treatment trials. However, aside from limited select safety data submitted per FDA request, data from these treatment trials were not submitted to support this EUA.

1. A 600 mg IM dose is being studied in TACKLE, a Phase 3 COVID-19 treatment trial in 910 non-hospitalized adults.
2. Both a 300 mg IV dose and 600 mg IM dose are being studied in ACTIV-2, a Phase 2/3 platform COVID-19 treatment trial in non-hospitalized adults (AstraZeneca opted not to continue in ACTIV-2 beyond the Phase 2 portion).
3. A 600 mg IV dose is being studied in ACTIV-3, a Phase 2/3 platform COVID-19 treatment trial in hospitalized adults. Tixagevimab and cilgavimab passed the futility analysis and continued into Phase 3.
4. A 600 mg IV dose is being studied in DisCoVeRy, a Phase 3 platform COVID-19 treatment trial in hospitalized adults.

Table 1: Clinical Trials with Data Submitted to Support this EUA Application

Study Number	IND, NDA, or Literature Reference	Type of Study	Population (N)	Study Design and Type of Control	Test Product(s); Dosing Regimens; Dosage Forms; Routes of Administration; Duration	Study Status
PROVENT (D8550C00002) NCT04625725	IND 150712	Efficacy, Safety, PK	**5197** adults at high risk for inadequate vaccine response or for SARS-CoV-2 exposure	Phase 3 randomized (2:1), double-blind, placebo-controlled trial	Single IM administration: 300 mg IM AZD7442 or placebo Assessments to Day 457, but primary endpoint measured through Day 183*	Ongoing but enrollment complete.
STORM CHASER (D8850C00003) NCT04625972	IND 150712	Efficacy, Safety, PK	**1121** asymptomatic adults within 8 days of exposure with documented SARS-CoV-2 infection	Phase 3 randomized (2:1), double-blind, placebo-controlled trial	Single IM administration: 300 mg IM AZD7442 or placebo Assessments to Day 457, but primary endpoint measured through Day 183*	Ongoing but enrollment complete.
D8850C00001, NCT04507256	IND 150712	Safety, PK, PD	**60** healthy adults	Phase 1, first in human, randomized (10:2), double-blind, placebo-controlled, single ascending dose trial	Single administrations of the following AZD7442 doses versus placebo: 300 mg IM, 300 mg IV, 1000 mg IV, and 3000 mg IV, and 3000 mg IV co-administered Assessments to Day 361	Ongoing but enrollment complete.

IND = investigational new drug application, PK = Pharmacokinetics; PD = Pharmacodynamics; IM = intramuscular; AZD7442 = tixagevimab and cilgavimab administered separately in a 1:1 ratio (e.g., 300 mg AZD7442 equals 150 mg tixagevimab plus 150 mg cilgavimab); IV = intravenous infusion
*Although the primary endpoint was measured through Day 183, the primary analyses for both PROVENT and STORM CHASER were endpoint driven, and the median durations of follow-up at the data cutoffs for the primary analyses were only 83 and 49 days, respectively. However, post-hoc analyses with later data cutoffs (median duration of follow-up approximately 6 months) were submitted midway through the EUA review.
Sources: EUA request Section 6.2, the individual study protocols, and clinicaltrials.gov (for the NCT numbers).

VIII. Human Clinical Efficacy[5]

PROVENT Trial

Trial Design

PROVENT is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study assessing the safety and efficacy of a single IM dose of AZD7442 compared to placebo for the prevention of COVID-19. Approximately 100 sites were to participate in this study. Subjects were adults ≥ 18 years of age who were candidates for benefit from passive immunization with antibodies, defined as having increased risk for inadequate response to active immunization (predicted poor responders to vaccines or intolerant of vaccine), or having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19, based on available risk assessment at time of enrollment. Subjects were enrolled into one of 2 cohorts:

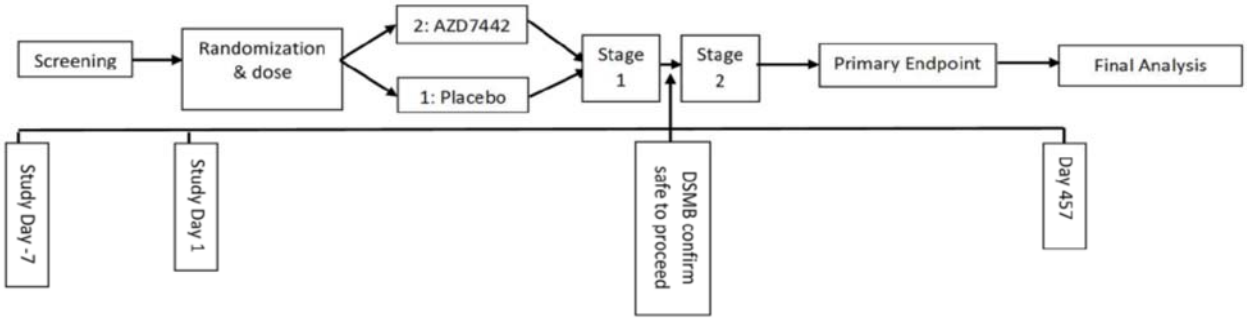
- Cohort 1: Adults ≥ 60 years of age. All subjects were considered as being at increased risk for inadequate response to active immunization on the basis of age (presumed immunosenescence). Cohort 1 was to be capped, not to exceed 80% of total subjects randomized. Within this cohort, randomization was stratified by residence in a long-term care facility or not.

- Cohort 2: Adults < 60 years of age. Cohort 2 was to be capped, not to exceed 80% of total subjects randomized. Within this cohort, randomization was stratified by risk of exposure to infection with SARS-CoV-2.

Following a screening period of ≤ 7 days, approximately 5150 subjects were to be randomized in a 2:1 ratio to receive a single dose of either 300 mg of AZD7442 (N = approximately 3433) or saline placebo (N = approximately 1717) on Day 1. Subjects were enrolled into the study in 2 stages, contingent upon safety evaluation of 7-day safety data of Stage 1 enrollment by an independent DSMB and its recommendation to proceed to Stage 2: approximately 300 subjects in Stage 1, followed by approximately 4850 subjects in Stage 2. After administration of the dose of AZD7442 or placebo on Day 1, subjects were followed for 15 months (until Day 457). Subjects in Stage 1 and Stage 2 were combined in the planned analyses.

[5] AZD7442 is used in Section VIII to refer to tixagevimab and cilgavimab

Figure 1: Study Design



Following screening (-7 to 0 days), randomization was to occur in 2 stages and was contingent on safety. The planned primary analysis was to occur after approximately 24 primary endpoint events were confirmed or 30% of study subjects became unblinded. The final analysis was to be conducted when all subjects completed the study (Day 457).
Source: Figure 1 of PROVENT Study Protocol-9.0

Subjects had scheduled visits on Days 1, 8, 29, 58, 92, 183, 366 and 457, as well as an early discontinuation visit. To determine the incidence of infection, study sites contacted subjects weekly (telephone/email/text) through Day 366 with reminders to monitor for COVID-19 symptoms. Subjects who presented with a COVID-19 qualifying symptom(s) after Day 1 were instructed to initiate Illness Visits and were tested locally for SARS-CoV-2.

Eligibility Criteria

Adults ≥ 18 years of age who are candidates for benefit from passive immunization with antibodies, defined in the protocol as either of the following:

a) Having increased risk for inadequate response to active immunization (predicted poor responders to vaccines OR intolerant of vaccine), defined as:
   - elderly ≥ 60 years,
   - obese, i.e., BMI ≥ 30,
   - congestive heart failure,
   - chronic obstructive pulmonary disease,
   - chronic kidney disease,
   - chronic liver disease,
   - immunocompromised state (HIV infection, blood or bone marrow transplant, immune deficiencies, solid organ transplant, or use of immunosuppressive therapy),
   - intolerant of vaccine

b) Having increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to

SARS-CoV-2 and COVID-19, based on available risk assessment at time of enrollment. (e.g., health care workers, workers in industrial settings, military personnel in high density settings, students in dormitory settings)

In addition, subjects should:

- Be medically stable
- Have a negative result from point of care SARS-CoV-2 serology testing at screening
- Have no evidence of acute illness, including fever
- Have no history of receipt of a COVID-19 vaccine or other mAb/biologic indicated for the prevention of SARS-CoV-2, and no history of SARS-CoV-2, SARS, or MERS infection

Analysis Sets

All participants analysis set: All subjects screened for the study, to be used for reporting disposition and screening failures.

Full analysis set: All randomized subjects who received at least one dose of AZD7442 or placebo, irrespective of their protocol adherence and continued participation in the study. Subjects were analyzed according to their randomized treatment irrespective of whether or not they have prematurely discontinued, according to the intent-to-treat principle. Subjects who withdrew consent or assent to participate in the study were included up to the date of their study termination.

Full pre-exposure analysis set: The full pre-exposure analysis set included all subjects in the full analysis set without having had a prior SARS-CoV-2 RT-PCR-positive confirmed COVID-19 infection (including a positive test taken at baseline that resulted after receipt of AZD7442 or placebo).

Safety analysis set: The safety analysis set consisted of all subjects who had received at least one dose of AZD7442 or placebo. Erroneously-treated subjects (e.g., those randomized to treatment A, but were actually given treatment B) are accounted for in this analysis set by assigning them to the treatment they actually received. A subject who had on one or several occasions received active AZD7442 was classified as active.

Endpoints

The primary endpoint is the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose of AZD7442 or placebo through Day 183. Subjects were to be included in the primary endpoint if they had RT-PCR-confirmed SARS-CoV-2 and met the qualifying symptoms summarized in ***Table 2***.

The key secondary endpoint was the incidence of subjects who had a post-treatment response (negative at baseline to positive at any time post-baseline) for SARS-CoV-2 nucleocapsid antibodies.

Other Secondary Endpoints included:

- The incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring post dose.
- The incidence of COVID-19-related Emergency Department visits occurring post dose.

Table 2 COVID-19 Qualifying Symptoms, PROVENT and STORM CHASER

Subject must present with at least one of the following symptoms:	
Duration	**Symptom**
No minimum duration	Fever
	Shortness of breath
	Difficulty breathing
	New onset confusion (only for subjects ≥ 60 yo)
	Appetite loss or decrease food intake (only for subjects ≥ 60 yo)
	Increased supplemental oxygen requirement (only for subjects ≥ 60 yo on baseline supplemental oxygen)
Must be present for ≥ 2 days	Chills
	Cough
	Fatigue
	Muscle aches
	Body aches
	Headache
	New loss of taste
	New loss of smell
	Sore throat
	Congestion
	Runny nose
	Nausea
	Vomiting
	Diarrhea

Source: Adapted from Table 9 of PROVENT Study Protocol-9.0

Estimands

The primary estimand used for the analysis of the primary efficacy endpoint was based on subjects in the full analysis pre-exposure set. For subjects with multiple events, only the first occurrence was used for the primary efficacy endpoint analysis. The set of intercurrent events for this estimand consists of subjects who became unblinded to treatment assignment and/or received a COVID-19 vaccine or other COVID-19 preventive product, in both cases prior to having met the primary efficacy endpoint. The intercurrent events were handled using a 'while on treatment' strategy, where subjects who experienced an intercurrent event were censored at the date of unblinding/receipt of first dose of COVID-19 product, whichever is earlier, within the primary estimand. Absence of data following subjects' withdrawal prior to having met the primary efficacy endpoint was treated as missing and subjects were considered as not having the event through the time of last observation. Deaths that are caused by COVID-19 and all hospitalizations due to COVID-19 were also considered as primary efficacy endpoints.

An estimand using the 'treatment policy' strategy, in which subjects who became unblinded to treatment assignment *were* included and analyzed regardless, was the first of two key supportive analyses of the primary endpoint and was included in the multiple testing hierarchy. A second key supportive analysis, in which the endpoint was defined as first case of SARS-CoV-2 RT-PCR-positive symptomatic illness or death from any cause post dose of AZD7442 or placebo and prior to Day 183, was also performed and was included in the multiple testing hierarchy.

Statistical Methodology

The Poisson regression model with robust variance (Zou 2004) was used to analyze the primary efficacy endpoint, which included age group (≥ 60 years, < 60 years) as the covariate as well as the log of the follow-up time as an offset. The efficacy was estimated from the model, which gives the relative risk reduction (RRR) in the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness. The efficacy is calculated as RRR = 100% × (1-relative risk), which is the incidence of infection in the AZD7442 group relative to the incidence of infection in the control group, expressed as a percentage. Following the same methodology outlined for the primary endpoint, each of these secondary endpoints were analyzed by a separate Poisson regression model with robust variance and they included age as a baseline covariate.

Methods to Control Multiplicity

A hierarchical approach was used to control for multiplicity of the primary, key supportive, and key secondary efficacy analyses. That is, the null hypotheses for these efficacy endpoints were tested in a hierarchical order, and the subsequent null hypothesis was tested at a significance level of 0.05 (2-sided) only if the prior null hypothesis was rejected (i.e., the treatment effect on the efficacy endpoint is

demonstrated at the significance level of 2-sided 0.05). The hierarchical approach included the below analyses as ordered:

1. The primary efficacy endpoint was assessed in the primary analysis, using the primary estimand, after approximately 24 primary endpoint events had been confirmed or 30% of study subjects had become unblinded, whichever occurred earlier. All primary endpoint events accrued up until the data cut-off were included in the primary analysis.

2. If the statistical significance of the primary efficacy endpoint is demonstrated at a 2-sided alpha of 0.05, a formal assessment of the primary endpoint using the first key supportive estimand (treatment policy strategy) would be conducted.

3. If the statistical significance of the first key supportive analysis of the primary endpoint is demonstrated at a 2-sided alpha of 0.05, a formal assessment of the primary endpoint using the second key supportive estimand (including death due to any cause) would be conducted.

4. If the statistical significance of the second key supportive analysis of the primary endpoint is demonstrated at a 2-sided alpha of 0.05, a formal assessment of the key secondary efficacy endpoint would be conducted.

Efficacy Results

Subject Disposition

In the PROVENT study, there were 3,500 and 1,754 subjects randomized to the AZD7442 and placebo arms respectively, with 98.9% and 99.0% of the subjects included in the full analysis set (FAS) and 98.3% and 98.7% of subjects included in the full pre-exposure analysis set (see ***Table 3***). Both analysis sets excluded subjects who were randomized and not dosed, 1.1% and 1.0% of subjects, with the full pre-exposure analysis set also excluding subjects with a prior SARS-CoV-2 positive confirmed COVID-19 infection, 0.5% and 0.3% of subjects.

As this study was ongoing during the May 5, 2021 data cut-off, no subjects had completed the study and the mean duration from first dose of AZD7442 or placebo to the primary analysis was approximately 84 days in each study arm. Early discontinuation rates were slightly lower in the AZD7442 arm compared to the placebo arm, 2.6% versus 3.1% (see ***Table 4***). The reasons for discontinuation were generally similar between treatment arms.

Approximately 30% of subjects were unblinded, 28.9% in the AZD7442 arm versus 31.0% in the placebo arm. As would be expected, the percentage of randomized subjects opting to receive the COVID-19 vaccination was lower in the AZD7442 arm compared to the placebo arm, 12.2% versus 30.2%. Although this difference appeared to be a disadvantage for the AZD7442 arm, the primary analysis of the

study was not affected by this difference since subjects were censored upon being unblinded under the while-on-treatment estimand, as discussed later.

Table 3: Key Analysis Sets, PROVENT (All Randomized Subjects)

Characteristic, n (%)	**AZD7442**	**Placebo**
Subjects Randomized	**3500 (100)**	**1754 (100)**
Subjects in Full Analysis Set (FAS)	**3460 (98.9)**	**1737 (99.0)**
Reason for Exclusion:		
Randomized and not dosed	40 (1.1)	17 (1.0)
Subjects in Full Pre-Exposure Analysis Set	**3441 (98.3)**	**1731 (98.7)**
Reason for Exclusion:		
Randomized and not dosed	40 (1.1)	17 (1.0)
Prior SARS-CoV-2 positive confirmed COVID-19 infection	19 (0.5)	6 (0.3)

Source: Adapted from EUA PROVENT Table 14.1.3

Table 4: Subject Disposition, PROVENT (All Randomized Subjects)

Characteristic, n (%)	**AZD7442**	**Placebo**
Subjects Randomized	**3500 (100)**	**1754 (100)**
Ongoing in Study	3409 (97.4)	1700 (96.9)
Completed Study[1]	0	0
Discontinued early from study	91 (2.6)	54 (3.1)
Due to Death	4 (0.1)	4 (0.2)
Due to AE	0	0
Lost to follow-up	11 (0.3)	8 (0.5)
Withdrawal by subject	(b) (4)	
Protocol deviation		
Physician decision		
Other	18 (0.5)	10 (0.6)
Subject unblinded	1012 (28.9)	543 (31.0)
Received COVID-19 vaccination	426 (12.2)	529 (30.7)

Source: Adapted from EUA PROVENT Table 14.1.1.1
1- As this study was ongoing during May 5, 2021 data cut-off, no subjects had completed the study and the mean duration from first dose of AZD7442 or placebo to primary analysis was approximately 84 days in each study arm.

Demographic and Baseline Characteristics

Demographic and baseline characteristics were generally well-balanced between the treatment groups (see **Table *5***). The mean age of subjects was 53.6 years and 53.3 years in the AZD7442 and placebo groups respectively. There were also no

substantial differences between treatment groups across subgroups based on the variables of age group, region, sex, ethnicity and race. Baseline risk factors were also generally well-balanced between the treatment groups.

Table 5: Demographic and Baseline Characteristics, PROVENT (FAS)

Characteristic	AZD7442 (N=3460)	Placebo (N=1737)
Age		
Mean (SD)	53.6 (15.0)	53.3 (14.9)
Median (Min, Max)	57 ((b) (4))	57 ((b) (4))
Age Group, n (%)		
18 to 59	1960 (56.6)	980 (56.4)
60 to 74	1352 (39.1)	687 (40.0)
75 and over	148 (4.3)	70 (4.0)
Region, n (%)		
North America	2487 (71.9)	1232 (70.9)
United Kingdom	611 (17.7)	312 (18.0)
European Union	362 (10.5)	193 (11.1)
Sex, n (%)		
Male	1865 (53.9)	935 (53.8)
Female	1595 (46.1)	802 (46.2)
Ethnicity, n (%)		
Hispanic or Latino	539 (15.6)	215 (12.4)
Not Hispanic or Latino	2731 (78.9)	1412 (81.3)
Not reported	116 (3.4)	72 (4.1)
Unknown	74 (2.1)	38 (2.2)
Race, n (%)		
White	2545 (73.6)	1249 (71.9)
Black or African American	597 (17.3)	302 (17.4)
Asian	110 (3.2)	60 (3.5)
Other	38 (1.1)	26 (1.5)
Not Reported, Unknown, Missing	170 (4.9)	100 (5.8)
Baseline BMI (kg/m^2) [2]		
Mean (SD)	29.6 (6.9)	29.6 (6.9)
Median (Min, Max)	28.6 ((b) (4))	28.4 ((b) (4))
Resident in long-term care facility, n (%)		
Yes	14 (0.4)	12 (0.7)
No	3446 (99.6)	1725 (99.3)
Smoking status, n (%)		
Never	1953 (56.4)	960 (55.3)
Former	785 (22.7)	407 (23.4)
Current	720 (20.8)	370 (21.3)
Missing	2 (0.1)	0
ECOG performance status, n (%)		
0	3114 (90.0)	1571 (90.4)
1	210 (6.1)	102 (5.9)
>1	58 (1.7)	30 (1.7)
Missing	78 (2.3)	34 (2.0)

SARS-CoV-2 status, n (%)		
Positive[1]	19 (0.5)	6 (0.3)
Negative	3334 (96.4)	1672 (96.3)
Missing	107 (3.1)	59 (3.4)
Increased risk of exposure to SARS-CoV-2 infection, n (%)		
Yes	1820 (52.6)	909 (52.3)
No	1640 (47.4)	828 (47.7)
Increased risk for inadequate response to active immunization, n (%)		
Yes	2546 (73.6)	1264 (72.8)
No	914 (26.4)	473 (27.2)
Any COVID-19 comorbidities[3], n (%)	2324 (67.2)	1194 (68.7)
Any high risk factors for severe COVID-19[4], n (%)	2666 (77.1)	1362 (78.4)
Obesity (> 30 kg/m2)	1474 (42.6)	729 (42.0)
Chronic kidney disease	184 (5.3)	86 (5.0)
Diabetes	492 (14.2)	242 (13.9)
Immunosuppressive disease	15 (0.4)	9 (5.0)
Immunosuppressive treatment	109 (3.2)	63 (3.6)
CV disease	272 (7.9)	151 (8.7)
COPD	179 (5.2)	95 (5.5)
Chronic liver disease	149 (4.3)	91 (5.2)
Hypertension	1229 (35.5)	637 (36.7)
Asthma	378 (10.9)	198 (11.4)
Cancer	250 (7.2)	133 (7.7)
Sickle cell disease	1 (0.03)	1 (0.1)

Source: Adapted from Applicant Tables 14.1.4.1 and 14.1.5.3

1-Subjects with positive SARS-CoV-2 Status at baseline were included in the FAS dataset but not the Full Pre-Exposure Analysis dataset. Of these subjects 3/19 (16%) in AZD7442 group and 0/6 (0%) in Placebo group developed COVID-19 symptoms.

2- There were 17 subjects (9 AZD7442, 8 placebo) with missing BMI assessments who were not included in the calculations

3- COVID-19 comorbidities identified from medical history at baseline (source: EUA 104 Request, submission 9/30/2021). Included history of chronic kidney disease, COPD, asthma, cystic fibrosis, pulmonary fibrosis, diabetes, sickle cell disease, serious heart conditions, thalassemia, high blood pressure, cerebrovascular diseases, obesity, organ transplant, dementia, or liver disease.

4- High risk factors for severe COVID-19 identified from medical history, concomitant medications, and predefined list collected via the CRF (source: EUA 104 Request, submission 9/30/2021)

Primary and secondary efficacy results

Primary efficacy results favored AZD7442 over placebo for both the primary estimand and the key supportive estimands (see ***Table 6***). For the primary estimand (censoring based on unblinding/receipt of COVID-19 preventive product), the percentage of subjects with SARS-CoV-2 RT-PCR-positive symptomatic illness was 8/3441 (0.2%) in the AZD7442 arm versus 17/1731 (1.0%) in the placebo arm, a relative risk reduction of 76.7% (95% CI: 46.1%, 90.0%), $p < 0.001$. For the key supportive estimands, similar results were observed. The relative risk reduction remained significant when considering first SARS-CoV-2 RT-PCR-positive symptomatic illness using a treatment policy approach (analysis regardless of unblinding/receipt of

COVID-19 vaccine) or when considering subjects with deaths (all-causes) as also meeting the endpoint using a while on treatment censoring approach.

Table 6: Primary Efficacy Results, PROVENT (Full Pre-Exposure Analysis Set)

Statistic	AZD7442 (N=3441)	Placebo (N=1731)
Primary Estimand: While On-Treatment Estimand		
First SARS-CoV-2 RT-PCR-Positive symptomatic illness (censored at unblinding/receipt of COVID-19 preventive product), n (%)	8 (0.2%)	17 (1.0%)
Relative Risk Reduction (95% CI)	76.7% (46.1%, 90.0%)	
P-value	P < 0.001	
Key Supportive Estimand: Treatment Policy Estimand		
First SARS-CoV-2 RT-PCR-Positive symptomatic illness (regardless of unblinding/receipt of COVID-19 preventive product), n (%)	10 (0.3%)	22 (1.3%)
Relative Risk Reduction (95% CI)	77.3% (52.0%, 89.3%)	
P-value	P < 0.001	
Key Supportive Estimand: While On-Treatment with All Cause Death		
First SARS-CoV-2 RT-PCR-Positive symptomatic illness including all death, n (%)	12 (0.3%)	19 (1.1%)
Relative Risk Reduction (95% CI)	68.8% (35.6%, 84.9%)	
P-value	P = 0.002	

Source: Adapted from Applicant Tables 14.2.1.1.1, 14.2.1.1.2, 14.2.1.1.3

In contrast to primary efficacy results, secondary efficacy results were not consistent (see ***Table 7***). Although findings for the key secondary endpoint, incidence of subjects who have a post-treatment response for SARS-CoV-2 nucleocapsid antibodies, significantly favored the AZD7442 arm, 0.7% versus 1.3%, a RRR of 51.1% (95% CI: 10.6%, 73.2%), p=0.02, findings for the other two secondary endpoints did not show significance or even trended towards favoring the placebo arm.

The percentage of subjects with first SARS-CoV-2 RT-PCR-positive severe symptomatic illness (other secondary endpoint) included (b) (4) and findings did not reach statistical significance. The percentage of subjects with a COVID-19 related emergency department visit (other secondary endpoint) favored the (b) (4) meeting this endpoint, p=0.082. The RRR and its 95% CI could not be estimated. Four of the six subjects in the AZD7442 group who had emergency department visits thought to be related to COVID-19 were subsequently diagnosed with COVID-19 and had these visits within 7 days of AZD7442 receipt, suggesting they may have been exposed to SARS-CoV-2 prior to AZD7442 receipt.

This finding is consistent with AZD7442 demonstrating benefit for pre-exposure prophylaxis but not for post-exposure prophylaxis (see the description of the STORM CHASER results in the next section).

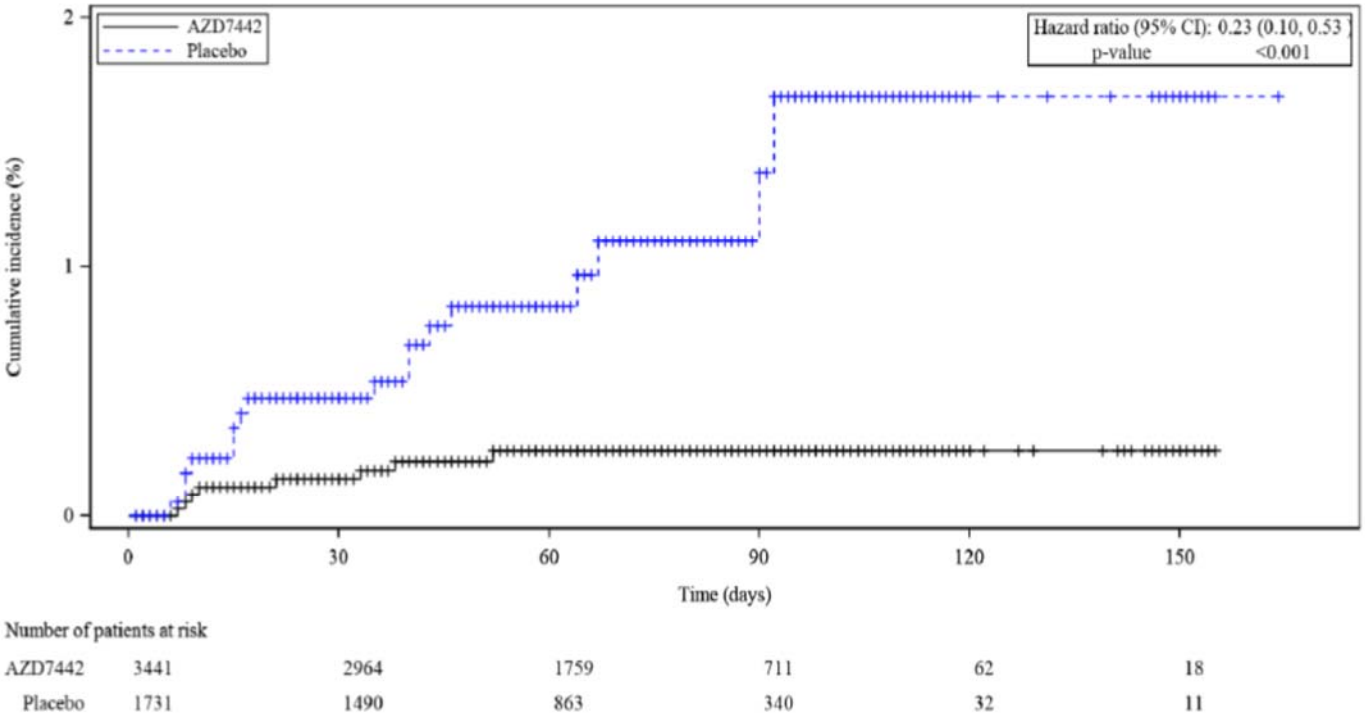
Table 7: Secondary Efficacy Results, PROVENT (Full Pre-Exposure Analysis Set)

Statistic	**AZD7442 (N=3123)**	**Placebo (N=1564)**
Key Secondary Endpoint		
Incidence of Subjects Who Have a Post-Treatment Response for SARS-CoV-2 Nucleocapsid Antibodies, n (%)	21 (0.7%)	21 (1.3%)
Relative Risk Reduction (95% CI)	51.1% (10.6%, 73.2%)	
P-value	P = 0.020	
Other Secondary Endpoint		
First SARS-CoV-2 RT-PCR-Positive severe symptomatic illness	(b) (4)	(b) (4)
Relative Risk Reduction (95% CI)	(b) (4)	
P-value	P = 0.159	
Other Secondary Endpoint		
COVID-19 related emergency department visit, n (%)	(b) (4)	(b) (4)
Relative Risk Reduction (95% CI)	(b) (4)	
P-value	P = 0.082	

Source: Adapted from Applicant Tables 14.2.2.1.1, 14.2.2.2.1, 14.2.2.3.1

The Kaplan-Meier curves for 'Time to First SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring Post Dose of AZD7442 or Placebo' are shown in ***Figure 2***. The separation in the curves for cumulative incidence rate begins at approximately Day 5 and continues to increase over time through Day 150. The hazard ratio is shown to favor the AZD7442 arm at 0.23 (95% CI: 0.10, 0.53) with a p-value of less than 0.001.

Figure 2: Time to First SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring Post Dose of AZD7442 or Placebo - Kaplan-Meier Curves by Treatment Group – Supplementary Analysis, PROVENT (Full Pre-Exposure Analysis Set)



Source: Applicant Figure 14.2.1.3.3

Primary efficacy results by subgroup are shown in **Table *8*** for the PROVENT study. In these comparisons, variable relative risk reductions were observed across subgroups, all favoring AZD7442 though some effects were smaller than the overall results and not significant, as would be expected with some comparisons. Subgroup variables observed to have substantial variability between categories included sex (M/F), COVID 19 co-morbidities (Y/N), high risk for severe COVID-19 (Y/N), COPD (Y/N) and cancer (Y/N). Note that the RRR in subjects who had immunosuppressive treatment at baseline (N=107) was similar to that of the overall population and the RRR in subjects with immunosuppressive disease at baseline (N=25) was not estimable since no events were observed in this subgroup.

Table 8: Primary Efficacy Results by Subgroup, PROVENT (Full Pre-Exposure Analysis Set)

First SARS-CoV-2 RT-PCR-Positive symptomatic illness by subgroup	**AZD7442 (N=3441)**	**Placebo (N=1731)**	
	Observed Events n/N (%)		**RRR (95% CI)**
Age Group			
< 60 years	5/1945 (0.3)	3/1496 (1.1)	77.6 (35.5, 92.2)
≥ 60 years	3/1496 (0.2)	6/755 (0.8)	75.1 (0.5, 93.8)
Sex			
Male	1/1855 (0.1)	10/934 (1.1)	95.1 (61.6, 99.4)
Female	7/1586 (0.4)	7/797 (0.9)	50.3 (-41.4, 82.5)
Race			
Asian	1/109 (0.9)	1/60 (1.7)	48.2 (-733.8, 96.8)
Black or African American	(b) (4)	(b) (4)	(b) (4)
White	7/2533 (0.3)	14/1243 (1.1)	76.1 (40.7, 90.4)
Other	0/22 (0.0)	0/14 (0.0)	NE (NE, NE)
Ethnicity			
Hispanic or Latino	2/531 (0.4)	2/215 (0.9)	59.2 (-190.2, 94.3)
Not Hispanic or Latino	6/2721 (0.3)	14/1406 (1.0)	78.3 (43.6, 91.7)
Resident in long-term care facility			
Yes	0/13 (0.0)	0/12 (0.0)	NE (NE, NE)
No	8/3428 (0.2)	17/1719 (1.0)	76.8 (46.2, 90.0)
Increased risk of exposure to infection with SARS-CoV-2			
Yes	4/1806 (0.2)	7/905 (0.8)	71.5 (3.3, 91.6)
No	4/1635 (0.2)	10/826 (1.2)	80.8 (39.2, 94.0)
Increased risk for inadequate response to active immunization			
Yes	7/2536 (0.3)	13/1260 (1.0)	73.8 (34.4, 89.6)
No	1/905 (0.1)	4/471 (0.8)	87.0 (-16.1, 98.6)
Region			
North America	6/2470 (0.2)	10/1228 (0.8)	70.7 (19.2, 89.3)
United Kingdom	1/611 (0.2)	4/311 (1.3)	86.8 (-17.9, 98.5)

European Union	1/360 (0.3)	3/192 (1.6)	83.4 (-59.6, 98.3)
COVID-19 co-morbidities			
None	(b) (4)	(b) (4)	(b) (4)
At least one	8/2314 (0.3)	9/1190 (0.8)	55.6 (-15.2, 82.9)
High risk for severe COVID-19			
Yes	8/2655 (0.3)	11/1358 (0.8)	63.6 (9.4, 85.4)
No	(b) (4)	(b) (4)	(b) (4)
Obesity (≥ 30 kg/m^2)			
Yes	5/1450 (0.3)	8/708 (1.0)	65.6 (-8.3, 89.1))
No	3/1982 (0.2)	9/1014 (0.9)	83.2 (38.1. 95.5)
Chronic Kidney Disease			
Yes	0/184 (0.0)	0/86 (0.0)	NE (NE, NE)
No	8/3257 (0.2)	17/1645 (1.0)	76.5 (45.6, 89.9)
Diabetes			
Yes	0/184 (0.0)	0/86 (0.0)	NE (NE, NE)
No	8/3257 (0.2)	17/1645 (1.0)	76.5 (45.6, 89.9)
COPD			
Yes	(b) (4)		
No	8/3263 (0.2)	15/1636 (0.9)	73.7 (38.0, 88.9)
Smoking			
Yes	2/715 (0.3)	2/369 (0.5)	49.3 (-276.9, 93.2)
No	6/2726 (0.2)	15/1362 (1.1)	80.6 (49.7, 92.5)
Immunosuppressive Disease			
Yes	0/15 (0.0)	0/9 (0.0)	NE (NE, NE)
No	8/3426 (0.2)	17/1722 (1.0)	76.7 (46.0, 90.0)
Immunosuppressive treatment			
Yes	1/109 (0.9)	2/63 (3.2)	73.2 (-241.3, 97.9)
No	7/3332 (0.2)	15/1668 (0.9)	77.0 (43.6, 90.6)
CV Disease			
Yes	0/270	0/151	NE (NE, NE)
No	8/3171(0.3)	17/1580 (1.1)	76.7 (46.0,90.0)
Hypertension			
Yes	2/1224(0.2)	6/634(0.9)	82.7 (14.2, 96.5)
No	6/2217(0.3)	11/1097 (1.0)	73.7 (28.9, 90.3)
Asthma			

Yes	1/377 (0.3)	1/198 (0.5)	51.2 (-682.3, 97.0)
No	7/3064 (0.2)	16/1533 (1.0)	78.3 (47.3, 91.1)
Cancer			
Yes	(b) (4)	(b) (4)	(b) (4)
No	8/3192 (0.3)	14/1598 (0.9)	71.7 (32.5, 88.1)

Source: Adapted from Applicant Table 14.2.1.5.1

Post-hoc Analysis of Primary Efficacy Results for PROVENT (August 29, 2021 cut-off)

In response to information requests from the Division, the Applicant provided top-line efficacy and safety data for the August 2021 datacuts from the PROVENT trial [6]. Based on post-hoc analyses using these updated data, the median follow-up was 6.5 months in both study arms.

For the primary estimand, the percentage of subjects with SARS-CoV-2 RT-PCR-positive symptomatic illness was 11/3441 (0.3%) in the AZD7442 arm versus 31/1731 (1.8%) in the Placebo arm, a relative risk reduction of 82.8% (95% CI: 65.8%, 91.4%), $p < 0.001$ (See ***Table 9***). For the key supportive estimands, similar findings were observed for subjects with first SARS-CoV-2 RT-PCR-positive symptomatic illness, using a treatment policy censoring strategy, and for subjects with deaths (all-cause) counted as meeting the endpoint using a while on treatment censoring strategy.

[6] The Applicant provided August data cuts for the PROVENT (and STORM CHASER) trials on November 12, 2001 (EUA 000104, S/N 0013) in response to the Division's information requests of October 28, 2021 and November 10, 2021.

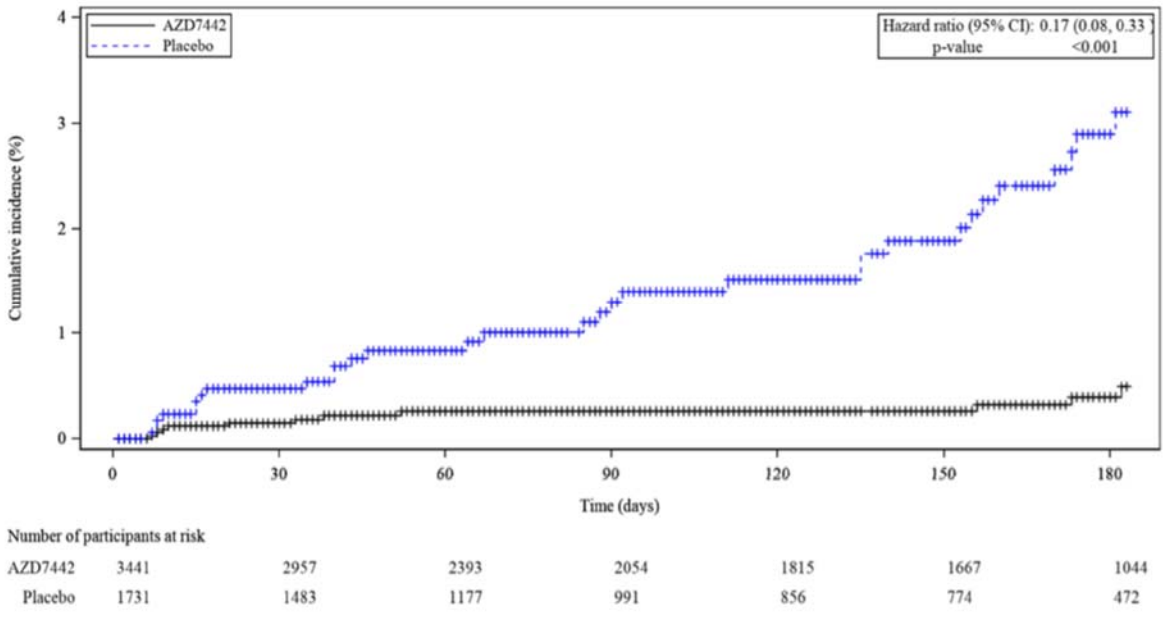
Table 9: Post-hoc Analysis of Primary Efficacy Results using August 29, 2021 cut-off, PROVENT (Full Pre-Exposure Analysis Set)

Statistic	AZD7442 (N=3441)	Placebo (N=1731)
Primary Estimand: While On-Treatment Estimand		
First SARS-CoV-2 RT-PCR-Positive symptomatic illness (censored at unblinding/receipt of COVID-19 preventive product), n (%)	11 (0.3%)	31 (1.8%)
Relative Risk Reduction (95% CI)	82.8% (65.8%, 91.4%)	
P-value	P < 0.001	
Key Supportive Estimand: Treatment Policy Estimand		
First SARS-CoV-2 RT-PCR-Positive symptomatic illness (regardless of unblinding/receipt of COVID-19 preventive product), n (%)	20 (0.6%)	44 (2.5%)
Relative Risk Reduction (95% CI)	77.4% (61.7%, 86.7%)	
P-value	P < 0.001	
Key Supportive Estimand: While On-Treatment with All Cause Death		
First SARS-CoV-2 RT-PCR-Positive symptomatic illness including all death, n (%)	18 (0.5%)	36 (2.1%)
Relative Risk Reduction (95% CI)	75.8% (57.3%, 86.2%)	
P-value	P < 0.001	

Source: Adapted from PROVENT EUA Tables 14.2.1.1.1B,14.2.1.1.2B, 14.2.1.1.3B, Submission of 11/21/2021

The Kaplan-Meier curves for 'Time to First SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring Post Dose of AZD7442 or Placebo' based on the August 2021 data cut-off are shown in ***Figure 3***. The separation in the curves for cumulative incidence rate begins at approximately Day 5 and continues to increase over time past Day 150. The hazard ratio is shown to favor the AZD7442 arm at 0.17 (95% CI: 0.08, 0.33) with a p-value of less than 0.001.

Figure 3: Time to First SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring Post Dose of AZD7442 or Placebo- Kaplan-Meier Curves by Treatment Group – Post-hoc Analysis based on August 29, 2021 Data Cut-off, PROVENT (Full Pre-Exposure Analysis Set)



Source: PROVENT EUA Figure 14.2.1.3.3B, Submission of 11/21/2021

In response to an information request from the Division on October 20, 2021, trends in efficacy were also evaluated by comparing the RRR observed within the first 3 months to the RRR observed within the period between 3-6 months. As shown in ***Figure 3*** and ***Table 10***, there is no decrease in efficacy up to 6 months and there is an numerical increase in efficacy in the 3-6 month period compared to 0-3 month period. Although no clinical data are available for repeat dosing with AZD7442, these data support that AZD7442 300 mg IM may provide protection for 6 months after dosing and consequently that a six-month redosing interval would be reasonable until further data are available. Note that due to limited data beyond 6 months, a dosing interval longer than 6 months would not be supported.

Table 10: RRR (95% CI) at Various Time Points to Evaluate Trends Over Time, PROVENT (Full Pre-Exposure Analysis Set, August, 29, 2021 cut-off)

Time point	AZD7442	Placebo
0-3-month efficacy		
N	3441	1731
No. of events	8 (0.2)	19 (1.1)
RRR (95% CI)	79 (52, 91)	
3-6-month efficacy		
N	2003	960
No. of events	3 (0.1)	12 (1.3)
RRR (95% CI)	88 (58, 97)	
Overall		
n	3441	1731
No. of events	11 (0.3)	31 (1.8)
RRR (95% CI)	83 (66, 91)	

Source: Adapted from PROVENT EUA Table 18, Submission of 11/21/2021

STORM CHASER Trial

Trial Design

STORM CHASER is a Phase 3, randomized, double-blind, placebo-controlled, multi-center study assessing the safety and efficacy of a single dose of AZD7442 compared to placebo for the prevention of COVID-19. Approximately 100 sites were to participate in this study.

Subjects were adults ≥ 18 years of age with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection, symptomatic or asymptomatic, who were therefore at appreciable risk of imminently developing COVID-19, based on available risk assessment at time of enrollment. Subjects were enrolled into one of 2 cohorts:

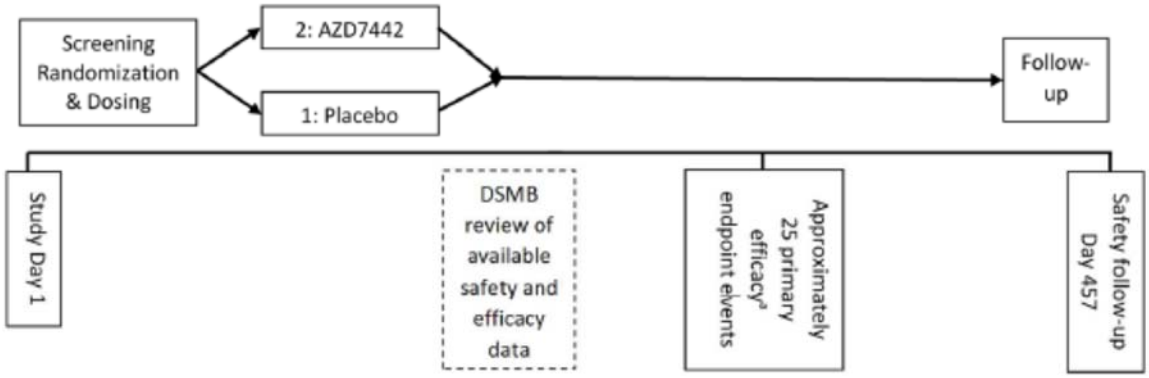
- Cohort 1: Adults ≥ 60 years of age, living in long-term care facilities. In this context, long-term care facilities include skilled nursing facilities, assisted living facilities, and independent living facilities for senior adults.

- Cohort 2: Other adults ≥ 18 years of age with potential exposure to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection. Such individuals may include, but were not limited to, those living in institutional residences (military lodging, dormitories, etc.), household contacts, health care

workers, long-term care facility workers, and workers in occupational or industrial settings in which close contact is common.

Following a screening evaluation, approximately 1125 subjects were to be randomized in a 2:1 ratio to receive a single dose of either 300 mg of AZD7442 (N = approximately 750) or saline placebo (N = approximately 375) on Day 1. After administration of the dose of AZD7442 or placebo on Day 1, subjects were to undergo follow-up until Day 457.

Figure 4: Trial Design, STORM CHASER



Primary analysis to be conducted 30 days after the 25th event was observed.
Note: An independent DSMB would review available safety and efficacy data after the first 100 subjects have been dosed, or after 4 weeks from first subject dosed, whichever came first. Enrollment would not be paused pending the DSMB's review.
Source: Figure 1 of STORM CHASER Study Protocol-6.0

Eligibility Criteria

- Subjects were ≥ 18 years with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection, symptomatic or asymptomatic, who were therefore at appreciable risk of imminently developing COVID-19, based on available risk assessment at time of enrollment, within any of the following settings:
    - Long-term care facilities, including skilled nursing homes, assisted living homes, independent living residences for the elderly. Residents, health care workers in such facilities, and other staff of such facilities were eligible under this criterion. For subjects entering the study from these settings, "potential exposure to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection" was defined to mean the occurrence of SARS-CoV-2 infection, symptomatic or asymptomatic, in another resident of the facility or in a staff member of the facility.
    - Industrial settings shown to have been at high risk for SARS-CoV-2 transmission, including but not limited to meatpacking plants. Workers in such facilities were eligible under this criterion.

- Military settings including but not limited to barracks, ships, or other close-quarters working environments. Military and civilian personnel exposed in such settings were eligible.
- Health care facilities. Health care workers and other staff exposed in such setting were eligible under this criterion.
- University or college dormitories. Students exposed in such setting were eligible.
- Household contacts. Any adult living in the same household as an index case were eligible under this criterion.
- Other settings of similar close or high-density inter-personal proximity. The potential for exposure in such settings may be assessed on a case-by-case basis by investigators. Individuals exposed in such settings were eligible under this criterion.

- Prior to enrollment, subjects must not have had COVID-19 symptoms within 10 days of dosing.

- Negative result from point of care SARS-CoV-2 serology testing at screening.

- No history of receipt of a COVID-19 vaccine or other mAb/biologic indicated for the prevention of SARS-CoV-2, and no history of SARS-CoV-2, SARS-CoV, or MERS-CoV infection.

Analysis Sets

All participants analysis set: All subjects screened for the study, to be used for reporting disposition and screening failures

Full analysis set: All randomized subjects who received at least one dose of AZD7442 or placebo, irrespective of their protocol adherence and continued participation in the study. Subjects were analyzed according to their randomized treatment irrespective of whether or not they have prematurely discontinued, according to the intent-to-treat principle. Subjects who withdrew consent or assent to participate in the study were included up to the date of their study termination.

Safety analysis set: The safety analysis set consists of all subjects who have received at least one dose of AZD7442 or placebo. Erroneously-treated subjects (e.g., those randomized to treatment A, but were actually given treatment B) are accounted for in this analysis set by assigning them to the treatment they actually received. A subject who has on one or several occasions received active AZD7442 is classified as active.

Pharmacokinetic analysis set: All subjects who received AZD7442 and from whom PK blood samples are assumed not to be affected by factors such as protocol violations and who had at least one quantifiable serum PK observation post dose were included in the PK analysis dataset.

Endpoints

The primary endpoint is the first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose of AZD7442 or placebo and prior to Day 183. Subjects are included in the primary endpoint if they had RT-PCR-confirmed SARS-CoV-2 and met the qualifying symptoms summarized in ***Table 2*** (same definition of primary endpoint as used for PROVENT).

The key secondary endpoint is the incidence of SARS-CoV-2 RT-PCR-positive severe or critical symptomatic illness occurring after dosing with AZD7442 or placebo.

Estimands

The primary estimand used for the analysis of the primary efficacy endpoint is based on subjects in the full analysis set. For subjects who become unblinded to properly consider vaccination for COVID-19 prior to having met the criteria for the primary efficacy endpoint, the data were collected and analyzed regardless (i.e., intercurrent events were handled using a treatment policy strategy).

For analysis of the key secondary efficacy endpoint intercurrent events were also handled using a treatment policy strategy.

Statistical Methodology

The Poisson regression model with robust variance (Zou 2004) was used to analyze the primary efficacy endpoint, which included the log of the follow-up time as an offset. If a subject's first case of SARS-CoV-2 RT-PCR positive symptomatic illness occurs after Day 183, the subject was considered as not having an event. The efficacy is estimated from the model, which gives the RRR in the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness. The efficacy is calculated as RRR = 100% × (1-relative risk), which is the incidence of infection in the AZD7442 group relative to the incidence of infection in the control group, expressed as a percentage.

Methods to Control Multiplicity

If the primary endpoint achieves statistical significance a hierarchical approach would be used to control for multiplicity of the primary and key secondary efficacy endpoint. With that, the overall Type I error is controlled at 0.05. Therefore, no further multiplicity adjustment was necessary.

Efficacy Results

Subject Disposition

In the STORM CHASER study, there were 756 and 375 subjects randomized to the AZD7442 and placebo arms respectively with 7 and 3 subjects excluded from the FAS analysis set for not being dosed (see **Table *11*Table *13***).

As this study was ongoing during April 07, 2021 data cut-off, no subjects had completed the study. Early discontinuation rates were slightly higher in the AZD7442 arm compared to the placebo arm, 2.0% versus 1.6% (see ***Table 12*Table *13***). The reasons for discontinuation were generally similar between treatment arms with 'withdrawal by subject' being the most common reason for early discontinuation in both study arms.

Approximately 10% of subjects were unblinded, 8.2% in the AZD7442 arm versus 14.2% in the placebo arm with 3.4% and 12.5% of randomized subjects receiving the COVID-19 vaccination after being unblinded. The smaller percentage of subjects receiving the COVID-19 vaccination appeared to be a disadvantage for the AZD7442 arm in the primary analysis of the study which did not censor subjects after being unblinded or receiving the vaccination under the treatment policy estimand, as discussed later.

Table 11: Key Analysis Sets, STORM CHASER (All Randomized Subjects)

Characteristic, n (%)	**AZD7442**	**Placebo**
Subjects Randomized	**756**	**375**
Subjects in Full Analysis Set (FAS)	749 (99.1)	372 (99.2)
Reason for Exclusion:		
Randomized and not dosed	7 (0.9)	3 (0.8)

Source: Adapted from EUA STORM CHASER Table 14.1.3

Table 12: Subject Disposition, STORM CHASER (All Randomized Subjects)

Characteristic	**AZD7442**	**Placebo**
Subjects Randomized	**756 (100)**	**375 (100)**
Randomized and not dosed	7 (0.9)	3 (0.8)
Ongoing in Study	741 (98.0)	369 (98.4)
Completed Study	0	0
Discontinued early from study,	15 (2.0)	6 (1.6)
Reason (n/N) %:		
Physician Decision	(b) (4)	
Protocol deviation		
Lost to follow-up		
Withdrawal by subject	7 (0.9)	3 (0.8)
Other	5 (0.7)	2 (0.5)
Subject unblinded,	62 (8.2)	53 (14.1)
Received COVID-19 vaccination subsequently	26 (3.4)	47 (12.5)

Source: Adapted from EUA STORM CHASER Table 14.1.1
As this study was ongoing during April 7, 2021 data cut-off, no subjects had completed the study and the mean duration from first dose of AZD7442 or placebo to primary analysis was approximately 52 days in each study arm.

Demographic and Baseline Characteristics

Demographic and baseline characteristics were generally well-balanced between the treatment groups (see **Table *13***). The mean age of subjects was 46.6 years and 46.0 years in the AZD7442 and placebo groups. There were also no substantial differences between treatment groups across subgroups based on the variables of age group, cohort, sex, ethnicity and race. Comorbidities at baseline were also observed to be generally similar between treatment arms. A slightly larger percentage of subjects in the placebo arm were observed to have COPD at baseline (3.0% versus 0.9%).

Table 13: Demographic and Baseline Characteristics, STORM CHASER (FAS)

Characteristic	**AZD7442 (N=749)**	**Placebo (N=372)**
Age		
Mean (SD)	46.6 (15.7)	46.0 (16.2)
Median (Min, Max)	48 (b) (4)	47 (b) (4)
Age Group, n (%)		
18 to 59	600 (80.1)	297 (79.8)
60 to 74	126 (16.8)	59 (15.9)
75 and over	23 (3.1)	16 (4.3)
Cohort, n (%)		
Adults ≥ 60 years residing in a long term care facility	5 (0.7)	2 (0.5)
Other adults ≥ 18 years	744 (99.3)	370 (99.5)

Sex, n (%)		
Male	376 (50.2)	191 (51.3)
Female	373 (49.8)	181 (48.7)
Ethnicity, n (%)		
Hispanic or Latino	435 (58.1)	210 (56.5)
Not Hispanic or Latino	299 (39.9)	159 (42.7)
Not reported	11 (1.5)	1 (0.3)
Unknown	4 (0.5)	2 (0.5)
Race, n (%)		
White	628 (83.8)	315 (84.7)
Black or African American	76 (10.1)	36 (9.7)
Asian	15 (2.0)	13 (3.5)
Other	12 (1.6)	5 (1.3)
Not Reported, Unknown	18 (2.4)	3 (0.8)

Source: Adapted from STORM CHASER EUA Table 14.1.4.1

Table 14: Other Baseline Characteristics and Comorbidities, STORM CHASER (FAS)

Characteristic	**AZD7442 (N=749)**	**Placebo (N=372)**
Baseline BMI (kg/m2)	N=746	N=372
Mean (SD)	29.7 (6.7)	29.9 (6.7)
Median (Min, Max)	28.6 ((b) (4))	29.1 ((b) (4))
Resident in long-term care facility, n (%)		
Yes	7 (0.9)	3 (0.8)
No	742 (99.1)	369 (99.2)
Smoking Status, n (%)		
Never	520 (69.4)	241 (64.8)
Former	85 (11.3)	60 (16.1)
Current	144 (19.2)	71 (19.1)
SARS-CoV-2 Status, n (%)		
Positive	34 (4.5)	14 (3.8)
Negative	646 (86.2)	328 (88.2)
Missing	69 (9.2)	30 (8.1)
High risk for severe COVID-19, n (%)		
Yes	492 (65.7)	244 (65.6)
No	257 (34.3)	128 (34.4)
Any COVID-19 Comorbidities[1], n (%)	375 (50.1)	173 (46.5)
Any High Risk Factors for Severe COVID-19[2], n (%)	492 (65.7)	244 (65.6)
Obesity (> 30 kg/m2)	225 (30.0)	108 (29.0)
Chronic kidney disease	14 (1.9)	7 (1.9)
Diabetes	90 (12.0)	38 (10.2)

Immunosuppressive disease	0	0
Immunosuppressive treatment	7 (0.9)	2 (0.5)
CV disease	19 (2.5)	14 (3.8)
COPD	7 (0.9)	11 (3.0)
Chronic liver disease	8 (1.1)	2 (0.5)
Hypertension	184 (24.6)	84 (22.6)
Asthma	49 (6.5)	27 (7.3)
Cancer	24 (3.2)	10 (2.7)
Smoking	144 (19.2)	71 (19.1)

Source: Adapted from STORM CHASER EUA Table 14.1.5.1
1. COVID-19 comorbidities identified from medical history at baseline (source: EUA 104 Request, submission 9/30/2021)
2. High risk factors for severe COVID-19 identified from medical history, concomitant medications, and predefined list collected via the CRF (source: EUA 104 Request, submission 9/30/2021)

Primary and key secondary efficacy results

The primary endpoint of this trial was the percentage of subjects with first SARS-CoV-2 RT-PCR-positive symptomatic illness. The percentage of subjects meeting this endpoint was lower in the AZD7442 arm versus the placebo arm, 3.1% versus 4.6% (see ***Table 15***). The relative risk reduction associated with the use of AZD7442 versus placebo was 33.3% (95% CI: -25.9%, 64.7%) which did not reach statistical significance, p=0.212. The key secondary endpoint was the percentage of subjects with SARS-CoV-2 RT-PCR-positive with severe or critical symptomatic illness, however, comparisons were limited as (b) (4) met this endpoint and significance was not reached.

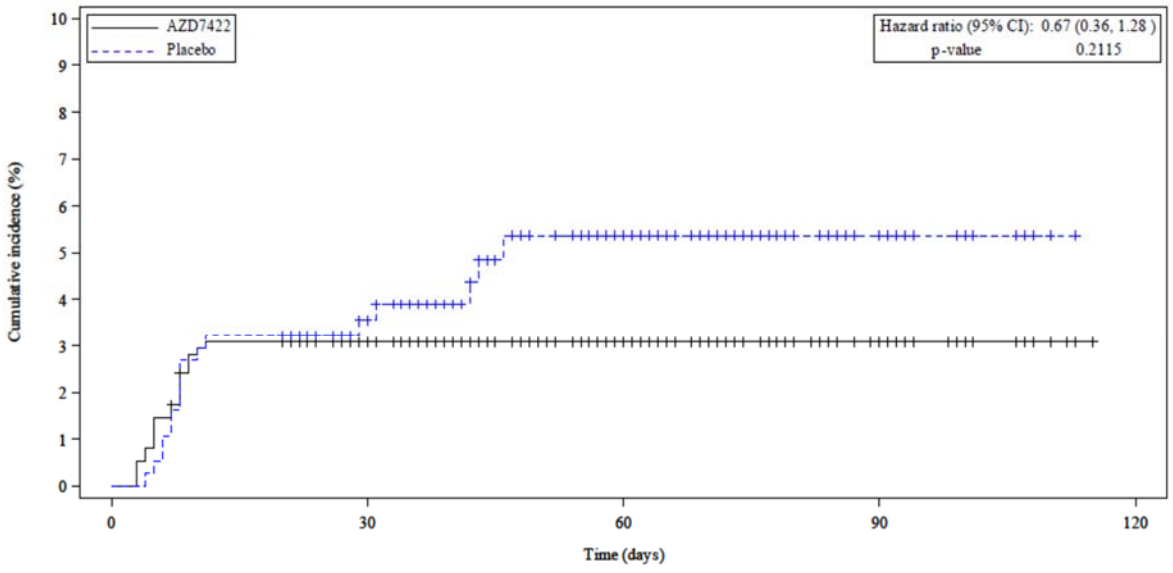
Table 15: Primary and Key Secondary Efficacy Results, STORM CHASER (FAS)

Statistic	**AZD7442 (N=749)**	**Placebo (N=372)**
Primary Endpoint		
First SARS-CoV-2 RT-PCR-positive symptomatic illness, n (%)	23 (3.1)	17 (4.6)
Relative Risk Reduction (95% CI)	33.3% (-25.9%, 64.7%)	
P-value	P = 0.212	
Key Secondary Endpoint		
SARS-CoV-2 RT-PCR-positive with severe or critical symptomatic illness, n (%)	(b) (4)	(b) (4)
Relative Risk Reduction (95% CI)	(b) (4)	
P-value	P = 0.664	

Source: Adapted from STORM CHASER EUA Table 14.2.1.1.1

The Kaplan-Meier curves for 'Time to First SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring Post Dose of AZD7442 or Placebo' are shown in ***Figure 5***. The separation in the curves for cumulative incidence rate does not begin until approximately Day 30 which indicates that subjects have similar risks after the initial exposure of SARS-CoV-2 that occurred prior to receipt of AZD7442 or placebo with a possible decrease in risk for subjects having subsequent exposures. The hazard ratio is shown to numerically favor the AZD7442 arm at 0.67 (95% CI: 0.36, 1.28) with a p-value near 0.2.

Figure 5: Time to First SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring Post Dose of AZD7442 or placebo - Kaplan-Meier Curves by Treatment Group – Supplementary Analysis, STORM CHASER (FAS)



Source: STORM CHASER EUA Figure 14.2.1.3.3

Primary efficacy results by subgroup are shown in ***Table 16*** for STORM CHASER. In general, relative risk reductions numerically favored AZD7442 across subgroups. For the SARS-CoV-2 RT-PCR status at baseline variable, AZD7442 reduced the risk of developing COVID-19 by 73.2% (95% CI: 27.1%, 90.1%) in subjects who were RT-PCR negative/missing at time of dosing when compared with placebo. In subjects who were SARS-CoV-2 RT-PCR positive at baseline, this reduction was not seen (AZD7442 17/34, placebo 6/14). Based on a Kaplan Meier estimate of the time to first SARS-CoV-2 RT-PCR positive symptomatic illness, as later shown in **Figure *6***, there was no apparent benefit of AZD7442 over placebo prior to Day 29, but the curves separated with more reported cases among placebo recipients after Day 29. These findings were reviewed as part of our recommendation to authorize for a pre-

exposure prophylaxis authorization. Review of these findings do not support a post-exposure prophylaxis authorization.

Table 16: Primary Efficacy Results by Subgroup, STORM CHASER (FAS)

First SARS-CoV-2 RT-PCR-Positive symptomatic illness by subgroup at baseline	AZD7442 (N=749)	Placebo (N=301)	
	Observed Events n/N (%)		RRR (95% CI)
Age Group			
< 60 years	19/600 (3.2)	13/297 (4.4)	26.23 (-50.5, 63.9)
≥ 60 years	4/149 (2.7)	75 4 (5.3)	54.7 (-85.8, 89.0)
Sex			
Male	9/376 (2.4)	6/191 (3.1)	25.1 (-112.5, 73.6)
Female	14/ 373 (3.8)	11/181 (6.1)	38.1 (-38.3, 72.3)
Race			
American Indian or Alaska Native	(b) (4)	(b) (4)	(b) (4)
Black or African American	(b) (4)	(b) (4)	(b) (4)
White	21/628 (3.3)	15/315 (4.8)	29.8 (-46.4, 65.5)
Other	0/17	0/14	NE (NE, NE)
Ethnicity			
Hispanic or Latino	5/435 (1.2)	6/210 (2.9)	58.6 (-36.7, 87.4)
Not Hispanic or Latino	18/299 (6.0)	11/159 (6.9)	17.8 (-77.4, 61.9)
COVID-19 co-morbidities			
None	14/374 (3.7)	10/199 (5.0)	23.5 (-74.5, 66.5
At least one	9/375 (2.4)	7/173 (4.1)	42.7 (-55.4, 78.9)
SARS-CoV-2 RT-PCR status at baseline			
Positive[2]	17/34 (50.0)	6/14 (42.9)	-49.2 (-373.3, 53.0)
Negative/missing	6/715 (0.8)	11/358 (3.1)	73.2 (27.1, 90.1)
High risk for severe COVID-19			
Yes	11/492 (2.2)	11/244 (4.5)	51.0 (-14.2, 78.9)
No	12/257 (4.7)	6/128 (4.7)	0.30 (-170.5, 63.3)
Obesity[1](≥ 30 kg/m^2)			
Yes	6/295 (2.0)	8/162 (4.9)	59.8 (-17.1, 86.2)
No	17/451 (3.8)	9/210 (4.3)	11.9 (-100.2, 61.2)
Diabetes			
Yes	2/90 (2.2)	2/38 (5.3)	63.1 (-170.2, 95.0)

No	21/659 (3.2)	15/334 (4.5)	28.5 (-40.0, 63.5)
Chronic kidney disease			
Yes	(b) (4)	(b) (4)	(b) (4)
No	23/735 (3.1)	15/365 (4.1)	23.9 (-56.9, 61.9)
Smoking			
Yes	2/144 (1.4)	3/71 (4.2)	65.8 (-106.7, 94.4)
No	21/605 (3.5)	14/301 (4.7)	26.82 (-45.5, 63.2)
Hypertension			
Yes	4/184 (2.2)	5/84 (6.0)	67.2 (-23.7, 91.3)
No	19/565 (3.4)	12/288 (4.2)	17.11 (-72.6, 60.2)
Asthma			
Yes	3/49 (6.1)	2/27 (7.4)	16.9 (-413.7, 86.6)
No	20/700 (2.9)	15/345 (4.4)	34.9 (-28.3, 67.0)
Cancer			
Yes	1/24 (4.2)	1/10 (10.0)	65.1 (-509.4, 98.0)
No	22/725 (3.0)	16/362 (4.4)	31.46 (-31.6, 64.3)

Source: Adapted from STORM CHASER EUA Table 14.2.1.5.1

1- There were 3 subjects (all in placebo arm) with missing BMI assessments who were not included in the calculations

2- Among subjects who were SARS-CoV-2 RT-PCR positive at baseline, AZD7442 recipients had a median number of symptoms of 4 versus 2.5 on placebo among subjects who developed symptoms, and 10/34 of AZD7442 subjects versus 2/14 placebo subjects had moderate to severe symptoms.

Post-hoc Analysis of Primary and Key Secondary Efficacy Results for STORM CHASER (August 19, 2021 cut-off)

In response to an information request from the Division, the Applicant provided top-line efficacy and safety data for the August 2021 datacuts from the STORM CHASER trial[7]. Based on post-hoc analyses using these updated data, the median follow-up was increased to 6 months in both study arms.

For the primary endpoint, the percentage of subjects with first SARS-CoV-2 RT-PCR-positive symptomatic illness was 27/749 (3.6%) in the AZD7442 arm versus 23/372 (6.2%) in the placebo arm, a relative risk reduction of 43.2% (95% CI: 0.1%, 67.7%), p = 0.049 (see **Table *17***). Note that this finding was not considered as statistically significant since it was based on post-hoc analysis conducted after the primary analysis of the study had failed. For the key secondary endpoint, the percentage of SARS-CoV-2 RT-PCR-positive subjects with severe or critical symptomatic illness,

[7] The Applicant provided August data cuts for the STORM CHASER (and PROVENT) trials on November 12, 2001 (EUA 000104, S/N 0013) in response to the Division's information requests of October 28, 2021 and November 10, 2021.

comparisons were limited as [redacted] met this endpoint and significance was not reached.

Table 17: Post-hoc Analysis of Primary and Key Secondary Efficacy Results using August 19, 2021 Cut-off, STORM CHASER (FAS)

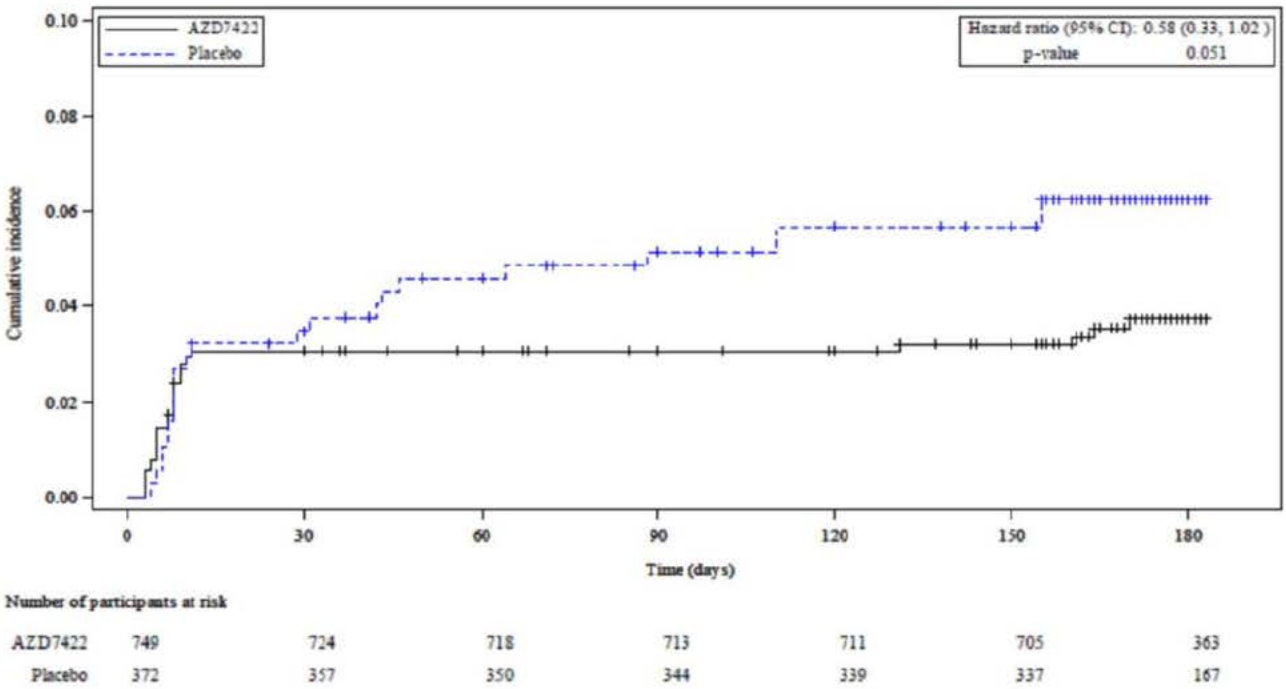
Statistic	**AZD7442 (N=749)**	**Placebo (N=372)**
Primary Endpoint		
First SARS-CoV-2 RT-PCR-positive symptomatic illness, n (%)	27 (3.6)	23 (6.2)
Relative Risk Reduction (95% CI)	43.2% (0.1%, 67.7%)	
P-value	P = 0.049	
Key Secondary Endpoint		
SARS-CoV-2 RT-PCR-positive with severe or critical symptomatic illness, n (%)	[redacted]	[redacted]
Relative Risk Reduction (95% CI)	[redacted]	
P-value	P = 0.664	

Source: Adapted from STORM CHASER EUA Table 14.2.1.1.1B, Submission of 11/21/2021

The Kaplan-Meier curves for 'Time to First SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring Post Dose of AZD7442 or Placebo' using the updated data with the August 12, 2021 data cut-off are shown below. As previously discussed, these curves showed that there was no treatment benefit in preventing COVID-19 in the first 30 days after randomization. However, there was a higher proportion of COVID-19 cases among placebo recipients after Day 29. The hazard ratio is shown to numerically favor the AZD7442 arm at 0.58 (95% CI: 0.33, 1.02) with a p-value of 0.051. Although STORM CHASER enrolled fewer subjects than PROVENT, the curves do not appear to further separate beyond about Day 120, suggesting that a dosing interval greater than 6 months is not supported.

Figure 6: Time to First SARS-CoV-2 RT-PCR-positive Symptomatic Illness Occurring Post Dose of AZD7442 or placebo - Kaplan-Meier Curves by

Treatment Group – Supplementary Analysis, August 19, 2021 cut-off, STORM CHASER (FAS)



Source: Applicant Figure 14.2.1.3.3B, Submission of 11/21/2021

Efficacy Conclusions

Efficacy data from PROVENT demonstrated a benefit of treatment with AZD7442 for pre-exposure prophylaxis. Efficacy data from STORM CHASER did not demonstrate a benefit of treatment with AZD7442 for post-exposure prophylaxis or treatment of asymptomatic infection.

The PROVENT study met its primary endpoint by showing a 76.7% relative risk reduction (95% CI: 46.1%, 90.0%) of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post dose of AZD7442 or placebo through Day 183. Kaplan-Meier plots showed that the reduction in cumulative incidence rate began near Day 5 and continued to increase over time past Day 150 (past Day 180 based on the August 2021 data cut-off). Findings were mostly supportive across secondary analyses and other analyses, including subgroup analyses, and no major efficacy concerns were noted. One issue was that emergency department visits were higher in the AZD7442 arm versus the placebo arm, (b) (4) p=0.082; however, four of the six subjects in the (b) (4) who had emergency department visits thought to be related to COVID-19 were subsequently diagnosed with COVID-19 and had these visits within 7 days of receiving (b) (4), suggesting they may have been exposed to SARS-CoV-2 prior to receiving (b) (4) This finding was not consistent with (b) (4) having benefit for post-exposure prophylaxis. Another issue was that of the 25 subjects in the PROVENT study who were SARS-CoV-2 positive at baseline, (b) (4)

(b) (4) in AZD7442 group and (b) (4) in placebo group developed COVID-19 symptoms which also suggests AZD7442 may not have a benefit for post-exposure prophylaxis.

The STORM CHASER study did not meet its primary endpoint, but did show a numeric trend favoring AZD7442 for the primary endpoint based on the percentage of subjects with first SARS-CoV-2 RT-PCR-positive symptomatic illness (relative risk reduction of 33.3% (95% CI: -25.9%, 64.7%)). Kaplan-Meier plots showed nearly identical incidence rates of first SARS-CoV-2 RT-PCR-positive symptomatic illness occurring up to 29 days post dose of AZD7442 or placebo with a higher proportion of COVID-19 cases among placebo recipients after Day 29. In the subgroup of subjects with negative/missing SARS-CoV-2 RT-PCR status at baseline variable, AZD7442 reduced the risk of developing COVID-19 by 73.2% (95% CI: 27.1%, 90.1%). However, similar to PROVENT, STORM CHASER showed a higher percentage of subjects in the AZD7442 arm who were SARS-CoV-2 positive at baseline developing COVID-19 symptoms, 17/34 (50%) versus 6/14 (43%). Similar trends were also observed when considering only cases of moderate to severe COVID-19 symptoms, 10/34 (29%) versus 2/14 (17%) and the number of symptoms among those who developed symptoms (median of 4 versus 2.5 symptoms). The STORM CHASER data were reviewed as part of our recommendation to authorize for a pre-exposure prophylaxis authorization. Review of these findings do not support either a post-exposure prophylaxis authorization or an early treatment authorization.

Overall findings across the PROVENT and STORM CHASER studies did not demonstrate a treatment benefit for post-exposure prophylaxis or treatment of asymptomatic infection, consequently the language in the authorization specifies that EVUSHELD is to be used for pre-exposure prophylaxis but not for post-exposure prophylaxis or treatment. Other limitations of the available clinical data related to lack of repeat-dosing and the study population. For example, the PROVENT population differed from the population for which the product is intended under EUA since no trial subjects were vaccinated before AZD7442 administration and adolescents were not included. In addition, the PROVENT population included only a limited number of subjects who were moderately to severely immunocompromised (approximately 3%) or who were intolerant of vaccines (0.5%).

IX. Human Clinical Safety[8]

EVUSHELD (tixagevimab coadministered with cilgavimab; AZD7442) is currently being evaluated in clinical trials in healthy adults, adults at risk for exposure to SARS-CoV-2, adults with recent confirmed exposure to SARS-CoV-2 without any symptoms of COVID-19, and adults with confirmed COVID-19 in outpatient and hospitalized settings. For the proposed EUA, the safety database contains a summary of interim unblinded safety data from the prophylactic and healthy adult trials in which 4260

[8]AZD7442 is used in Section IX to refer to tixagevimab and cilgavimab

subjects were exposed to AZD7442 doses of 300 mg or higher, of whom 4220 received the 300 mg IM dose.

Table 18 summarizes the sources for the available safety database for this review. Of note, the original EUA submission only contained safety data from PROVENT and STORM CHASER with a median follow-up time of 83 and 49 days, respectively. However, at FDA request, preliminary topline safety summaries using later data cut-off dates were submitted midway through the review. The safety results with the later data cut-off dates are similar to the earlier results in terms of safety findings for AZD7442 versus placebo, although the overall numbers of AEs for both AZD7442 and placebo recipients were higher due to the longer follow-up times (median of 196 and 180 days, respectively, for PROVENT and STORMCHASER). The safety analysis will focus on the initially submitted safety database with the earlier data cut-off date except where otherwise noted.

The safety population of the currently ongoing prevention trials is mostly similar to the intended population for use under EUA in that these subjects did not have COVID-19 at baseline. Key differences with the intended population for use under EUA for which safety may differ include the following:

- Repeat dosing: No clinical data were included with repeat dosing of AZD7442, and repeat dosing will likely be needed for a pre-exposure prophylaxis authorization. Safety may differ with repeat dosing based on hypersensitivity reactions and development of anti-drug antibodies.
- COVID-19 vaccination: Prior receipt of a COVID-19 vaccine was an exclusion criterion for trial participation, whereas many people in the intended EUA population may have previously received a COVID-19 vaccine.
- Adolescent population: Adolescents 12 to ≤ 17 years of age, and weighing at least 40 kg were not included in the trials (the safety database only includes adults).
- Immune compromised population: Only a small percentage (approximately 3%) of subjects in the safety database had moderate to severe immune compromise.
    - A total of 194/5197 subjects (3.7%) in PROVENT were flagged as having immunosuppressive disease or being on immunosuppressive treatment, including 123/3461 subjects (3.6%) who received AZD7442.
    - A total of 9/1121 subjects (0.8%) in STORM CHASER were flagged as being on immunosuppressive treatment (no subjects in STORM CHASER were flagged as having immunosuppressive disease), including 7/749 subjects (0.9%) who received AZD7442.
- History of severe adverse reaction to vaccination: Only a small percentage of subjects (<1%) in the safety database had a history of severe adverse reaction to prior vaccination.
    - A total of 24/5197 subjects (0.5%) in PROVENT were classified as being “intolerant of vaccine” at baseline (defined in the protocol as previous history of severe adverse event or serious adverse event after

receiving any approved vaccine), including 15/3461 (0.4%) who received AZD7442.

- As prior COVID-19 vaccination at baseline was excluded, no subjects in either PROVENT or STORM CHASER had a history of severe adverse reaction to a COVID-19 vaccine.

Table 18: Summary of tixagevimab and cilgavimab safety database for this EUA

Study	Objective	Number of Subjects	^Duration of Follow-Up in Initial EUA Submission#
PROVENT	Primary evaluation of safety data in support of EUA request	3461	*Median: 83 days Range: 3-166 days
STORM CHASER	Additional unblinded safety data	749	Median: 49 days Range: 5-115 days
D8850C00001	Additional unblinded safety data of longer duration of follow-up and higher doses (up to 3000 mg IV)	50 (10 who received 300 mg IM)	270 days (300 mg IM and 300 mg IV , n=20) and up to 211 days (higher doses)

^The median durations of follow-up in PROVENT and STORM CHASER were identical or almost identical (49 versus 48 days in STORM CHASER) for the AZD7442 and placebo groups, respectively.
*The median duration of follow-up in PROVENT was provided for the pre-exposure analysis set, which excluded 25 subjects in the safety analysis set who were SARS-CoV-2 RT-PCR positive at baseline.
#Preliminary topline data with a later data cutoff (median [range] follow-up of 196 days [3, 282] for PROVENT and 180 days [5, 249] for STORM CHASER) were submitted at FDA request midway through the review.
Sources: EUA request, section 6.2, PROVENT EUA table 14.2.1.4, and STORM CHASER EUA table 14.2.1.4.

PROVENT Safety Results

The safety analysis population from the pivotal trial, PROVENT, includes 3461 AZD7442 recipients and 1736 placebo recipients. The numbers for the safety population differ from the numbers in the pre-exposure analysis population used in the efficacy analyses because: 1) the 25 subjects (19 AZD7442 recipients and 6 placebo recipients) who were SARS-CoV-2 positive at baseline are included in the safety analysis, and 2) one subject who was randomized to receive placebo actually received AZD7442 and is included as an AZD7442 recipient in the safety analysis. Adverse events in PROVENT were graded according to a five point scale adapted from the toxicity grading scale of the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 from the National Institutes of Health. Clinical events related to COVID-19, including deaths and SAEs, could be included as AEs.

The primary safety analysis from PROVENT had the following limitations (in addition to the limitations related to the population for the safety database listed previously):

1. Duration of AE collection, Database lock: The duration over which AEs were collected per study subject ranged >50-fold because the EUA submission only contained AEs collected through the database lock date regardless of the date of enrollment and study product administration. However, the follow-up durations were similar and equally varied between individual subjects when comparing the AZD7442 and placebo groups (in the safety analysis set, the

median duration [range] was 83 days [4, 166] for AZD7442 recipients and 83 days [3, 166] for placebo recipients). Consequently, despite this limitation, a safety comparison can still provide an adequate assessment on the overall safety of the product.

2. Duration of AE collection, Half-life: The duration over which AEs were collected did not extend to the latest time point when the study product would be expected to still be in the body (five half-lives for AZD7442 is ~450 days), so AEs resulting in prolonged exposure may not be captured.
    a. The Phase 1 data, with follow-up duration of up to 271 days, was submitted as supportive data.
3. Unblinding: During the AE reporting period, approximately 30% of subjects were unblinded in each treatment group, and approximately 12% of AZD7442 recipients and 31% of placebo recipients received the COVID-19 vaccine (unblinding and vaccination were censoring events for the efficacy analyses but not the safety analyses). However:
    a. One would expect that unblinding would lead to less AE reporting in the placebo group and more AE reporting in the AZD7442 group, which would make it less likely that unblinding would obscure true safety signals.
    b. One of the more common AEs in the placebo group (2% of placebo recipients and 1% of AZD7442 recipients) was “vaccination complication”, suggesting that AEs common to vaccination (injection site pain, myalgias, etc.) that occurred on the day of or after vaccination could be distinguished from AEs related to study product.
4. Clonal cell line, Cell pool: A total of 92 subjects received product derived from the AZD7442 clonal cell line while 3369 subjects received product derived from the AZD7442 cell pool. A comparison of safety events by the AZD7442 source was limited by both the small number of subjects who received the product derived from the clonal cell line and the different durations of follow-up times between the subjects who received AZD7442 from the clonal cell line versus the cell pool; the median (range) of follow-up time was 49 days (42, 55) for the 92 subjects who received product from the AZD7442 clonal cell line and 84 days (4, 166) for the 3369 subjects who received product derived from the AZD7442 cell pool. Due to these limitations, this comparison was not considered informative and so will not be further discussed in this review.

Safety Overview

Table 19 below shows the summary of safety events in PROVENT. In general, rates of overall safety events were similar between treatment groups. AZD7442 was administered sequentially as two separate IM injections (one for each mAb), so it was theoretically possible that an AE could develop so quickly as to prevent or delay the second injection; however, this occurrence was not reported.

Table 19: Summary of Safety (PROVENT)

Adverse Events, n (%)	AZD7442 (N=3461)	Placebo (N=1736)
Any AE	1221 (35%)	593 (34%)
AE related to study treatment	286 (8%)	116 (7%)
Any Grade 3 or higher AE	73 (2%)	33 (2%)
SAE	50 (1%)	23 (1%)
SAE related to study treatment	(b) (4)	(b) (4)
AEs with outcome of death	4 (<1%)	4 (<1%)
Fatal AEs related to study treatment	0	0
AEs of special interest (AESI)*	93 (3%)	37 (2%)
AESI related to study treatment	87 (3%)	37 (2%)
Medically attended AEs (MAAEs)	360 (10%)	157 (9%)
MAAEs related to study treatment	12 (<1%)	3 (<1%)

*AEs of special interest included anaphylaxis, other serious hypersensitivity reactions (including immune complex disease), and injection site reactions
Source: adapted from PROVENT EUA tables 14.3.1.1.1 and 14.3.1.4.1 and the PROVENT SAE narratives

Deaths
As of the May 5, 2021 database lock, a total of 8 deaths (4 in each treatment arm; 0.12% and 0.23% in the AZD7442 and placebo arms, respectively) occurred in PROVENT. Two were related to COVID-19 (both in placebo recipients who were censored from the primary efficacy analysis due to unblinding prior to death). Four were related to (b) (4) (two placebo recipients and two AZD7442 recipients). One (b) (4) One (b) (4) died on (b) (4)

In the topline data from the August 29, 2021 database lock, there were an additional 8 deaths (5 in the AZD7442 arm and 3 in the placebo arm). Among (b) (4) recipients, these included two deaths from pre-existing conditions after (b) (4) for non-COVID-19-related reasons (b) (4), a death due to (b) (4), death due to (b) (4), and a death attributed to (b) (4). Among placebo recipients, the three additional deaths were attributed to (b) (4).
Overall, proportionally fewer AZD7442 recipients versus placebo recipients had an outcome of death (9/3461 (0.26%) versus 7/1736 (0.40%), respectively).

Overall, the deaths reported in PROVENT do not raise safety concerns. There was a higher rate of deaths in the placebo group (0.26% in AZD7442 versus 0.40% in placebo groups), and the study enriched for subjects with comorbidities that would

put them at risk for severe COVID-19 but which would also put them at higher risk for death from other causes.

Serious Adverse Events
A total of 83 SAEs were reported in 73 subjects: 50 (1%) AZD7442 recipients and 23 (1%) placebo recipients. No single SAE was seen in more than 0.1% of subjects, and the SAEs ranged across the different system organ classes (SOCs), with the most SAEs in the infections and infestations SOC (13 subjects: 8 AZD7442 recipients and 5 placebo recipients), the injury, poisoning, and procedural complications SOC (12 subjects: 4 AZD7442 recipients and 8 placebo recipients), and the nervous system disorders SOC (9 subjects: (b) (4) AZD7442 recipients and (b) (4) placebo recipients). The only specific SAEs seen in more than one subject were acute myocardial infarction (b) (4) AZD7442 recipients, (b) (4) placebo recipients), myocardial infarction (b) (4) AZD7442 recipients, (b) (4) placebo recipients), musculoskeletal chest pain (b) (4) AZD7442 recipients, (b) (4) placebo recipients), transient ischemic attack (b) (4) AZD7442 recipients (b) (4) placebo recipients), leukocytosis (b) (4) AZD7442 recipients, (b) (4) placebo recipients), COVID-19 (b) (4) AZD7442 recipients, (b) (4) placebo recipients), cellulitis (b) (4) AZD7442 recipients, (b) (4) placebo recipients), acute kidney injury (b) (4) AZD7442 recipients, (b) (4) placebo recipients), nephrolithiasis (b) (4) AZD7442 recipients, (b) (4) placebo recipients), and hypertension (b) (4) AZD7442 recipients, (b) (4) placebo recipients). These data should be considered in the context of twice as many subjects receiving AZD7442 as placebo in PROVENT.

Please see the assessment of cardiac SAEs across the unblinded AZD7442 trials later in this section.

One SAE, (b) (4), was assessed as (b) (4) by the investigator.

- The subject was a (b) (4)
  - (b) (4)

(b) (4)

(b) (4)

Common Adverse Events

A total of 35% (1221/3461) of AZD7442 recipients and 34% (593/1736) placebo recipients reported at least one AE by the May 5, 2021 database lock (median 83 days of follow-up). The most common AEs are shown in ***Table 20***. The prevalence of specific AEs were overall balanced between the treatment groups. About half of the subjects who reported AEs (628/3461, or 18%, of AZD7442 recipients and 284/1736, or 16%, of placebo recipients) reported AEs within 14 days of investigational product receipt. The only AEs reported in >2% of subjects within 14 days of investigational product receipt were headache (119/3461, or 3%, of AZD7442 recipients and 53/1736, or 3%, of placebo recipients) and fatigue (76/3461, or 2%, of AZD7442 recipients and 31/1736, or 2%, of placebo recipients). A total of 94% of AZD7442 recipients and 94% of placebo recipients who reported AEs had a maximum severity grade of mild or moderate. AEs considered related to study treatment were infrequent (reported in 8% and 7% of AZD7442 and placebo recipients, respectively) and overall balanced between treatment groups; the only specific AE considered related to study treatment reported in at least 2% of subjects in either treatment group was headache (59/3461, or 2%, of AZD7442 recipients versus 24/1736, or 1%, of placebo recipients).

Table 20: Adverse Events Reported by ≥2% of Subjects in Either Treatment Group in PROVENT through May 5, 2021

Preferred Term, n (%)	AZD7442 (n=3461)	Placebo (n=1736)
Subjects with at least 1 AE	1221 (35%)	593 (34%)
Headache	194 (6%)	93 (5%)
Fatigue	132 (4%)	56 (3%)
Cough	88 (3%)	44 (3%)
Diarrhea	85 (2%)	34 (2%)
Oropharyngeal pain	84 (2%)	34 (2%)
Rhinorrhea	79 (2%)	26 (1%)
Nausea	67 (2%)	23 (1%)
Nasal Congestion	67 (2%)	21 (1%)
Urinary Tract infection	54 (2%)	23 (1%)
Myalgia	53 (2%)	22 (1%)
Back pain	41 (1%)	28 (2%)
Vaccination Complication	40 (1%)	27 (2%)

Source: Adapted from Table 51 in the EUA Request

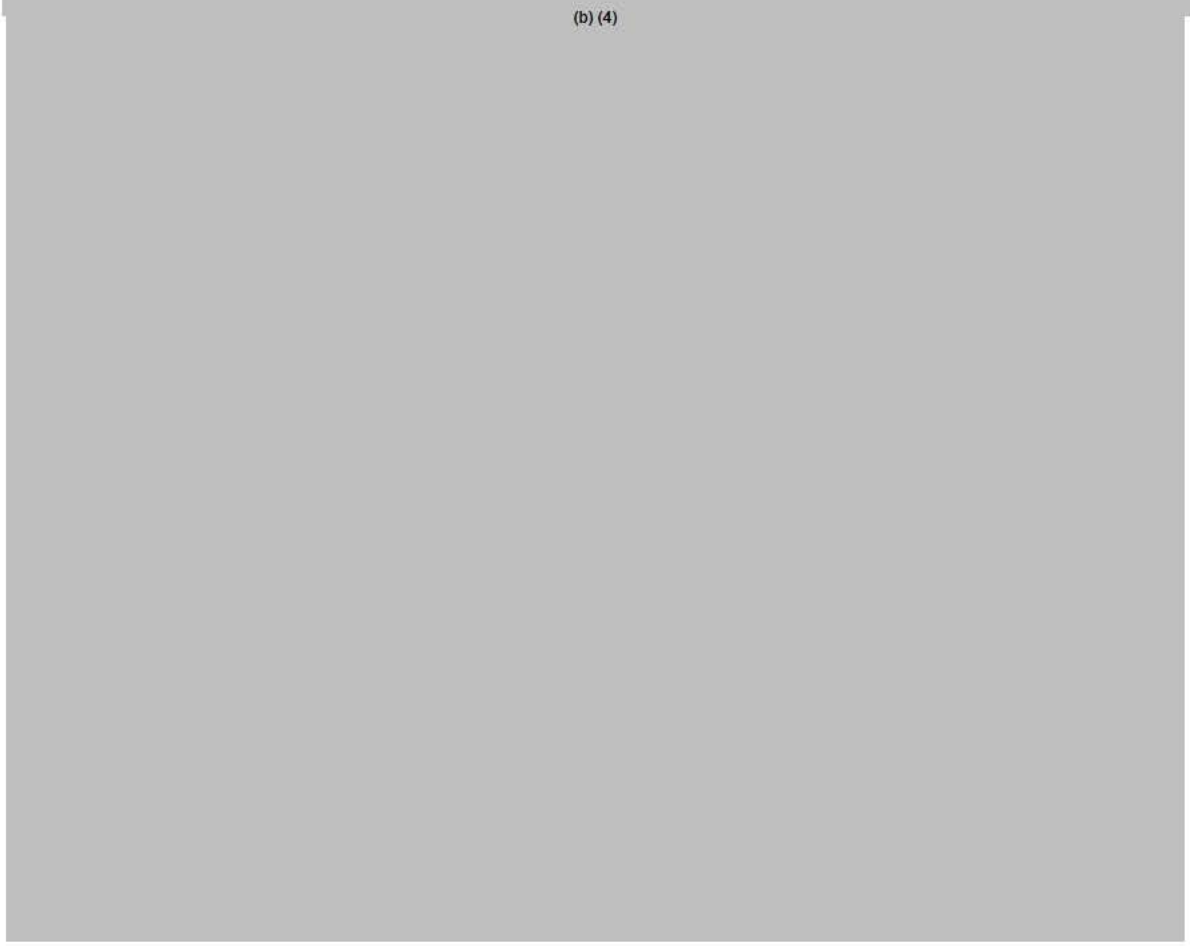
Adverse Events of Special Interest

The AESIs for AZD7442 were anaphylaxis and other serious hypersensitivity reactions, including immune complex disease, and injection site reactions. AESIs were reported at a slightly higher rate in AZD7442 versus placebo recipients. A total of 93/3461 (3%) AZD7442 recipients and 37/1736 (2%) placebo recipients had AESIs. Most (93%) of subjects reporting AESIs had a maximum severity of mild, and no AESIs were graded higher than moderate in intensity. The most common category of AESI was injection site reaction, which was reported in 82 (2%) and 36 (2%) of AZD7442 and placebo recipients, respectively. The most common injection site reaction was injection site pain (28 and 16 AZD7442 and placebo recipients, respectively). The median day of onset of injection site reactions was Day 1, and the median duration of injection site reactions was 2 days.

One subject (b) (4) which was considered by the investigator to be (b) (4) :

- Subject (b) (6) was a (b) (4) (b) (4) ,

(b) (4)



Medically Attended Adverse Events

Medically attended AEs were defined as AEs leading to medically-attended visits that were not routine visits. Overall, 10% of AZD7442 recipients and 9% of placebo recipients had medically attended AEs through the data cutoff date. Most of these were in the infections and infestations SOC (3% and 2% of AZD7442 and placebo recipients), the musculoskeletal and connective tissue disorders SOC (2% and 1% of AZD7442 and placebo recipients), and the gastrointestinal disorders SOC (1% and 1% of AZD7442 and placebo recipients). No medically attended AEs were reported in >0.5% of subjects. The most common medically attended AEs were urinary tract

infection (17 and 9 AZD7442 and placebo recipients, respectively), hypertension (14 and 9 AZD7442 and placebo recipients, respectively), and cough (12 and 6 AZD7442 and placebo recipients, respectively).

Laboratory Findings and Vital Signs
Changes in laboratory parameters and vital signs from baseline were similar between the AZD7442 and placebo groups.

Immunogenicity Data
Separate MSD-ECL assays are used for detection of anti-drug antibodies (ADA) specific to each antibody (tixagevimab and cilgavimab) using a multi-tiered (screening and confirmation) approach. The proposed assays for detection of anti-AZD1061 or anti-AZD8895 antibodies in human serum have been adequately validated and are tolerant with respect to the onboard drug levels of AZD1061 (13.5 μg/mL) and of AZD8895 (14.2 μg/mL) when given as consecutive IM injections at an individual dose of 150 mg. All AZD7442 patient samples tested to date have screened negative, therefore neutralizing ADA assays have not yet been validated. The proposed immunogenicity assay and strategy are acceptable to support the EUA.

Limited immunogenicity results were provided for PROVENT.

- Midway through the EUA review (11/11/21), ADA data were provided for 10% of subjects at baseline (340 AZD7442 recipients and 165 placebo recipients) and approximately 1% of subjects post-baseline.
    - Baseline ADA samples were positive against either tixagevimab or cilgavimab in 1-2% of subjects
    - The only positive post-baseline ADA sample was in a placebo recipient
- At the end of the EUA review period (12/2/21), the Applicant sent (b) (4)
    - Among the subjects with SAEs of (b) (4)
        - Subject (b) (6) (b) (4) (b) (4)
        - Subject (b) (6), (b) (4) (b) (4)
        - Subject (b) (6), (b) (4)

(b) (4)

- Among the subjects with SAEs of (b) (4) (6 AZD7442 recipients and 1 placebo recipient), no subjects had documented (b) (4). However, one subject ((b) (6)), an (b) (4)
- In addition:
  - An (b) (4) ((b) (6)) (b) (4)
  - An (b) (4)

- These data are difficult to interpret. Positive ADA could theoretically lead to clumping of study product and possibly increased thrombotic risk, and more subjects with myocardial infarctions had positive ADA results than in the general PROVENT population. However, the (b) (4) recipient with a myocardial infarction by Day 183 had positive ADA results too, and not all (b) (4) recipients with myocardial infarctions had positive ADA results. ADA results for the remainder of the subjects in PROVENT will be included as a condition of authorization, and we have asked the Applicant to prioritize conducting these assays on the subjects with thrombotic SAEs from the Phase 2/3 trials.

STORM CHASER Safety Results

The supportive safety analysis population from STORM CHASER includes 749 AZD7442 recipients and 372 placebo recipients. Adverse events in STORM CHASER were graded according to a five point scale adapted from the toxicity grading scale of the CTCAE version 5.0 from the National Institutes of Health. Clinical events related to COVID-19, including deaths and SAEs, could be included as AEs.

The safety analysis from STORM CHASER included data from approximately one fifth as many subjects as PROVENT and also had several similar limitations to PROVENT:

1. Duration of AE collection, Database lock: The duration over which AEs were collected per study subject ranged >20-fold as the EUA submission only contained AEs collected through the database lock date regardless of the date of enrollment and study product administration. However, the follow-up durations were similar and equally varied between individual subjects when comparing the AZD7442 and placebo groups (the median duration [range] was 49 days [5, 115] for AZD7442 recipients and 48 days [20, 113] for placebo recipients).

2. Duration of AE collection, Half-life: The duration over which AEs were collected did not extend to the latest time point when the study product would be expected to still be in the body (five half-lives for AZD7442 is ~450 days).
3. Unblinding: During the AE reporting period, 8% and 14% of the AZD7442 and placebo recipients were unblinded, and 3% and 13% of the AZD7442 and placebo recipients received COVID-19 vaccine.

Safety Overview

Table 21 below shows the summary of safety events in STORM CHASER. In general, rates of overall safety events were similar between treatment groups, with proportionally more overall AEs, AEs related to study treatment, grade 3 or higher AEs, and AESIs reported in the placebo group. AZD7442 was administered sequentially as two separate IM injections (one for each mAb), so it was theoretically possible that an AE could develop so quickly as to prevent or delay the second injection; however, this occurrence was not reported.

Table 21: Summary of Safety (STORM CHASER)

Adverse Events, n (%)	**AZD7442 (n=749)**	**Placebo (n=372)**
Any AE	162 (22%)	111 (30%)
AE related to study treatment	37 (5%)	22 (6%)
Any Grade 3 or higher AE	8 (1%)	6 (2%)
SAE	5 (<1%)	3 (<1%)
SAE related to study treatment	0	0
AEs with outcome of death	0	0
AEs of special interest (AESI)*	4 (<1%)	5 (1%)
AESI related to study treatment	3 (<1%)	5 (1%)
Medically attended AEs (MAAEs)	32 (4%)	16 (4%)
MAAEs related to study treatment	3 (<1%)	1 (<1%)

*AEs of special interest included anaphylaxis, other serious hypersensitivity reactions (including immune complex disease), and injection site reactions

Source: adapted from STORM CHASER EUA tables 14.3.1.1.1 and 14.3.1.4.

Deaths

There were no deaths in STORM CHASER through the data cut off period for the primary analysis. In the topline data from the August 19, 2021 database lock, three deaths were reported: (b) (4) , and "death" with no other details provided ((b) (4)). The rate of death was equal in both treatment arms (0.27% and 0.27%).

Serious Adverse Events

A total of 11 SAEs were reported in 8 subjects: (b) (4) . The only SAE reported in more than one subject was pneumonia (reported in one AZD7442 and one placebo recipient). SAEs reported in (b) (4) recipients (one subject each) included pneumonia, COVID-19, (b) (4) , basal ganglia hemorrhage, (b) (4) , and (b) (4) . No cardiac SAEs

were reported in STORM CHASER (with either the primary analysis data or the topline data with the August data cut-off date). No SAEs were considered related to study treatment.

Common Adverse Events

A total of 22% (162/749) of AZD7442 recipients and 30% (111/372) placebo recipients reported at least one AE by the April 7, 2021 database lock (median 49 days of follow-up). The most common AEs are shown in ***Table 22***. The prevalence of specific AEs were similar between the treatment groups, with slightly more placebo recipients proportionally reporting most AEs; this prevalence should be interpreted in the context of STORM CHASER having a safety population with 22% of the subjects and a 34-days-shorter median follow-up period compared to PROVENT. Over half of the subjects who reported AEs (108/749, or 14%, of AZD7442 recipients and 73/372, or 20%, of placebo recipients) reported AEs within 14 days of investigational product receipt. A total of 95% of AZD7442 recipients and 95% of placebo recipients who reported AEs had a maximum severity grade of mild or moderate. A total of 7 (b) (4) recipients reported AEs with a maximum severity grade of severe (one subject each had severe pneumonia, sepsis, (b) (4) upper limb fracture, decreased appetite, dizziness, syncope, basal ganglia hemorrhage, anxiety, (b) (4) , and acute kidney injury), and one (b) (4) recipient reported an AE with a maximum severity grade of potentially life-threatening ((b) (4) and (b) (4) AEs considered related to study treatment were infrequent (reported in 5% and 6% of AZD7442 and placebo recipients, respectively) and overall balanced between treatment groups; the only specific AE considered related to study treatment reported in at least 2% of subjects in either treatment group was headache (9/749, or 1%, of AZD7442 recipients versus 8/372, or 2%, of placebo recipients).

Table 22: Adverse Events Reported by ≥2% of Subjects in Either Treatment Group in STORM CHASER through April 7, 2021

Preferred Term, n (%)	AZD7442 (n=749)	Placebo (n=372)
Subjects with at least 1 AE	162 (22%)	111 (30%)
Headache	40 (5%)	30 (8%)
Fatigue	24 (3%)	17 (5%)
Cough	22 (3%)	16 (4%)
Oropharyngeal pain	23 (3%)	12 (3%)
Nasal Congestion	22 (3%)	10 (3%)
Rhinorrhea	22 (3%)	10 (3%)
COVID-19	15 (2%)	13 (3%)
Pain	11 (1%)	13 (3%)
Chills	12 (2%)	11 (3%)
Pyrexia	14 (2%)	9 (2%)
Myalgia	9 (1%)	10 (3%)
Nausea	9 (1%)	10 (3%)
Diarrhea	6 (<1%)	11 (3%)
Urinary Tract Infection	8 (1%)	6 (2%)

Source: Adapted from Table 61 in the EUA Request

Adverse Events of Special Interest
The AESIs for AZD7442 were anaphylaxis and other serious hypersensitivity reactions, including immune complex disease, and injection site reactions. By the data cut off date, 4 (<1%) AZD7442 recipients and 5 (1%) placebo recipients had reported an AESI. No subjects had anaphylaxis or serious hypersensitivity reactions, and no AESIs were considered SAEs. The AESIs included injection site pain (3 AZD7442 recipients and 1 placebo recipient), pruritus (1 AZD7442 recipient and 3 placebo recipients), and "injection site reaction" (1 (b) (4) recipient).

Medically Attended Adverse Events
Medically attended AEs were defined as AEs leading to medically-attended visits that were not routine visits. Overall, 4% of AZD7442 recipients and 4% of placebo recipients had medically attended AEs through the data cutoff date. No specific medically attended AEs were reported in >0.5% of subjects. The most common medically attended AEs were urinary tract infection (2 and 2 AZD7442 and placebo recipients, respectively) and headache (3 and 1 AZD7442 and placebo recipients, respectively).

Laboratory Findings and Vital Signs
Changes in laboratory parameters and vital signs from baseline were similar between the AZD7442 and placebo groups.

Immunogenicity Data
No immunogenicity results were provided for STORM CHASER, although these analyses are ongoing.

D8850C00001 Safety Results

The supportive safety analysis from D8850C0001 includes 50 AZD7442 recipients in five dose cohorts and 10 placebo recipients. AZD7442 recipients (N=10 per dose cohort) received single doses of 300 mg IM, 300 mg IV, 1000 mg IV, 3000 mg IV, and 3000 mg IV co-administered (i.e., both mAbs administered combined in a single infusion rather than separate sequential infusions). Follow-up data for this study extends to 271 days for the 300 mg IM and 300 mg IV cohorts and up to 211 days in the 1000 mg and 3000 mg cohorts; 2 placebo recipients were enrolled with each dose cohort, so the follow-up time for the placebo group should be approximately the average of the AZD7442 dose cohorts. The population enrolled in D8850C0001 differed from PROVENT and STORM CHASER in that all subjects were healthy adults 18-55 years of age with a maximum BMI of 30.0 kg/m^2. Adverse events in D8850C0001 were graded according to a three point scale:

1. Mild (awareness of sign or symptom, but easily tolerated)
2. Moderate (discomfort sufficient to cause interference with normal activities)
3. Severe (incapacitating with inability to perform normal activities

By the data cut-off date (June 6, 2021), there were no deaths, SAEs, AEs leading to discontinuation of study product, or AEs graded as severe. One subject in the (b) (4) AEs of arthralgia and headache. However, these AEs resolved after stopping the infusion and ECG and vital signs were normal, and the infusion was restarted and completed without further recurrence of AEs.

With the caveat that the follow-up time was longer in the lower dose cohorts, there were no dose-related increases in occurrence of overall AEs or specific AEs, and the placebo group had a higher proportion of subjects reporting AEs than any of the AZD7442 dosing groups. AEs were reported in 7/10 (70%) placebo recipients, 1/10 (10%) 300 mg IM AZD7442 recipients, 5/10 (50%) 300 mg IV AZD7442 recipients, 6/10 (60%) 1000 mg IV AZD7442 recipients, 5/10 (50%), 3000 mg IV AZD7442 sequential administration recipients, and 5/10 (50%) 3000 mg IV AZD7442 co-administered recipients. The one AE reported in the 300 mg IM AZD7442 group, the dose proposed in this EUA, was mild nasopharyngitis. In the pooled AZD7442 by IV administration groups (n=40), the most common AEs were headache (7/40, or 18%, versus 2/10, or 20%, in the placebo group), back pain (3/40, or 8%, versus 1/10, or 10%, in the placebo group), and fatigue (3/40, or 8%, versus 0 in the placebo group).

Immunogenicity Data

Samples were collected from all subjects in D8850C00001 from all subjects pre-dose and 7, 14, 30, 90, 150, 210, and 360 days post-dose, and data was available through Day 211 by the data cut-off date (June 6, 2021). No subjects tested positive for ADA to either AZD8895 or AZD1061 through Day 211.

Safety Issues of Concern

Issue 1: Cardiac Serious Adverse Events

Issue: An imbalance in cardiac SAEs related to coronary artery disease or myocardial ischemia (e.g., myocardial infarctions) was observed in both PROVENT and the outpatient COVID-19 treatment trial TACKLE, but not STORM CHASER, through the original data cut-off dates for the primary analyses. In addition, the imbalance in overall cardiac SAEs, including SAEs related to coronary artery disease or myocardial ischemia, appeared to become more pronounced in PROVENT with additional follow-up time using the August 2021 data cut-off date, at which time an imbalance in cardiac failure SAEs was also seen.

Cardiac SAEs that occurred through Day 183 in PROVENT through the August 2021 data cut-off date are shown in ***Table 23*****Error! Reference source not found.** below.

Table 23: Cardiac SAEs in PROVENT through Day 183 with the 8/29/21 Data Cut-off

	AZD7442 (n=3461)	**Placebo (n=1736)**
Subjects with any cardiac SAE*#	22 (0.64%)	3 (0.17%)
SAEs related to coronary artery disease or myocardial ischemia^	10 (0.29%)	2 (0.12%)
Myocardial infarctions+	*8 (0.23%)*	*1 (0.06%)*
SAEs related to cardiac failure[α]	6 (0.17%)	1 (0.06%)
SAEs related to an arrhythmia[β]	4 (0.12%)	1 (0.06%)
Other (cardiomegaly, cardiomyopathy, and cardio-respiratory arrest)	3 (0.09%)	0

*Includes all cardiac disorder System Organ Class (SOC) SAEs plus an AZD7442 recipient with an SAE of troponin increased under the Investigations SOC which was diagnosed during the hospitalization as a non-ST elevation myocardial infarction, a subject with an SAE of heart rate irregular under the investigations SOC, and a placebo recipient with an SAE of arteriosclerosis under the vascular disorder SOC which referred to worsening coronary atherosclerosis.
#One AZD7442 recipient had SAEs of both arrhythmia and cardiomyopathy, and one placebo recipient had SAEs of both acute left ventricular failure and arteriosclerosis.
^Includes the preferred terms angina pectoris, coronary artery disease, arteriosclerosis, troponin increased, acute myocardial infarction, and myocardial infarction.
+Includes the preferred terms acute myocardial infarction, myocardial infarction, and troponin increased.
αIncludes the preferred terms cardiac failure congestive, acute left ventricular failure, cardiac failure, and cardiac failure acute.
βIncludes the preferred terms atrial f brillation, arrhythmia, paroxysmal atrioventricular block, and heart rate irregular.
Source: adapted from Tables 14.3.2.1.1B and 14.3.2.6.1B and the updated ADAE dataset in the August 2021 data cutoff update.

In the AstraZeneca-sponsored Phase 3 AZD7442 trials PROVENT, STORM CHASER, and TACKLE, SAEs related to coronary artery disease or myocardial ischemia were reported in:

- PROVENT (through Day 183 using the August data cut-off):
  - A total of [redacted](b) (4)(one fatal)
    - [redacted](b) (4)
      [redacted](b) (6)
)

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
    - A total of [redacted]
    - [redacted]
    - [redacted]

- STORM CHASER: no cardiac SAEs (out of 749 AZD7442 recipients and 372 placebo recipients) were reported with either the original or the later data cut-off dates.
    - *Notably, the study subjects in STORM CHASER versus PROVENT were younger (median age 48 versus 57 years) and less likely to have baseline*

hypertension (24% versus 36%), diabetes (11% versus 14%), cardiovascular disease (3% versus 8%), or chronic kidney disease (2% versus 5%).

- TACKLE (in which subjects with mild to moderate COVID-19 were randomized 1:1 to receive AZD7442 600 mg IM versus placebo):
  - A total o (b) (4) (one fatal), plus an additional SAE of (b) (4)
    - (b) (4)
  - A total of (b) (4) **recipients**

In addition, in PROVENT through Day 183 with the August data cut-off date, SAEs related to cardiac failure were reported in:

- A total of (b) (4) **recipients**
  - (b) (4), (b) (6)
- A total of (b) (4) **ecipients**
  - (b) (4) (Subject number (b) (4)

Assessment:

- Although infrequent overall (less than 0.5%), a four-fold higher proportion of AZD7442 (0.23%) versus placebo (0.06%) recipients reported myocardial infarction SAEs, and a three-fold higher proportion of AZD7442 (0.20%) versus placebo (0.06%) recipients reported cardiac failure SAEs, through Day 183.
- All of the subjects with cardiac SAEs had pre-existing cardiac risk factors that would put them at risk for cardiac ischemia events. However, baseline cardiac risk factors appeared to be balanced between treatment groups (see Table 24 below), and one could argue that subjects with cardiac risk factors might be the population where a cardiac ischemia safety signal would first be detected.

Table 24: Baseline Cardiac Risk Factors by Treatment Group in PROVENT

	AZD7442 (n=3460)	Placebo (n=1737)
Age in years: Median (Min, Max)	57 (b) (4)	57 ((b) (4)
Number (%) ≥ 65 years	817 (24%)	409 (24%)
Number (%) male	1865 (54%)	935 (54%)
Number (%) with baseline: BMI ≥30 kg/m^2	1456 (42%)	712 (41%)
Hypertension	1229 (36%)	637 (37%)
Smoking	720 (21%)	370 (21%)
Diabetes	492 (14%)	242 (14%)
Cardiovascular Disease	272 (8%)	151 (9%)
Chronic Kidney Disease	184 (5%)	86 (5%)

Source: Adapted from PROVENT table 14.1.4.1, in the EUA Request

- There was no clear temporal pattern, with events reported from several hours after AZD7442 receipt through the end of the follow-up period.
- There was no nonclinical signal for cardiac toxicity. No off-target binding for either antibody contained in AZD7442 (cilgavimab or tixagevimab) was seen in the tissue cross reactivity studies.
- There is no in vitro evidence that when tixagevimab and cilgavimab reach the blood stream, they will aggregate more than natural, endogenous antibodies.
  - An in vitro study suggests that the combination of the TM and YTE mutations (contained in both tixagevimab and cilgavimab) can result in lower thermostability, greater C_H2 conformational flexibility, and poorer solubility and aggregation profiles (*Borrok MJ et al. An "FC-Silenced" IgG1 Format with Extended Half-Life Designed for Improved Stability. Journal of Pharmaceutical Sciences: 2017; 104 (4): 1008-1017*).
  - However, based on in vitro characterization studies of cilgavimab and of tixagevimab, it does not appear that they would form aggregates at levels exceeding those expected from other IgG1 or endogenous antibodies.
- There is no evidence that the cardiac ischemia events were related to binding of cilgavimab or tixagevimab to SARS-CoV-2 antigens. None of the subjects listed in PROVENT with cardiac ischemia events with the May data cut-off had

evidence of SARS-CoV-2 infection at the time of the event, and none of them had received a COVID-19 vaccine prior to the event.

- A consult done by colleagues in the Division of Cardiology and Nephrology of the data submitted with the original data cut-off dates concluded that the empirical imbalance may have been by chance (see the review by Dr. Fortunato Senatore from 11/15/2021 in DARRTS).
  - *Of note, we sent three information requests to the Applicant requesting their assessment of the imbalance in cardiac events (for the Applicant's responses, see IND 150712 SDN 69 from 9/3/2021, EUA 104 SDN 9 from 10/22/2021, and EUA 104 SDN 15 from 11/17/2021).*

Conclusion: Given the seriousness of the events (including the myocardial infarction that resulted in death) and what appears to be a clustering of events with similar pathophysiologies, the imbalance will be communicated in the Fact Sheets. The Fact Sheets will also specify that health care providers should advise patients to seek immediate medical attention if they experience any signs or symptoms suggestive of a cardiovascular event. However, as it is unclear if the PROVENT imbalances in myocardial infarction SAEs, and in cardiac failure SAEs with the later data cut-off date, are by chance or are related to the study product, the Fact Sheets will also include that a causal relationship between EVUSHELD and these events has not been established.

We will continue to monitor for these events through monthly aggregate safety reports for SAEs in the Cardiac Disorder SOC and other non-cardiac thrombotic SAEs (in-period and cumulative plus narratives). In addition, we are asking the Applicant to collect the following biomarkers for thrombotic events before dosing and at the visits following dosing in the repeat dose substudy (d-dimer, P-selectin, thrombin, and Factor VIII).

Issue 2: Seizures

Issue: A potential safety concern of an imbalance in AEs of seizures has been raised with other COVID-19 mAb products.

Assessment: There was not an imbalance in seizure and partial seizure AEs in the AZD7442 data submitted:

- In PROVENT, 3/3461 AZD7442 recipients versus 2/1736 placebo recipients reported AEs of seizure or partial seizure.
- In STORM CHASER, there were no AEs of seizure or partial seizure reported.
- In response to an information request, the Applicant also informed us that there were no AEs of seizure or partial seizure in TACKLE, their outpatient COVID-19 treatment trial in which subjects were randomized to AZD7442 600 mg IM (n=452) versus placebo (n=451).

Conclusion: There is no discernible safety signal for seizures with AZD7442 use in the Phase 3 trials PROVENT, STORM CHASER, and TACKLE.

X. Specific Populations

Rationale for Inclusion of Adolescents Under EUA

As of November 11, 2021 over 6.6 million children have tested positive for COVID-19 in the United States, Puerto Rico, and Guam (https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/). Based on these data, for the week ending November 11, 2021, children represent 27% of all COVID-19 cases. While COVID-19 is typically milder in children, some pediatric patients require hospitalization and ICU-level care (Götzinger et al. 2020). Given that COVID-19 can be a serious and life-threatening disease in adolescent patients (particularly in those with risk factors for the development of severe illness and hospitalization), the similarities in physiology to adults, the similar PK in adolescents weighing ≥40 kg based on modeling, and safety profile, and existing concerns in immune compromised and those with a history of severe adverse reactions to the vaccine or vaccine products for adolescents, there is prospect of benefit for this population.

Based on the totality of evidence to support the prospect of benefit, and that it is reasonable to believe the known and potential benefits outweigh the known and potential risks, the authorization of tixagevimab and cilgavimab administered together for pre-exposure prophylaxis also includes adolescents who are 12 years of age and older and who weigh at least 40 kg.

Dosing Considerations for Specific Populations

- No dosage adjustment is recommended in pediatric individuals who weigh at least 40 kg and are 12 years of age and older. Tixagevimab and cilgavimab is not recommended for pediatric individuals weighing less than 40 kg or those less than 12 years of age.
- Safety and PK data of tixagevimab and cilgavimab are not available in pediatrics, pregnant women, lactating women, or patients with hepatic insufficiency. No dosage adjustment is recommended based on age, sex, race, body weight, renal impairment, during pregnancy or while lactating, or for disease severity (see *Section XI*).
- Nonclinical reproductive toxicology studies with tixagevimab and cilgavimab have not been conducted.
- No binding of clinical concern was seen with either tixagevimab or cilgavimab in a tissue cross-reactivity study in select human fetal tissues.
- No specific risks to pregnant or lactating women have been identified based on nonclinical safety data.

XI. Human Clinical Pharmacology

AZD7442 (EVUSHELD) is a combination of two recombinant human IgG1 monoclonal antibodies (mAbs), AZD8895 (tixagevimab) and AZD1061 (cilgavimab). The clinical pharmacology program for tixagevimab and cilgavimab is ongoing. ***Table 25*** provides an overview of a Phase 1 PK study in adults as well as two Phase 3 trials evaluating AZD7442 administered intramuscularly for pre-exposure prophylaxis and post-exposure prophylaxis of COVID-19 in adults. Descriptive serum PK results are comparable between tixagevimab and cilgavimab for all cohorts, with a terminal half-life of approximately 90 days (IM and IV). Administering tixagevimab and cilgavimab separately compared to combined did not alter the PK profile. PK serum samples were analyzed using a validated bioanalytical method using HPLC MS/MS. Of note, no multiple (or repeat) dose, nor specific population (e.g., pediatrics), clinical studies or trials have been conducted.

Table 25: Overview of Clinical Trials (IND 150712) with Reported Single Dose PK

Study Number	Dose(s) and Route	No. Adults	GeoMean C_{max} (mcg/mL)		GeoMean $AUC_{0\text{-}210,\ day}$ (day·mcg/mL)	
			Tixagevimab	Cilgavimab	Tixagevimab	Cilgavimab
D8850C00001 (Phase 1)	300 mg IM[a]	10	16.5	15.3	2,010	1,721
	300 mg IV[a]	10	52.7	50.1	2,936	2,580
	1000 mg IV[b]	10	162.2	154.3	7,858[e]	8,049[e]
	3000 mg IV[c]	10	505.8	465.5	25,300	24,110
	3000 mg IV[c,d]	10	447.8	419.3	24,990	24,310
D8850C00002 (Phase 3; PROVENT)	150 mg IM[a]	1222	11.9[f]	11.3[f]	--	--
D8850C00003 (Phase 3; STORM CHASER)		128	11.4[f]	11.0[f]	--	--

[a] 300 mg is 150 mg tixagevimab and 150 mg cilgavimab
[b] 1000 mg is 500 mg tixagevimab and 500 mg cilgavimab
[c] 3000 mg is 1500 mg tixagevimab and 1500 mg cilgavimab
[d] co-administration (i.e., not sequential).
[e] n=9
[f] 28-days post dose;(other times not shown, i.e., 7, 28, 57, 91,182, 365 and 456 days post-dose). Data is not yet available in most patients 180 and greater days post-dose.

Data are presented as geometric means (GeoMean) and geometric %CV. Intramuscular = IM (ventrogluteal muscle); C_{max}, maximum concentration; $AUC_{0\text{-}210,\ day}$ = area under the serum concentration-time curve from time zero to Day 211

Source: D8850C00001 CSR Tables 14.2.4.1 and 14.2.4.2, IND 150712, SN 0068. D8850C00002 EUA PROVENT Table 14.2.4.2, EUA 000104 SN 01. D8850C00003 STORM CHASER EUA Table 14.2.5.1, EUA 000104 SN01

Proposed Prophylaxis Dose and Drug Exposures

The proposed prophylaxis dose is 300 mg (150 mg of tixagevimab and 150 mg cilgavimab) AZD7442 administered by sequential IM injections, at different injection sites. A summary of PK parameters, properties, and PK of serum tixagevimab and cilgavimab following administration of 300 mg EVUSHELD IM in adults are provided in ***Table 26***.

Table 26: Summary of Serum Tixagevimab and Cilgavimab Exposure Metrics Following a Single 300 mg EVUSHELD IM Dose

Exposure Metrics [1]	Tixagevimab (n=10)	Cilgavimab (n=10)
$C_{1, day}$ (mcg/mL)	4.4 (92.2)	3.9 (94.4)
C_{max} (mcg/mL)	16.5 (35.6)	15.3 (38.5)
$C_{150, day}$ (mcg/mL)	6.6 (25.5)	5.5 (35.2)
$C_{210, day}$ (mcg/mL)	4.0 (31.6)	3.7 (37.1)
$AUC_{0-210, day}$ (day·mcg/mL)	2,010 (28.50)	1,721 (30.51
AUC_{inf} (day·mcg/mL)[2]	2,529 (30.22)	2,133 (31.66)
PK Parameter or Property	**Tixagevimab**	**Cilgavimab**
Absorption		
Bioavailability (F) (%)	68.5	65.8
T_{max} (days) [3]	14.0 (3.1 – 30)	14.0 (3.1 – 60.2)
Distribution		
Volume of Distribution (V/F) (L)[4]	7.66 (1.97)	8.68 (2.74)
NLF:Serum Penetration Ratio[5,6]	0.0158 (0.008, 0.0286)	0.0205 (0.008, 0.0282)
Elimination		
Half-life (days)	87.9 (13.95)	82.9 (12.26)
Apparent Clearance (CL/F) (L/day)[7]	0.0618 (0.0188)	0.0739 (0.0281)
Metabolism	Catabolic pathways; Same manner as endogenous IgG	
Excretion	Unknown; Not likely to undergo renal excretion	

[1] Geometric Mean (geometric %CV)
[2] % AUC_{inf} extrapolated is <20% in all adults receiving a single 300 mg EVUSHELD IM dose.
[3] Median (range)
[4] This apparent volume of distr bution at pseudo-distribution equilibrium (Vz/F) is similar to the pooled population PK estimate of the steady state Volume of distribution (Vss = V1+V2 for two-compartment model) after considering bioavailability (F) (EUA request, Table 72, pg 213).
[5] The range of NLF:serum ratio is dose-independent based on the IV infusion dosing of 300 mg to 3000 mg (data not shown, D8850C00001 clinical study). Additionally, the NLF:serum ratio is monoclonal antibody-independent and in the same range for 7 and 30 days post-dose (data not shown). Given these observations, the applicant pooled all available data and calculated an NLF:serum penetration ratio of 1.81% used for subsequent in vitro to in vivo PK/PD translation.
[6] median (25^{th}, 75^{th} percentile)
[7] This apparent clearance (CL/F) is similar to the pooled population PK estimate of CL after considering bioavailability (F) (EUA request, Table 72, pg 213).

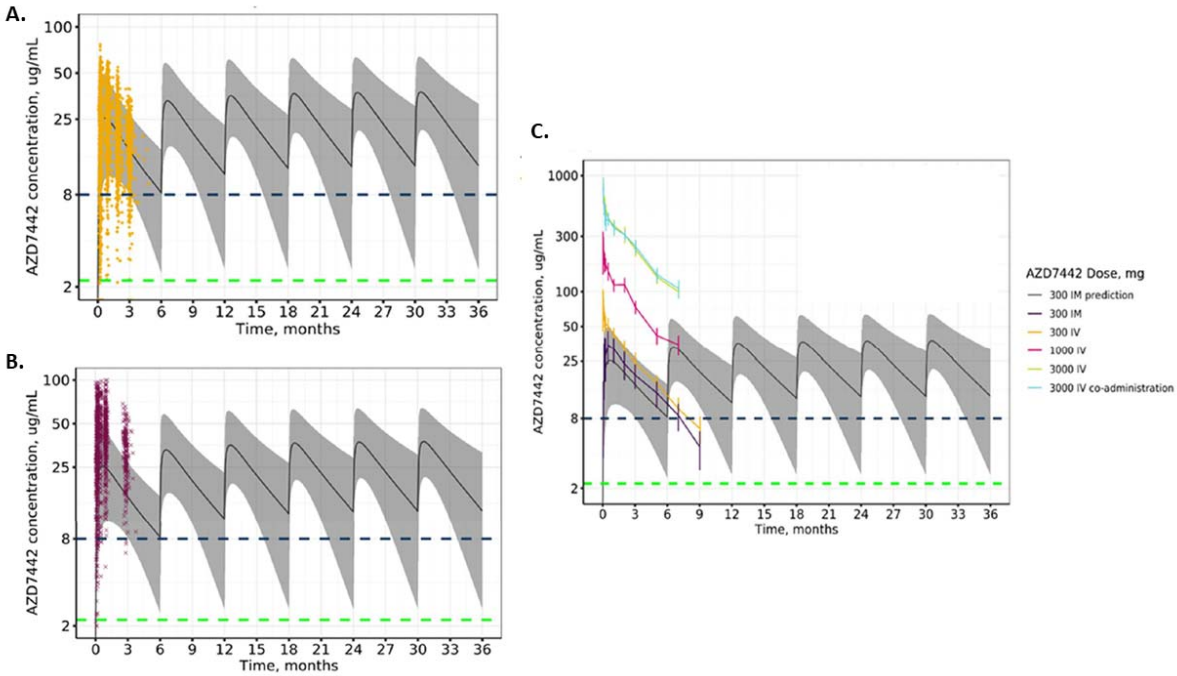
$C_{1, day}$ = observed concentration 1 day after dosing, i.e., on day 2; C_{max}, maximum concentration; T_{max} = time to maximum concentration; $C_{210, day}$ = observed concentration 210 days after dosing, i.e., on day 211; $AUC_{0-210, day}$ = area under the serum concentration-time curve from time zero to Day 211, NLF = nasal lining fluid

Source: D8850C00001 CSR Figure 5 and Tables 13, 14.2.2.3, 14.2.4.1 and 14.2.4.2, 14.2.6.1 IND 150712, SN 0068.

No repeat dosing PK studies have been conducted. Simulated serum concentrations of AZD7442 with the proposed repeat-dosing regimen for long-term pre-exposure prophylaxis are shown in ***Figure 7***. The results of these simulations show that predicted serum AZD7442 C_{trough} for repeat dosing is equal to or greater than the expected mean day 183 concentrations in serum following the single 300 mg EVUSHELD IM dose in PROVENT. Steady-state serum concentrations of AZD7442 are expected to be achieved after a third dose with overall exposures 42% greater following a third dose ($AUC_{18-24\ months}$ 4,142 mcg·day/mL) compared to following the first dose ($AUC_{0-6\ months}$ 2,920 mcg·day/mL). Thus, predicted steady-state serum tixagevimab and cilgavimab trough concentrations after 6-month repeat EVUSHELD dosing are in the range of the observed mean Day 150 and mean Day 210 concentration in serum (***Table 26***) following a single EVUSHELD dose. In addition, none of the predicted concentrations following the proposed repeat dosing regimen

are expected to exceed those experienced in TACKLE (600 mg AZD7442 IM) and D8850C00001 (3000 mg AZD7442 IV) clinical trials and deemed safe. To date, no dose limiting or dose-dependent toxicities have been identified across the clinical drug development program (See *Section IX Clinical Safety*).

Figure 7: Pooled Population-PK Model Predicted Median (90% Prediction Intervals) Serum AZD7442 Concentration with 6 Months Dosing Interval Following Administration of 300 mg EVUSHELD IM, Overlaid with Observed EVUSHELD Serum Concentrations from Phase 3 PROVENT trial following 300 mg EVUSHELD IM (A), Phase 3 TACKLE trial following a single 600 mg AZD7442 IM Dose (B), and Phase 1 DC8850C00001 trial following single doses up to 3000 mg AZD7442 IV (C).



Green dashed horizontal line corresponds to 2.2 mcg/mL (Applicant's proposed minimum protection concentration) and Navy- dashed line corresponds to 8 mcg/mL (median serum AZD7442 concentration at 6 months). See Dose Rationale for Pre-Exposure Prophylaxis of COVID-19 Subsection for more details.

Source: Response to FDA Information Request, Fig 2 (pg.7), Fig 3 (pg.7), Fig 4 (pg.8) EUA 000104, SN 0010

Dose Rationale for Pre-Exposure Prophylaxis of COVID-19

Pre-Exposure Prophylaxis Indication

- In the ongoing Phase 3 trial PROVENT, 300 mg EVUSHELD IM reduced the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness by 82.8% compared to placebo ($p<0.001$) (primary endpoint, median follow-up time 196 days) (See *Section VIII Human Clinical Efficacy*).
- Supportive of the above interim 6-month clinical pre-exposure prophylactic efficacy are the in vitro AZD7442 driven 80% and 90% SARS-CoV-2 cell entry inhibition concentrations (EC_{80} and EC_{90}) with human PK data suggesting serum AZD7442 concentrations of 2.2 mcg/mL (best base case) to 5 mcg/mL (conservative base case) as hypothetical "minimum" protective thresholds for adequate upper respiratory in vivo antiviral activity. While this is hypothetical, a

duration of protection against SARS-CoV-2 infection is predicted to be between 3 and 6 months following a single 300 mg EVUSHELD IM dose based on percentages of simulated patients achieving the upper respiratory tract targets or thresholds (in vitro EC_{80} or EC_{90}) (***Table 27***). Of note, the Applicant's model-informed translational pharmacology approach was not developed to predict clinical outcomes but to provide some guiding principles to consider when designing a trial and interpreting clinical trial results. No clinical PK-PD relationships or threshold of protection have been identified. Forecasting accuracy of this translational PK-PD modeling approach is not established.

- Also supportive of the above interim 6-month clinical pre-exposure prophylactic efficacy are observations from two nonhuman primate models of SARS-CoV-2 infection suggesting serum AZD7442 concentrations of approximately 20 mcg/mL (rhesus macaques) and 9.1 mcg/mL (cynomolgus macaques) but not 1 mcg/mL (cynomolgus macaques) are potentially protective against SARS-CoV-2 infection based on virologic assessments in bronchoalveolar lavage, lung tissue, and nasal swab samples.
- Limitations of the above evidence include but are not limited to: **(i)** uncertainty in the in vivo validity of using in vitro EC_{80}'s or EC_{90}'s from a microneutralization assay, for which results are likely dependent on specific conditions and platform, as the PD metric associated with clinical protection, **(ii)** uncertainty regarding the relevant respiratory tract site(s) of drug action (e.g., nasal or bronchoalveolar epithelial lining fluid, interstitial space), **(iii)** uncertainty regarding the specific and accurate measurement of drug(s) at these principal sites of drug action, **(iv)** lack of accounting for between strain differences in EC_{80}- or EC_{90}-values, **(v)** NHP to human translation based on serum drug PK data assumes drug penetration from serum to the upper respiratory tract in NHPs is the same or less than that in humans, thus without measuring there is the potential to produce a critical miscalculation about the drug exposure expected at the infection site. **(vi)** uncertainty regarding the relevance of SARS-CoV-2-related pathology (or the lack thereof) in NHPs to predict the onset, prevention, or attenuation of COVID-19 in humans.

Table 27: Pooled Population PK Model Predicted % of Participants That Will Have AZD7442[1] Concentrations ≥ a Minimum Protective Concentration[2] Threshold for AZD7442 Against Wuhan-Hu-1 Strain of SARS-CoV-2

	Time (Months)	% of participants	
		EC_{80} target	EC_{90} target
Median NLF penetration ratio[3]	3	100	99
	6	96	81
	9	77	45
	Time (Months)	**% of participants**	
		EC_{80} target	EC_{90} target
Random NLF penetration ratio[4]	3	98	87
	6	87	63
	9	66	40

[1] AZD7442 concentration = the sum of the tixagevimab and cilgavimab concentrations

[2] This minimum protective concentration was set as a target by the Applicant based on the EC_{80} representing a "near-maximal" effect (i.e., small gain in response with increasing drug exposure above 80% of maximal inh bitory concentration) and an in-silico SARS-CoV-2 viral dynamics modeling approach (predicting changes in the viral load kinetics) which suggests 80% SARS-CoV-2 inh bition is minimally

required for a pre-exposure prophylactic effect (not evaluated by FDA review team). Alternatively, a minimum protective concentration was considered as a target by the FDA review team based on the EC_{90} more typically used. The AZD7442 driven 80% SARS-CoV-2 cell entry inhibition concentration (EC_{80}) is 40 ng/mL based on in vitro SARS-CoV-2 Wuhan-Hu-1 strain microneutralization assay concentration-response data (4 × EC_{50} of 10 ng/mL is 40 ng/mL, assuming a Hill coefficient of 1). This value is similar to ex vivo IC_{80} values derived over time (Day 8 to 211) from the live SARS-CoV-2 nAb titers measured in Phase 1/3 samples using the Wuhan-Hu-1 strain. The AZD7442 driven 90% SARS-CoV-2 cell entry inhibition concentration (EC_{90}) is 90 ng/mL based on in vitro SARS-CoV-2 Wuhan-Hu-1 strain microneutralization assay concentration-response data (9 × EC_{50} of 10 ng/mL is 40 ng/mL, assuming a Hill coefficient of 1). Protection is predicted against SARS-CoV-2 if the AZD7442 concentration is at least 40 ng/mL (best base case) or 90 ng/mL (conservative base case) in the upper respiratory tract.

[3] A proportionality factor (1.81%: nasal lining fluid (NLF) to serum ratio) was applied to serum concentrations to predict upper respiratory tract drug concentrations.

[4] Variability in the NLF penetration ratio was incorporated by randomly drawing a value from a truncated (2 SD) normal distribution having a mean and standard deviation (see Phase 1 study) on the log scale. The randomly drawn NLF: serum ratios on the log scale were subsequently back transformed to the original scale. FDA Reviewer's analysis.

Sources: EUA Request Document, simulated adult AZD7442 PK data file SDTAB8390.dat EUA000104, SN0007 and D8850C00001 CSR Tables 14.2.6.1 IND 150712, SN 0068

From a translational pharmacology perspective, a similar duration of protection against most SARS-CoV-2 variants of concern, variants of interest, and circulating SARS-CoV-2 variants identified can be reasonably anticipated based on the results of cell culture neutralization studies evaluating the neutralizing activity of AZD7442 against these variants, or against virus-like particles pseudotyped with the spike proteins of these variants (EUA Request, Fig 16-17; Section 6.1.1.4.3, SN001). The Mu (B.1621) variant showed the greatest reduction in susceptibility to AZD7442 in cell culture, with a 7.5-fold increase in EC_{50} value. The relationship between susceptibility in cell culture and clinical efficacy remains unclear, including the effect on the duration of protection for preventing COVID-19.

From a translational pharmacology perspective, a similar overall expectation of therapeutic benefit can be reasonably anticipated in a general adult population at the present time from the general adult population evaluated in the PROVENT trial based on the predominate SARS-CoV-2 variants circulating in the United States and their associated (similar) in vitro AZD7442 EC_{50}'s at PROVENT trial initiation (e.g., Alpha variant), PROVENT trial data cut-off (August 2021)(e.g., Delta variant), and now (November 2021)(e.g., Delta variant). The susceptibility of the recently identified Omicron variant to AZD7442 has not yet been determined.

See *Section XIII Nonclinical Data to Support Efficacy* (Clinical Virology) for more details.

Redosing for Pre-Exposure Prophylaxis Authorization

- In response to a repeat dose prophylaxis information request from the Division on October 20, 2021, the Applicant submitted PROVENT findings showing no trends in decreased efficacy over time out to 6 months post dose (See *Section VIII Human Clinical Efficacy*). Although no clinical data are available for repeat AZD7442 dosing, these data support that AZD7442 300 mg IM may provide protection for 6 months after dosing and consequently that a six-month redosing interval would be reasonable until further data are available (repeat dosing regimen: 300 mg EVUSHELD IM administered every 6 months). Note that due to

limited data beyond 6 months, a dosing interval longer than 6 months would not be supported.

- AZD7442 C_{trough} values after the second and subsequent doses are expected to be equal to or greater than those observed following the first dose, following the administration of the proposed dosing regimen (***Figure 7***). Since long-term pre-exposure prophylactic efficacy has not been evaluated in clinical trials, maintenance dosing to maintain similar or slightly greater drug exposures to those observed close to the timepoint where efficacy was determined for the single dose is a reasonable approach to ensure prophylactic effects for individuals in whom long-term protection is determined to be appropriate (e.g., immunocompromised).
- Serum AZD7442 concentrations out to the 183-Day efficacy endpoint are likely adequate to achieve antiviral activities in vivo based on nonclinical PK and PK-PD evaluations (See *Section II Recommendations Dose Rationale for Pre-Exposure Prophylaxis of COVID-19*).
- Safety of the proposed dosing regimen is supported by D8850C00001, PROVENT, STORM CHASER, and TACKLE trials (*See Section XI Clinical Safety*). The maintenance portion of the proposed dosing regimen (i.e., the second dose onwards) is predicted to produce steady-state serum drug concentrations nominally (42%) higher than drug concentrations evaluated in PROVENT and STORM CHASER, but less than those studied in TACKLE and D8850C00001.
- No concerning signal for anti-drug antibodies (ADA) from single doses of AZD7442 have been detected, but limited data are currently available. PROVENT ADA data are available out to Day 58 (N=46). D8850C00001 ADA data are available out to Day 210. Repeat dosing of 300 mg EVUSHELD IM will be initiated as a sub-study in PROVENT to provide multiple-dose safety, immunogenicity, and PK data before individuals receiving 300 mg EVUSHELD IM under an emergency use authorization would require their second dose.

<u>Dosing Recommendation Rationale for Pediatric Patients and other Specific Populations</u>

Based on a pooled Phase 1/3 population PK analysis, the PK profile of tixagevimab and cilgavimab were not affected by sex, age (b) (4) years of age), race or ethnicity. Population PK model-based simulations suggest that body weight had no clinically relevant effect on the PK of tixagevimab and cilgavimab in adults over the range of (b) (4) kg.

Pediatrics

The PK, safety, and effectiveness of tixagevimab and cilgavimab has not been studied in any pediatric population. The recommended dosing regimen is expected to result in comparable serum exposures of tixagevimab and cilgavimab between pediatric patients 12 years of age and older and weighing at least 40 kg and adults. Adults down to (b) (4) kg with body weigh (b) (4)) have been included in PROVENT (67 adults between (b) (4) kg).

Geriatrics
Of the 2029 participants in the pooled PK analysis, 23% (N = 461) were 65 years of age or older and 3.3% (N = 67) were 75 years of age or older. There were no observed clinically meaningful differences in observed serum concentrations of tixagevimab and cilgavimab over time in geriatric patients (age ≥65 years) compared to younger adult patients (age < 65 years) administered a single 300 mg EVUSHELD IM dose (data not shown, Sponsor's response to Question 7 of Information Request, SN 0007). In addition, there was no statistical difference (p=0.61) in AZD7442 clearance between these two groups based on the individual post-hoc estimates of clearance for AZD7442 from the pooled Phase 1/3 population PK model.

Renal Impairment
No dedicated studies have been conducted to examine the effects of renal impairment on the PK of tixagevimab and cilgavimab. Based on the pooled Phase 1/3 population PK analysis, there is no difference in the clearance of tixagevimab and cilgavimab in patients with mild (eGFR 60 to 89 mL/min) or moderate (eGFR 30 to 59 mL/min) compared to patients with normal (eGFR> 90 mL/min) renal function.

Renal impairment is not expected to impact the PK of tixagevimab and cilgavimab, since mAbs with molecular weight >69 kDa are known not to undergo renal elimination. Similarly, dialysis is not expected to impact the PK of tixagevimab and cilgavimab.

Hepatic Impairment
No dedicated studies have been conducted to examine the effects of hepatic impairment on the PK of tixagevimab and cilgavimab. The impact of hepatic impairment on the PK of tixagevimab and cilgavimab is unknown.

Concomitant Medication
Drug-drug interaction studies have not been performed. Based on key elimination pathways, tixagevimab and cilgavimab interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely.

Comparison Between Clinical Trial AZD7442 Product and Proposed EUA AZD7442 Product
Drug substance materials have been demonstrated to be analytically comparable between the proposed EUA clonal cell line-derived AZD7442 materials and clinical trial non-clonal cell pools-derived AZD7442 materials (See Product Quality review of IND 150712 Amendment 0013).

Phase 3 PROVENT and STORM CHASER trials were initiated with non-clonal cell pools-derived AZD7442 product. Once clonal cell line-derived AZD7442 product (for proposed EUA) became available an additional cohort was added in the PROVENT trial to provide comparisons between clonal cell line-derived AZD7442 product and non-clonal cell pools-derived AZD7442 product. Serum concentration and

neutralizing antibody titer data from the clonal cell line-derived AZD7442 product were available in 79 participants.

No notable differences were observed between serum concentrations of tixagevimab and cilgavimab (Data not shown, D8850C00002 PROVENT EUA Tables 14.2.4.2, EUA 000104, SN 0001) or AZD7442 serum concentration to 80% SARS-CoV-2 neutralizing antibody titer relationships based on visual inspection between the non-clonal cell pools-derived and clonal cell line-derived AZD7442 products (Data not shown, EUA Request Document, Figure 44 (pg.,238), EUA 000104, SN 0001).

XII. Nonclinical Data to Support Safety

- Tixagevimab and cilgavimab were evaluated together in a GLP single-dose toxicology study in cynomolgus monkeys with an 8-week recovery using both intravenous (IV) and intramuscular (IM) dosing.
  - No adverse, drug-related findings were observed in this study up to the highest doses tested (300 mg/kg/mAb IV and 75 mg/kg/mAb IM). The exposure multiple at the NOAEL of 75 mg/kg/mAb IM is greater than 40X relative to the authorized human dose of 150 mg/mAb (based on AUC values).
- GLP tissue cross-reactivity studies were conducted in cynomolgus monkey and human (adult and select fetal) tissues. No binding of clinical concern was observed with either tixagevimab or cilgavimab in either species in these studies.

XIII. Nonclinical Data to Support Efficacy

Summaries of the key findings from the study reports describing mechanism of action and nonclinical virology studies are provided below:

Mechanism of Action

Study Report MCBS7442-0001, "AZD7442 Binding Kinetics and Mechanism of Action" (IND 150712 SDN 060/SN 0061). The binding of cilgavimab, tixagevimab, tixagevimab and cilgavimab, or recombinant human ACE2 to a recombinant prefusion-stabilized trimeric SARS-CoV-2 S protein by surface plasmon resonance. Cilgavimab, tixagevimab, tixagevimab and cilgavimab, or ACE2 bound to SARS-CoV-2 S protein with K_D values of 13 pM, 2.8 pM, 14 pM, or 43,000 pM, respectively. Tixagevimab and cilgavimab bound to recombinant RBD with K_D values of 2,180 and 2,150 pM, respectively. The ability of cilgavimab, tixagevimab, and tixagevimab and cilgavimab to inhibit the binding of recombinant SARS-CoV-2 RBD to recombinant human ACE2 was determined using ELISA. Cilgavimab, tixagevimab, and tixagevimab and cilgavimab interfered with the binding of RBD to ACE2 with IC_{50} values of 531 pM, 318 pM, and 433 pM, respectively.

Study Report MCBS7442-0002, "AZD7442 Binds to Unique Epitopes on the Receptor Binding Domain of the SARS-CoV-2 Spike Protein" (IND 150712 SDN 060/SN 0061). An X-ray crystallography study was used to define the RBD contact residues of tixagevimab and cilgavimab. Cilgavimab contacts RBD at R346 and K444.

Tixagevimab forms a hydrophobic pocket that surrounds residue F486 and adjacent residues, G485 and N487. According to the Sponsor, these structural analyses verify that tixagevimab and cilgavimab have unique, non-overlapping binding sites and that steric blocking of RBD binding to ACE2 is the mechanism of action for both mAbs. A biolayer interferometry experiment indicated that tixagevimab and cilgavimab are not antagonistic for binding to RBD, regardless of which mAb binds first.

Antiviral Activity in Cell Culture

Study Report MCBS7442-0003, "AZD7442 Potently Neutralizes SARS-CoV-2" (IND 150712 SDN 004/SN 0004). The antiviral activities of cilgavimab, tixagevimab, and tixagevimab and cilgavimab against SARS-CoV-2 (strain USA-WA1/2020) were determined in 3 different cell culture models of infection, the focus reduction neutralization test (FRNT) on Vero-furin cells, a microneutralization assay on Vero E6 cells, and a cytopathic effect (CPE)-based assay Vero E6 cells. Cilgavimab, tixagevimab, or tixagevimab and cilgavimab inhibited replication with EC_{50} values of 114 ng/mL, 212 pM (32 ng/mL), or 172 pM (26 ng/mL), respectively, in the FRNT assay, with EC_{50} values of 212 pM (32 ng/mL), 61 pM (9 ng/mL), or 66 pM (10 ng/mL), respectively, in the microneutralization assay, or with EC_{99} values of 7.3 pM (1.1 ng/mL), 6.6 pM (1.0 ng/mL), or 5.3 pM (0.8 ng/mL), respectively, in the CPE assay. The combination of the two mAbs (tixagevimab and cilgavimab) showed activity comparable to that of tixagevimab, which was consistently the more potent of the two mabs against the tested strain of SARS-CoV-2. These data indicate that the two component mAbs of tixagevimab and cilgavimab do not appear to be antagonistic, or at minimum, that cilgavimab does not appear to antagonize tixagevimab.

The antiviral activities of cilgavimab, tixagevimab, or tixagevimab and cilgavimab against a lentivirus-based virus like particle (VLP) pseudotyped to bear the SARS-CoV-2 S protein from USA-WA1/2020 or a D614G-expressing variant were determined. Cilgavimab, tixagevimab, or tixagevimab and cilgavimab neutralized the VLP expressing the USA-WA1/2020 S protein with EC_{50} values of 31 pM (4.7 ng/mL), 8.6 pM (1.3 ng/mL), or 33 pM (5.7 ng/mL), respectively, and the VLP expressing the D614G variant S protein with EC_{50} values of 11 pM (1.7 ng/mL), 2.0 pM (0.3 ng/mL), or 4.6 pM (0.7 ng/mL), respectively. The presence of the YTE or TM Fc substitutions were also shown to have no effect on the antiviral activity of cilgavimab or tixagevimab in a VLP neutralization assay.

Study Report MCBS7442-0004, "The Combination of AZD7442 is More Effective than Individual Monoclonal Antibodies for Neutralizing SARS-CoV-2" (IND 150712 SDN 004/SN 0004). This was a combination antiviral activity study that demonstrated that tixagevimab and cilgavimab were not antagonistic in a VLP neutralization assay.

Studies in Animal Models of SARS-CoV-2 Infection

Study Report MCBS7442-006, "In Vivo Activity of AZD7442 in Non-Human Primate Model of SARS-CoV-2 Infection" (IND 150712 SDN 031/SN 0033). Rhesus macaques (n=3 or 4 per group) received a single 4 mg/kg or 40 mg/kg IV dose of

tixagevimab and cilgavimab 3 days prior to challenge with SARS-CoV-2 (USA-WA1/2020) in a pre-exposure prophylaxis study. A separate group of rhesus macaques received a single 40 mg/kg IV dose of tixagevimab and cilgavimab 24 hours after SARS-CoV-2 infection in a treatment/post-exposure prophylaxis study. Control animals received an isotype-matched mAb or 4 mg/kg of a modified version of tixagevimab and cilgavimab, tixagevimab/cilgavimab-YTE, that lacked the TM Fc modification. Macaques in all groups were infected by intranasal and intratracheal challenge on Day 0 with 1×10^5 $TCID_{50}$ of the USA-WA1/2020 strain of SARS-CoV-2.

Virus replication was measured using quantitative RT-PCR for subgenomic viral RNA, a replicative intermediate that is not packaged efficiently into virions, thereby allowing for a distinction between viral RNA from the challenge virus and its progeny. Control animals showed a mean peak of 5.32 log_{10} (subgenomic) RNA copies/swab in nasal specimens and a mean peak of 4.57 log_{10} RNA copies/mL in bronchoalveolar lavage (BAL) on Day 2. In contrast, little or no viral RNA was detected in either nasal or BAL samples from animals that received the 4 or 40 mg/kg dose of tixagevimab and cilgavimab or the 4 mg/kg dose of tixagevimab/cilgavimab-YTE. The 40 mg/kg dose of tixagevimab and cilgavimab administered 1-day post-challenge did not reduce the peak levels of viral RNA in either the lungs or nasal mucosae. However, the time to cessation of virus shedding in animals that received tixagevimab and cilgavimab was shorter, at approximately 4 days in BAL and 7 days in nasal swabs, while animals in the control group had viral RNA detected for up to 10 days in both specimen types. These results indicate that tixagevimab and cilgavimab may reduce virus replication and shedding when administered shortly after infection in this model.

Study Report MCBS7442-008, “In Vivo Prophylactic Activity of AZD7442-TM in the Syrian Hamster Model of SARS-CoV-2 Infection” (IND 150712 SDN 031/SN 0033). The prophylactic activity of tixagevimab and cilgavimab was evaluated in a Syrian hamster model of SARS-CoV-2 infection. According to the Sponsor, the presence of the YTE substitutions in the Fc domain of antibodies causes rapid elimination in rodents. tixagevimab/cilgavimab-TM, which lacks the YTE Fc modification, was used as a surrogate for tixagevimab and cilgavimab in these experiments.

Syrian hamsters were intraperitoneally administered 2 mg (n=11), 0.2 mg (n=11), 0.02 mg (n=11), or 0.002 mg (n=10) of tixagevimab/cilgavimAB-TM or 2 mg of an isotype control mAb (n=11). One day later, all animals were challenged intranasally with 1×10^5 plaque forming units (pfu) of SARS-CoV-2 strain USA-WA1/2020. The impact of tixagevimab/ cilgavimab-TM on viral load and lung pathology were evaluated on Days 3 and 7 post-infection.

The 2 mg dose of tixagevimab/cilgavimab-TM protected animals from weight loss/failure to gain weight, while lower doses conferred less, if any, protection relative to controls. Hamsters that received the isotype control mAb showed a mean of 6.7 log_{10} pfu/mL infectious virus in their lungs on Day 3 post-infection. In contrast, hamsters that received tixagevimab/cilgavimab-TM showed a dose-dependent reduction in replicating virus, with animals in the 2 mg tixagevimab/cilgavimab-TM

having infectious virus below level of detection. All animals showed infectious virus titers below level of detection at Day 7 post-infection.

Viral subgenomic RNA showed a pattern similar to that of infectious virus titers in the lungs of infected animals. Hamsters that received the isotype control mAb showed a mean viral RNA concentration of nearly 9.0 $\log_{10}$ copies/mL at Day 3 post-infection. In contrast, hamsters that received tixagevimab/cilgavimab-TM showed dose-dependent reduction in viral sgRNA levels in the lungs, with hamsters that received the 2 mg dose of tixagevimab/cilgavimab-TM having a mean viral RNA concentration of ~6.0 $\log_{10}$ copies/mL at Day 3. By Day 7, levels of viral sgRNA in the lungs of all animals were below level of detection. Collectively, these data indicate that tixagevimab/cilgavimab-TM administered prophylactically inhibits SARS-CoV-2 replication in a dose-dependent manner. Notably, there was no evidence of ADE for viral replication or disease in this study, which included sub-neutralizing doses of tixagevimab/cilgavimab TM.

An immunohistochemistry-based analysis of lung pathology for SARS-CoV-2 inflammation and alveolar damage indicated that tixagevimab/cilgavimab TM dosed at 0.2 mg or 2 mg reduced inflammation, bronchiolar epithelial necrosis, alveolar fibrin deposition, and hemorrhage; results that are consistent the evaluations of viral replication.

Study Report MCBS7442-013, “Evaluation of AD7442 Efficacy to Reduce Viral Burden and Lung Pathology in Cynomolgus Monkey Model of SARS-CoV-2 Challenge” (IND 150712 SDN 060/SN 0061). The prophylactic and therapeutic activities of tixagevimab and cilgavimab were evaluated in a second nonhuman primate study. Cynomolgus macaques received IV infusions of 40 mg/kg isotype control mAb or tixagevimab and cilgavimab at doses of 0.04 mg/kg, 0.4 mg/kg, or 4 mg/kg three days prior to infection (for prophylaxis analyses), or 40 mg/kg tixagevimab and cilgavimab 24 hours after infection. One additional group of cynomolgus macaques was administered 40 mg/kg of tixagevimab/cilgavimab-YTE, which lacks the TM substitutions, 24 hours after infection to evaluate effector function contribution to antiviral activity. All NHPs were challenged with 1×10^5 $TCID_{50}$ of SARS-CoV-2 strain USAWA1/2020 split between intratracheal and intranasal inoculations. All NHPs were euthanized for histologic evaluations on Day 5. There were 3 animals per group.

NHPs that received tixagevimab and cilgavimab before challenge showed a dose-dependent reduction in culturable virus titers and viral RNA in BAL relative to control animals. The 4 mg/kg dose was sufficient to reduce infectious titers in BAL to undetected levels, although it is possible that this effect was due at least in part to residual mAb in samples, and animals in this dose showed an approximately 2 $\log_{10}$ RNA copies/mL reduction in BAL on Days 1 and 2, the peak times in the control group. In comparison, higher titers (mean of 6.5 $\log_{10}$ $TCID_{50}$ on Day 1) and viral RNA concentrations (mean of 5.0 to 5.2 $\log_{10}$ copies/mL on Days 1 and 2) were measured in the BAL samples of control NHPs that received isotype control antibody. Viral

concentration in BAL correlated with those in lung tissues at Day 5, showing a dose-dependent reduction of viral RNA in NHPs that received tixagevimab and cilgavimab prophylaxis as compared to control NHPs. These data indicate that prophylactic tixagevimab and cilgavimab administration reduced SARS-CoV-2 replication, and perhaps prevented infection, in the lower respiratory tract.

NHPs that received either tixagevimab and cilgavimab or tixagevimab/cilgavimab-YTE on Day 1 had culturable virus and viral RNA levels in BAL and lung tissues comparable to those of control NHPs. However, infectious virus titers in the BAL were reduced to below levels of detection within 1 day of tixagevimab and cilgavimab or tixagevimab/cilgavimab-YTE administration, while titers remained at quantifiable levels in control NHPs through Day 5. There was no obvious difference in RNA levels between the tixagevimab and cilgavimab, tixagevimab/cilgavimab-YTE, or control mAbs. These data indicate that therapeutic/post-exposure prophylaxis tixagevimab and cilgavimab or tixagevimab/cilgavimab-YTE administration may accelerate virus clearance from the lower respiratory tract, assuming that quantitative culture assay was not confounded by carryover mAb. Interestingly, tixagevimab and cilgavimab and tixagevimab/cilgavimab-YTE demonstrated comparable activities, indicating that effector functions ablated by the TM substitutions may not contribute to activity in this model. However, it should be noted that the YTE substitutions may also reduce Fc-mediated activity, so the tixagevimab/cilgavimab-YTE mAbs should not be expected to be equivalent to the unmodified mAbs.

Tixagevimab and cilgavimab was associated with a generally dose-dependent reduction in pathology, as expected based on the antiviral activity evaluations. There was no obvious difference between histopathological scoring of tissues from animals that received tixagevimab and cilgavimab vs. those that received tixagevimab/cilgavimab -YTE.

Effect of Tixagevimab and Cilgavimab on SARS-CoV-2 Vaccine Response

Study Report MCBS7442-009, "Evaluation of Cellular and Humoral Immune Responses Elicited by SARS-CoV-2 Vaccination Subsequent to AZD7442 -TM Administration in Mice" (IND 150712 SDN 060/SN 0061). Adult (9- to 10-week-old) BALB/c mice were intraperitoneally (IP) administered 400 µg of isotype control mAb or tixagevimab/cilgavimab-TM, which incorporates the TM Fc substitutions but lacks the YTE Fc substitutions that lead to the rapid elimination of mAbs in rodents, at doses ranging from 5 µg to 400 µg; this range of doses was intended to simulate reducing serum mAb concentrations at different times post-administration. One additional group of mice received 400 µg tixagevimab/cilgavimab-WT (wild-type), which does not have either TM or YTE substitutions in the Fc region. Mice were immunized intramuscularly (IM) with 1×10^8 infectious units (IU) of AZD1222, the Oxford-AstraZeneca adenovirus-vectored SARS-CoV-2 vaccine.

Animals were separated into 2 cohorts, with each cohort containing 7 groups of 6 animals each. Animals in Cohort 1 received only a single dose of AZD1222 one day after mAb administration, while mice in Cohort 2 received two doses of AZD1222 four weeks apart, with the first dose administered one day after mAb administration.

Control mice received 400 µg tixagevimab/cilgavimab-TM followed by the administration of PBS instead of AZD1222 (no vaccine control group). The mice were euthanized 2 weeks after either prime or boost immunization.

Mouse and human Ab titers to spike protein and RBD were evaluated in mouse sera collected 4 weeks after the first AZD1222 immunization (Day 28) and 2 weeks following the second dose of AZD1222 (Day 42) by ELISA. To minimize tixagevimab/cilgavimab-TM or tixagevimab/cilgavimab-WT occlusion of potential binding sites for vaccine-elicited mouse Abs in these assays, all serum samples were pre-incubated with anti-idiotype antibodies that specifically block tixagevimab and cilgavimab antibodies from binding to spike or RBD. Addition of the anti-idiotype Abs to sera collected on Day 28 and Day 42 resulted in near complete reduction of the human Ab titer for binding to spike or RBD. As expected, mice that received tixagevimab/cilgavimab-TM but were not vaccinated did not develop mouse antibodies that bind to SARS-CoV-2 spike protein or RBD. Regardless of the mAb administered (isotype control mAb, tixagevimab/cilgavimab-TM, or tixagevimab/cilgavimab-WT) on Day -1, mice from all vaccinated groups demonstrated near-equivalent mouse Ab titers for binding to spike and RBD. Similar results were observed with a single vaccine administration and after both doses of AZD1222, suggesting that tixagevimab/cilgavimab-TM administration did not affect the development of Abs following vaccination in mice. Similarly, no obvious effect on the development of SARS-CoV-2 spike protein-targeting $CD8^+$ T cells was observed. Collectively, these data indicate that tixagevimab/cilgavimab-TM did not significantly alter the immune responses of these mice to a COVID-19 vaccine, although it remains unclear whether similar results would be observed for different vaccine types (e.g., mRNA).

Study Report MCBS7442-012, "Evaluation of Cellular and Humoral Immune Responses Elicited by SARS-CoV-2 Vaccination Subsequent to AZD7442 Administration in Non-Human Primates" (IND 150712 SDN 060/SN 0061). The impact of tixagevimab and cilgavimab on vaccine-elicited cellular and humoral immune responses in a nonhuman primate (NHP) model of SARS-CoV-2 infection was evaluated. Unmodified tixagevimab and cilgavimab was used for this study. Two- to three-year-old cynomolgus monkeys (*Macaca fascicularis*) were divided into 5 groups (n=4 to 5 per group) and intravenously (IV) administered 12 mg/kg of an isotype control mAb or tixagevimab and cilgavimab at doses of 0.2 mg/kg, 1.0 mg/kg, 4.0 mg/kg, or 12 mg/kg 3-days before being immunized IM with 7.8×10^8 IU of AZD1222 (AstraZeneca's adenovirus-based COVID-19 vaccine) on Day 0. Animals received a second immunization 4 weeks later. Whole blood was collected from the NHPs at various timepoints to evaluate the effect of tixagevimab and cilgavimab on vaccine response.

Monkey and human Ab titers for binding to spike or RBD were evaluated in NHP sera collected 4 weeks after the first AZD1222 immunization (Day 28) and 4 weeks following the second dose of AZD1222 (Day 56). All serum samples were preincubated with anti-idiotype antibodies at >200-fold excess of tixagevimab and

cilgavimab concentrations in the sera. No SARS-CoV-2 spike protein- or RBD-targeting monkey Ab titers were detected in serum collected on Day 0 (prior to AZD1222 immunization). In contrast, serum collected on Day 28 after a single AZD1222 immunization revealed overall monkey Ab titers that were approximately 4 log_{10} for binding to spike protein and greater than 3 log_{10} for binding to RBD.

Spike- and RBD-specific monkey Ab titers were equivalent across the different groups of animals, regardless of the mAb or dose administered (isotype control mAb or tixagevimab and cilgavimab), in the animals that received a single immunization. In comparison, there were ~0.5 log_{10} reductions in RBD-specific monkey Ab titers at Day 56 from monkeys that received 4 or 12 mg/kg tixagevimab and cilgavimab and vaccinated twice relative to controls, although the potential clinical significance of these reductions is unclear. The effect of tixagevimab and cilgavimab on the development of Ab titers for binding to spike did not achieve statistical significance, but otherwise appeared to be similar to the anti-RBD Ab reductions. No obvious reductions in SARS-CoV-2-specific $CD8^+$ T cell responses were observed.

This study indicates that tixagevimab and cilgavimab administration to NHPs may reduce the antibody response to a COVID-19 vaccine, although the reductions appeared to be modest, and the potential clinical significance of such a reduction is unclear. It is also unclear whether different types of vaccines (e.g., mRNA vaccines) would produce similar results.

Resistance Selection in Cell Culture

Study Report MCBS7442-010, "Generation and Characterization of AZD7442 Monoclonal Antibody-Resistant Mutant Viruses" (IND 150712 SDN 060/SN 0061). SARS-CoV-2 (USA-WA-1/2020) was passaged serially in Vero E6 cultures with tixagevimab, cilgavimab, or tixagevimab and cilgavimab, at mAb concentrations beginning at their respective EC_{50} values (ranging from 46 pM to 112 pM) and increased stepwise with each passage to a final mAb concentration equivalent to their respective EC_{90} values (ranging from 79 pM to 238 pM) over a total of 10 passages. Virus was passaged in the absence of antibody as a control. Following the final passage, viruses were evaluated for susceptibility against the mAb used for selection or tixagevimab and cilgavimab at a final concentration of 10-fold the EC_{90} value by plaque assay.

Neutralization escape variants were selected only for virus that was serially passaged and cultured in the presence of cilgavimab; no escape variants were detected following serial passaging of virus in either tixagevimab or tixagevimab and cilgavimab. Plaques (n=6) were randomly selected, and the spike-encoding gene sequenced. All 6 plaque-purified variants encoded the same three amino acid substitutions in spike, N74K (N-terminal domain), R346I (RBD), and S686G (S1/S2 furin cleavage site). It is possible that virus with reduced susceptibility to tixagevimab could have been selected using different methodologies (e.g., by infecting at low multiplicity of infection, starting the passages with lower mAb concentrations, and then increasing mAb concentrations after detecting increased replication).

The plaque-purified viruses were not phenotypically characterized. Instead, susceptibility shifts were assessed using HIV-1-based VLPs pseudotyped to express the cilgavimab-selected substitutions, whether in this study (N74K, R346I, S686G) or in a study described by Dong et al., 2021, who selected for VLPs with reduced susceptibility to Cilgavimab (K444E and K444R). Cilgavimab maintained full neutralization activity against S686G-bearing VLPs, indicating that S686 may be a compensatory or cell culture adaptive substitution, as described previously (Klimstra et al., 2020).

Cilgavimab did not exhibit neutralization activity against VLPs with R346I, K444E, or K444R at the highest tested mAb concentrations, resulting in >200-fold decreases in susceptibility compared to the reference. VLPs bearing spike glycoprotein with N74K could not be produced to levels sufficient for testing. Tixagevimab maintained activity against the tested VLP variants.

A biolayer interferometry-based binding study indicated that cilgavimab maintained binding to N74K spike trimer to levels equivalent to the reference spike trimer. Consistent with the pseudotyped VLP assay, cilgavimab but not tixagevimab demonstrated reduced binding to spike protein with R346I, K444E, or K444R relative to reference D614G spike protein. Collectively, these data indicate that the reduced susceptibility to cilgavimab conferred by R346 and K444 is due to a loss of binding for the variants.

The Sponsor investigated the degree of amino acid conservation for N74, R346, K444, and S686 using the GISAID database. Of the 1,717,766 unique spike sequences that were available on 22 June 2021, the wild-type amino acid is present at frequencies ≥99.9% at all positions. The frequencies of N74K, R346I, K444E, K444R, and S686G were 0.0007%, 0.0044%, not listed, 0.0086%, and 0.0001%, respectively.

Although variants with reduced susceptibility to tixagevimab have not been selected successfully to date, mutagenesis studies reported by Zost et al., 2020 and Dong et al., 2021 indicate that the introduction of substitutions to F486 or N487 of the SARS-CoV-2 spike protein result in a loss of tixagevimab binding.

Surveillance of Circulating SARS-CoV-2 Strains

The Sponsor, in an ongoing collaboration with other laboratories—including a lab at the FDA—is evaluating the susceptibilities of circulating SARS-CoV-2 variants to cilgavimab, tixagevimab, and tixagevimab and cilgavimab. These evaluations include assays using authentic SARS-CoV-2 isolates and VLPs bearing the complete or partial SARS-CoV-2 spike proteins of these variants. Tested variants include Alpha (B.1.1.7 [± L455F, E484K, E484K/F490S, Q493R, S494P,]), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2 [±K417N]), Epsilon (B.1.427/429), Eta (B.1.525 [+E484K]), Iota (B.1.526 [+S477N, E484K]), Kappa (B.1.617.1), Lambda (C.37), Mu (B.1.621), and Zeta (P.2).

In neutralization assays using recombinant VLPs pseudotyped with SARS-CoV-2 spike and harboring individual spike amino acid substitutions identified in circulating SARS-CoV-2, variants with reduced susceptibility to cilgavimab alone included those with R346I (>200-fold), K444E (>200-fold), K444Q (>200-fold), K444R (>200-fold), V445A (21- to 51-fold), G446V (4.2-fold), N450K (9.1-fold), or L452R (5.8-fold) substitutions. Variants with reduced susceptibility to tixagevimab alone included those with Q414R (4.6-fold), L455F (2.5- to 4.7-fold), G476S (3.3-fold), E484D (7.1-fold), E484K (6.2- to 12- fold), E484Q (3.0-fold), F486S (>600-fold), F486V (121- to 149-fold), Q493K (2.4- to 3.2-fold), Q493R (7.9-fold), E990A (6.1-fold), or T1009I (8.2-fold) substitutions. Variants harboring an E484K (2.4- to 5.4-fold), Q493R (3.4-fold), E990A (5.7-fold), or T1009I (4.5-fold) substitution exhibited low level reduced susceptibility to tixagevimab and cilgavimab.

VLPs pseudotyped with the SARS-CoV-2 spike of variant strains with reduced susceptibility to cilgavimab included those with R346K/E484K/N501Y (Mu, 21-fold), and those with reduced susceptibility to tixagevimab included those harboring E484K (Alpha, 18.5-fold; Beta, 3.5- to 15-fold). Similar results were observed, where data was available, in neutralization assays using authentic SARS-CoV-2 variants strains.

Tixagevimab and cilgavimab retained neutralization activity against pseudotyped VLPs and/or authentic SARS-CoV-2 variant strains harboring all spike substitutions identified in Alpha (B.1.1.7, 0.4- to 5.2-fold), Beta (B.1.351, 1.0- to 5.5-fold), Gamma (P.1, 0.8- to 2.0-fold) and Delta (B.1.617.2, 0.6- to 1.2-fold) variants of concern, and Eta (B.1.525, 1.8- to 3.1-fold), Iota (B.1.526, 0.3- to 3.4-fold), Kappa (B.1.617.1, 0.5- to 3.4-fold) Lambda (C.37, 0.7-fold), and Mu (B.1.621, 7.5-fold) Variants of Interest. tixagevimab and cilgavimab also retained neutralizing activity against Epsilon (B.1.427 / B.1.429, 0.8- to 3.5-fold), A.23.1 (0.4-fold), A.27 (0.8-fold), AV.1 (5.9-fold), B.1.1.519 (1.0- to 1.4-fold), B.1.214.2 (0.8-fold), B.1.616 (0.4- to 0.5-fold), B.1.619.1 (3.3-fold), C.36.3 (2.3-fold), P.2 (2.9-fold), and R.1 (3.5-fold).

The susceptibility of the recently identified Omicron (B.1.1.529) variant to cilgavimab, tixagevimab, and tixagevimab and cilgavimab has not yet been determined.

XIV. Supply Information

One treatment course of EVUSHELD per individual for the proposed EUA consists of one single-dose vial of tixagevimab (150 mg/1.5 mL) and one single-dose vial of cilgavimab (150 mg/1.5 mL).

In a correspondence dated December 7, 2021, the Applicant indicated that a monthly supply of (b) (4) doses of product manufactured at (b) (4) is projected for the months of (b) (4), respectively, for US distribution. These projections are subject to revision based on FDA authorization, manufacturing performance, and activities supporting clinical development and other activities.

XV. Chemistry, Manufacturing, and Controls Information

Cilgavimab (AZD1061) and tixagevimab (AZD8895) are recombinant human IgG1κ monoclonal antibodies (mAbs) that are produced in Chinese Hamster Ovary (CHO) cells. Each of these mAbs is composed of two identical heavy chains and two identical light chains. The heavy chain CH2 domain is engineered to contain two sets of three amino acid substitutions: TM (L to F, L to E, and P to S) mutations to reduce Fc-mediated effector functions; and YTE (M to Y, S to T, and T to E) mutations to extend serum half-life via enhanced binding affinity to neonatal Fc receptor (FcRn). Tixagevimab and cilgavimab target different locations in the receptor binding domain of the spike (S) protein of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) to block its binding to the associated receptor, human angiotensin-converting enzyme 2 (ACE2), thereby inhibiting the entry of virus into host cells.

Tixagevimab and cilgavimab are supplied as sterile and preservative-free liquid in individual single-dose vials. Each vial contains 150 mg cilgavimab or tixagevimab (at 100 mg/mL concentration) in 1.5 mL formulation buffer composed of 2.4 mg L-Histidine, 3.0 mg L-Histidine hydrochloride monohydrate, 123.2 mg sucrose, 0.6 mg polysorbate 80, pH 6.0.

The manufacturing processes are adequately controlled to support consistent production of materials for EUA that are safe, pure, and potent. The overall control strategy for drug substance (DS) and drug product (DP) is comprehensive for control of raw materials, performance, and product quality attributes. DS and DP of tixagevimab and cilgavimab EUA materials are separately manufactured at (b) (4)
(b) (4)
The DP is filled into Type I clear glass vials and are stored at 2-8°C. Details of the manufacturing processes and controls are provided in IND 150712.

(b) (4)

(b) (4) The cell banks are tested in accordance with ICH Q5A to demonstrate assurance of safety for production. Process and product controls including, but not limited to, (b) (4), are acceptable to support the safety, quality, and potency of materials to be used under the EUA. Detailed characterization data, including primary, secondary, and high order structure, established and/or potential mechanisms of actions, product- and process-related impurities are provided in IND 150712. Comparability data provided, including in-process testing data, release data, characterization data, and comparative stability data, support that the quality of materials to be distributed under the EUA is comparable to that of materials used in clinical studies to support the EUA.

The proposed expiry for tixagevimab and cilgavimab DP is 18 months when stored at 2-8°C; and for tixagevimab and cilgavimab DS is (b) (4) when stored at (b) (4). The proposed DS and DP expiry is supported by the totality of stability results provided including, but not limited to, the available stability data under the long term, accelerated and stressed storage conditions, stability results from representative lots and comparative stability data. The stability protocols provided are adequate to detect potential changes in critical quality attributes during storage. The Sponsor committed to update IND 150712 with stability data from ongoing studies to further support the proposed shelf life, and to notify the Agency in the event that Out of Specification (OOS) results occur.

XVI. Manufacturing Site Inspections

Table 28 Manufacturing Sites

Manufac-turing Site Identifier	Drug Substances/ Intermediates/ Drug Product/ Testing/Labeler/ Packager	Location (US and Non-US)	Associated NDA, BLA, or IND	Commercial Sponsor/ Applicant	Inspection Dates	GMP Status (if known)
(b) (4)	Drug substance and drug product manufacturing, release and stability testing, and storage; (b) (4)	(b) (4)	IND 150712	AstraZeneca Pharmaceuticals LP	(b) (4)	Acceptable [1]
(b) (4)	(b) (4)	(b) (4)	IND 150712	AstraZeneca Pharmaceuticals LP	(b) (4)	Acceptable
	DP labeling, secondary packaging, and storage		IND 150712	AstraZeneca Pharmaceuticals LP		Acceptable
AstraZeneca AB (b) (4))	DP labeling, secondary packaging, and storage	Sodertalji, Sweden	IND 150712	AstraZeneca Pharmaceuticals LP	[redacted]	Acceptable

1. (b) (4) . The facility is acceptable to support AZD1061 and AZD8895 DS and DP manufacture and testing for the purpose of EUA.

Based on FDA's evaluation of the manufacturing process and control strategy, and the listed facilities, FDA considers the following conditions to the authorization as necessary to product the public health[9]:

- AstraZeneca will manufacture EVUSHELD Injection (Tixagevimab 150 mg and Cilgavimab 150 mg injection co-packaged for intramuscular use) to meet all quality standards and per the manufacturing process and control strategy as detailed in AstraZeneca's EUA request. AstraZeneca will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product, without notification to and concurrence by the Agency as described under condition D.

[9] See the evaluation documented in OMQ's Authorization Recommendation Memo for Emergency Use Authorization in CMS Case #619644 dated 12/8/2021, as well as OPQ's Chemistry, Manufacturing, and Controls EUA Assessment Memo (dated 11/24/2021) and OPMA's Product Quality Microbiology/Facility Assessment Memo (dated 11/29/2021) both associated with EUA 104.

- All manufacturing, packaging, and testing sites for both drug substance and drug product will comply with current good manufacturing practice requirements of the Federal Food, Drug, and Cosmetic Act Section 501(a)(2)(B).

- AstraZeneca will submit information to the Agency within three working days of receipt concerning significant quality problems with distributed drug product of EVUSHELD Injection that includes the following:
    - Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; or
    - Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet established specifications.

  If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information should be submitted for all potentially impacted lots.

  AstraZeneca will include in its notification to the Agency whether the batch, or batches, in question will be recalled. If FDA requests that these, or any other batches, at any time, be recalled, AstraZeneca must recall them.

  If not included in its initial notification, AstraZeneca must submit information confirming that AstraZeneca has identified the root cause of the significant quality problems, taken corrective action, and provide a justification confirming that the corrective action is appropriate and effective. AstraZeneca must submit this information as soon as possible but no later than 45 calendar days from the initial notification.

- AstraZeneca will list EVUSHELD Injection with a unique product NDC under the marketing category of Emergency Use Authorization. Further, the listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at each such establishment.

XVII. Clinical Trial Site Inspections

Clinical site inspections were not conducted for this EUA.

XVIII. Animal Study Site Inspections (Efficacy and PK/PD)

Nonclinical site inspections were not conducted for this EUA.

XIX. Recommendations From Treatment Guidelines and Other Sources

For COVID-19 pre-exposure prophylaxis in adults and pediatric patients 12 years of age and older, the following consensus panels and expert guidelines recommend use

of the approved Pfizer COVID-19 vaccine, COMIRNATY, or (in adults only) the other authorized COVID-19 vaccines (from Moderna and Janssen):

- The Center for Disease Control (CDC), in conjunction with the Advisory Committee on Immunization Practices (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html, accessed 11/5/2021).
- The National Institutes of Health (NIH) COVID-19 Treatment Guidelines (https://www.covid19treatmentguidelines.nih.gov/, last updated 10/19/2021). The rating of the recommendation is strong. The rating of evidence is I, one or more randomized trials without major limitations.
    - The NIH COVID-19 treatment guidelines also recommend against the use of any drugs for SARS-CoV-2 pre-exposure prophylaxis, except in a clinical trial. The rating of the recommendation is strong. The rating of evidence is III, expert opinion.

EVUSHELD is not currently included in COVID-19 treatment or prevention guidelines as it is currently not approved nor authorized for emergency use in the United States at the time of this review.

XX. Risk-Benefit Assessment and Recommendations for Emergency Use

EVUSHELD (AZD7442) is a combination product of two recombinant human IgG1κ monoclonal antibodies, tixagevimab and cilgavimab, directed against unique epitopes on the receptor binding domain of the SARS-CoV-2 spike protein. The Fc domain of both tixagevimab and cilgavimab include amino acid substitutions that extend antibody half-life (YTE) and that reduce Fc-mediated effector functions (TM). Both tixagevimab and cilgavimab have demonstrated activity in cell culture and animal models against SARS-CoV-2, and EVUSHELD is currently being evaluated in clinical trials for prophylaxis and treatment of COVID-19.

Based on FDA's review of the totality of scientific evidence available, including data from PROVENT (NCT04625725), a randomized, double-blind, placebo-controlled, Phase 3 trial of EVUSHELD administered as pre-exposure prophylaxis against the development of symptomatic SARS-CoV-2 infection in non-vaccinated individuals, it is reasonable to believe that EVUSHELD may be effective for use as pre-exposure prophylaxis for COVID-19 in certain adults and pediatric individuals (12 years of age and older weighing at least 40 kg) who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2. FDA has also determined that the known and potential benefits of EVUSHELD, when used for the pre-exposure prophylaxis of COVID-19 as described in Section III of this memorandum, outweigh the known and potential risks of the product.

The primary endpoint for PROVENT was the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness that occurred after administration and prior to Day 183. Only events that occurred prior to unblinding or vaccine receipt were included. At the time of the primary analysis, which was event driven, the median follow-up time post-

administration was 83 days (range 3 to 166 days). Event rates for the primary endpoint were 8/3441 (0.2%) in the EVUSHELD group versus 17/1731 (1.0%) in the placebo group. EVUSHELD administration resulted in a 77% (95% CI: 46, 90) reduction in incidence of SARS-CoV-2 RT-PCR positive symptomatic illness compared to placebo. Similar results were observed for EVUSHELD versus placebo recipients in the reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness or death from any cause (69% relative risk reduction, 95% CI: 36, 85) and in reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness regardless of unblinding or vaccine receipt (77% relative risk reduction, 95% CI: 52, 89).

Topline efficacy data using a later data cut-off date, with a median follow-up time post-administration of 196 days (range 3 to 282 days) became available during the EUA review. Event rates for the primary endpoint with the later data cut-off date were 11/3441 (0.3%) in the EVUSHELD group versus 31/1731 (1.8%) in the placebo group, corresponding to a relative risk reduction of 83% (95% CI: 66, 91) for incidence of SARS-CoV-2 RT-PCR positive symptomatic illness for EVUSHELD compared to placebo recipients. In addition, the relative risk reduction at 3 to 6 months (88%) was similar to the relative risk reduction at 0-3 months (79%), indicating that protective efficacy may last for six months. Although these data were limited, events beyond 6 months in EVUSHELD versus placebo recipients suggest that protective efficacy may not extend beyond six months.

The EUA also contained data from STORM CHASER, a randomized, double-blind, placebo-controlled, Phase 3 trial of EVUSHELD administered as post-exposure prophylaxis against the development of symptomatic SARS-CoV-2 infection in non-vaccinated individuals following potential exposure (within 8 days) to an identified individual with laboratory-confirmed SARS-CoV-2 infection. The primary efficacy analysis, comparison of the incidence of a subject's first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post-dose and before Day 183, did not show a statistically significant effect for EVUSHELD versus placebo with 23 cases of COVID-19 in the EVUSHELD arm (3.1%) and 17 cases in the placebo arm (4.6%) (relative risk reduction of 33%, 95% CI: -26, 65). However, in a pre-planned subgroup analysis by SARS-CoV-2 RT-PCR status at baseline, EVUSHELD reduced the risk of developing COVID-19 by 73% (95% CI: 27, 90) in subjects who were RT-PCR negative/missing at time of dosing when compared with placebo. In subjects who were SARS-CoV-2 RT-PCR positive at baseline (EVUSHELD N= 34, placebo N= 14), EVUSHELD recipients versus placebo recipients were as likely to develop COVID-19 symptoms (17/34 versus 6/14), more likely to have a higher number of symptoms (median 4 versus 2.5 symptoms among subjects who developed symptoms), and more likely to experience moderate to severe symptoms (10/34 versus 2/14, respectively). Based on a Kaplan Meier estimate of the time to first SARS-CoV-2 RT-PCR positive symptomatic illness, there was no apparent benefit of EVUSHELD over placebo prior to Day 29, but the curves separated with more reported cases among placebo recipients after Day 29. The STORM CHASER data were reviewed as part of our recommendation to authorize for a pre-exposure prophylaxis authorization.

Review of these findings do not support either a post-exposure prophylaxis authorization or an early treatment authorization.

Regarding assessment of the known and potential risks, the overall safety database for EVUSHELD is comprised of over 4,220 subjects who received the tixagevimab 150 mg IM and cilgavimab 150 mg IM dose, with at least topline follow-up safety data through a median of six months. Overall, safety was similar between EVUSHELD and placebo recipients, with slightly lower incidence of death among EVUSHELD recipients (11/4210, or 0.26%, EVUSHELD recipients versus 8/2108, or 0.38%, placebo recipients in PROVENT and STORM CHASER combined through the later data cut-off dates). Although infrequent overall, an imbalance was noted in the number of cardiac serious adverse events in PROVENT, particularly events of myocardial infarction (8/3461 (0.23%) EVUSHELD recipients versus 1/1736 (0.06%) placebo recipients) and cardiac failure (6/3461 (0.17%) EVUSHELD recipients versus 1/1736 (0.06%) placebo recipients, through Day 183 with the later data cut-off). Given the seriousness of the events (including one myocardial infarction that resulted in death) and what appears to be a clustering of events with similar pathophysiologies, the imbalance will be communicated in the Fact Sheets. The Fact Sheets will also specify that health care providers should advise patients to seek immediate medical attention if they experience any signs or symptoms suggestive of a cardiovascular event. However, as it is unclear if the PROVENT imbalances in myocardial infarction SAEs, and in cardiac failure SAEs with the later data cut-off date, are by chance or are related to study product, the Fact Sheets will also include that a causal relationship between EVUSHELD and these events has not been established. The other major adverse events of concern were hypersensitivity reactions including anaphylaxis. One EVUSHELD recipient in PROVENT was reported as having anaphylaxis within minutes of receiving his EVUSHELD dose. Otherwise, the only hypersensitivity reactions reported in PROVENT were mild to moderate injection site reactions (3% of EVUSHELD recipients). To mitigate the risk of hypersensitivity reactions, individuals should be clinically monitored for at least one hour after EVUSHELD administration. Finally, given the theoretical concern that SARS-CoV-2 spike protein-directed monoclonal antibodies could blunt the immune response to COVID-19 vaccination by binding the vaccine antigen, the limits of authorization will specify that EVUSHELD should be administered at least two weeks after COVID-19 vaccination in individuals for whom vaccination is recommended.

EVUSHELD is expected to retain activity against SARS-CoV-2 Variants Being Monitored, including the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Epsilon (B.1.427 and B.1.429), Eta (B.1.525), Iota (B.1.526), Kappa (B.1.617.1), Mu (B.1.621), and Zeta (P.2), and Variants of Concern, Delta (B.1.617.2 and AY), based on cell culture neutralization data from authentic SARS-CoV-2 assays and/or pseudotyped virus-like particle (VLP) data. The susceptibility of the recently identified Omicron (B.1.1.529) variant to cilgavimab, tixagevimab, and tixagevimab and cilgavimab has not yet been determined.

In selecting the authorized population, the FDA carefully considered findings from PROVENT and STORM CHASER, the two Phase 3 trials evaluating an EVUSHELD dose of 150 mg IM tixagevimab and 150 mg IM cilgavimab, as well as other products authorized or approved for pre-exposure prophylaxis (i.e., COVID-19 vaccines). As STORM CHASER did not meet its primary endpoint for post-exposure prophylaxis, and as the benefit of this EVUSHELD dose for treatment of COVID-19 has not been observed, limitations of use in the EUA Fact Sheet will specify that EVUSHELD is not authorized for post-exposure prophylaxis or treatment. In addition, based on the safety, efficacy, and widespread availability of approved and/or authorized COVID-19 vaccines in the US, the authorization for EVUSHELD is limited to either individuals with moderate to severe immune compromise who may not mount an adequate immune response to COVID-19 vaccination or individuals for whom COVID-19 vaccination is not recommended due to a severe adverse reaction to a COVID-19 vaccine or its components.

Based on FDA's review of the totality of scientific evidence available, including data from PROVENT (NCT04625725), a randomized, double-blind, placebo-controlled, Phase 3 trial of EVUSHELD administered as pre-exposure prophylaxis against the development of symptomatic SARS-CoV-2 infection in non-vaccinated individuals, it is reasonable to believe that EVUSHELD may be effective for use as pre-exposure prophylaxis for COVID-19 in certain adults and pediatric individuals (12 years of age and older weighing at least 40 kg) who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2. FDA has also determined that the known and potential benefits of EVUSHELD, when used for the pre-exposure prophylaxis of COVID-19 as described in Section III of this memorandum, outweigh the known and potential risks of the product. Therefore, the Review Division and the Office of Infectious Diseases conclude that the statutory criteria under section 564(c) of the Federal Food, Drug, and Cosmetic Act are met and recommend authorization of an EUA for EVUSHELD, at a dose of 150 mg IM tixagevimab and 150 mg IM cilgavimab, for pre-exposure prophylaxis of COVID-19 as described above.

XXI. Considerations for Adverse Event (AE) Monitoring

This product will either be used in clinical trials or in clinical practice under EUA. Investigational product will be used in clinical trials conducted under IND. FDA IND safety reporting regulations will apply.

EUA-labeled product will be made available under the EUA. In the setting of a pandemic where practicing physicians will have competing priorities, adverse event reporting under this EUA will be streamlined through the MEDWATCH system.

AstraZeneca will be responsible for mandatory reporting of all medication errors and all serious adverse events associated with the use of EVUSHELD under the EUA to the Agency. Similarly, the prescribing health care provider and/or the provider's designee will be responsible for mandatory reporting of all medication errors and all

serious adverse events occurring during EVUSHELD use and considered potentially related to EVUSHELD within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "EVUSHELD use for COVID-19 under Emergency Use Authorization (EUA)." The Fact Sheet for Healthcare Providers also directs healthcare providers to provide a copy of the Form 3500 submitted to FDA to AstraZeneca. The Fact Sheet for Patients, Parents and Caregivers provides information on the reporting of side effects through FDA's MedWatch program.

XXII. Mandatory and Discretionary Requirements for Use of the Product Under the EUA

Refer to the Letter of Authorization and the authorized Fact Sheet for Health Care Providers.

XXIII. Information to Be Conveyed to Health Care Providers and Recipients of the Product

Fact sheets will be available to health care providers and individuals through electronic links.

- The URL is http://www.evusheld.com/.

FDA agrees with the plan for implementation for dissemination of the Fact Sheets.

- Fact Sheet for Health Care Providers (See Section XXVI. Appendices)
- Fact Sheet for Patients and Parents/Caregivers (See Section XXVI. Appendices)

XXIV. Outstanding Issues/Data Gaps

The EUA for EVUSHELD is primarily based on safety and efficacy data through an event driven efficacy data cut-off from the ongoing study PROVENT, with a median (range) of follow-up of 83 days (3-166 days). The topline efficacy and safety results from an additional data cut-off to provide updated analyses with a median (range) of follow-up of 196 days (3-282 days) are similar to the primary analysis data and therefor are supportive of the EUA. However, final results from PROVENT remain critical to confirm the initial benefit-risk assessment and the optimal dosing regimen for EVUSHELD. Pending results from PROVENT include safety data through Day 457 (which corresponds to five half-lives), ADA assessments for all subjects at the protocol-defined time points (Days 1, 29, 58, 183, and 366 and optionally at Day 457), and the proposed sub-study to investigate safety, immunogenicity, and pharmacokinetics with repeat dosing in approximately 500 subjects. As such, we are requiring that the Applicant submit the following information as conditions of authorization:

- All anti-drug antibody (ADA) assessments that have not been completed at the time of this authorization for subjects from the PROVENT clinical trial for days 1, 29, 58, and 183 by April 22, 2022.

- Interim analysis results through Day 28 for the first 50 subjects to receive a second dose from the PROVENT repeat-dose sub-study by April 22, 2022.
- AstraZeneca must conduct an additional study attempting to select for SARS-CoV-2 with reduced susceptibility to tixagevimab in culture. Such study must employ alternative strategies as agreed upon between AstraZeneca and the Agency. AstraZeneca must provide the Agency with a proposed protocol by January 7, 2022. AstraZeneca must submit a report of summary findings as soon as available, but no later than June 30, 2022.
- Report from AstraZeneca's study evaluating the potential for tixagevimab and cilgavimab to mediate antibody-dependent enhancement of infection using sub-saturating concentrations of each monoclonal antibody by June 30, 2022.
- Final results from PROVENT and STORM CHASER by December 30, 2022.
- Results, to include baseline and all subsequent study visits, of the following biomarkers from the PROVENT repeat-dose sub-study: d-dimer, P-selectin, thrombin, and Factor VIII.
- Topline data, to include safety, pharmacokinetic, ADA, and biomarker results for thrombotic events from the first 9 months of the PROVENT repeat-dose sub-study by January 31, 2023.
- Monthly aggregate reports for serious adverse events in the Cardiac Disorder System Order Class (SOC) and other non-cardiac thrombotic serious adverse events.

XXV. References

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Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004;159(7):702-6. doi:10.1093/aje/kwh090.

XXVI. Appendices

1. Fact Sheet for Health Care Providers
2. Fact Sheet for Patients and Parent/Caregivers

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR EVUSHELD™ (tixagevimab co-packaged with cilgavimab)

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use EVUSHELD™ under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for EVUSHELD.

EVUSHELD (tixagevimab) injection; (cilgavimab) injection, co-packaged for intramuscular use
Original EUA Authorized Date: 12/2021

----------EUA FOR EVUSHELD----------
The U.S. Food and Drug Administration has issued an EUA for the emergency use of the unapproved product EVUSHELD (tixagevimab co-packaged with cilgavimab), SARS-CoV-2 spike protein-directed attachment inhibitor, for the pre-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in adults and pediatric individuals (12 years of age and older weighing at least 40 kg):

- Who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 **and**
  - Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments **and** may not mount an adequate immune response to COVID-19 vaccination **or**
  - For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s).

EVUSHELD has been authorized by FDA for the emergency use descr bed above. EVUSHELD is not FDA-approved for any use, including use for pre-exposure prophylaxis of COVID-19. (1)

EVUSHELD is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of EVUSHELD under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

LIMITATIONS OF AUTHORIZED USE

- EVUSHELD is not authorized for use in individuals:
  - For treatment of COVID-19, or
  - For post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2.
- Pre-exposure prophylaxis with EVUSHELD is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended. Individuals for whom COVID-19 vaccination is recommended, including individuals with moderate to severe immune compromise who may derive benefit from COVID-19 vaccination, should receive COVID-19 vaccination.
- In individuals who have received a COVID-19 vaccine, EVUSHELD should be administered at least two weeks after vaccination.

See Full Fact Sheet for Healthcare Providers for examples of medical conditions or treatments that may result in moderate to severe immune compromise and an inadequate immune response to COVID-19 vaccination, the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19. (1)

----------DOSAGE AND ADMINISTRATION----------
The dosage of EVUSHELD for emergency use is 150 mg of tixagevimab and 150 mg of cilgavimab administered as two separate consecutive intramuscular injections. See Full Fact Sheet for Healthcare Providers for detail on preparation and administration. (2)

----------DOSAGE FORMS AND STRENGTHS----------
Injection:

- tixagevimab 150 mg/1.5 mL (100 mg/mL) in a single-dose vial. (3)
- cilgavimab 150 mg/1.5 mL (100 mg/mL) in a single-dose vial. (3)

----------CONTRAINDICATIONS----------
EVUSHELD is contraindicated in individuals with previous severe hypersensitivity reactions, including anaphylaxis, to any component of EVUSHELD. (4)

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity Including Anaphylaxis: Serious hypersensitivity reactions, including anaphylaxis, have been observed with IgG1 monoclonal antibodies l ke EVUSHELD. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy. Clinically monitor individuals after injections and observe for at least 1 hour. (5.1)
- Clinically Significant Bleeding Disorders: As with any other intramuscular injection, EVUSHELD should be given with caution to individuals with thrombocytopenia or any coagulation disorder. (5.2)
- Cardiovascular Events: A higher proportion of subjects who received EVUSHELD versus placebo reported myocardial infarction and cardiac failure serious adverse events. All of the subjects with events had cardiac risk factors and/or a prior history of cardiovascular disease, and there was no clear temporal pattern. A causal relationship between EVUSHELD and these events has not been established. Consider the risks and benefits prior to initiating EVUSHELD in individuals at high risk for cardiovascular events, and advise individuals to seek immediate medical attention if they experience any signs or symptoms suggestive of a cardiovascular event. (5.3)

----------ADVERSE REACTIONS----------
Most common adverse events (all grades, incidence ≥3%) are headache, fatigue, and cough. (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to EVUSHELD (1) by submitting FDA Form 3500 online, (2) by downloading this form and then submitting by mail or fax, or (3) contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to *AstraZeneca* by Fax at 1-866-742-7984 or call 1-800-236-9933. (6.4)

See PATIENT AND PARENTS/CAREGIVER FACT SHEET.

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FULL FACT SHEET FOR HEALTHCARE PROVIDERS

1 EMERGENCY USE AUTHORIZATION

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of the unapproved product EVUSHELD (tixagevimab co-packaged with cilgavimab) for the pre-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in adults and pediatric individuals (12 years of age and older weighing at least 40 kg):

- Who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 **and**
  - Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments **and** may not mount an adequate immune response to COVID-19 vaccination[1] **or**
  - For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s).

EVUSHELD has been authorized by FDA for the emergency use described above. EVUSHELD is not FDA-approved for any use, including use for pre-exposure prophylaxis of COVID-19.

EVUSHELD is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of EVUSHELD under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Medical conditions or treatments that may result in moderate to severe immune compromise and an inadequate immune response to COVID-19 vaccination include but are not limited to[1]:

- Active treatment for solid tumor and hematologic malignancies
- Receipt of solid-organ transplant and taking immunosuppressive therapy
- Receipt of chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)
- Moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Advanced or untreated HIV infection (people with HIV and CD4 cell counts <200/mm^3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV)
- Active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory (e.g., B-cell depleting agents)

LIMITATIONS OF AUTHORIZED USE

- EVUSHELD is not authorized for use in individuals:
  - For treatment of COVID-19, or

[1] For additional information please see https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html.Healthcare providers should consider the benefit-risk for an individual patient.

    - For post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2.
- Pre-exposure prophylaxis with EVUSHELD is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended. Individuals for whom COVID-19 vaccination is recommended, including individuals with moderate to severe immune compromise who may derive benefit from COVID-19 vaccination, should receive COVID-19 vaccination.
- In individuals who have received a COVID-19 vaccine, EVUSHELD should be administered at least two weeks after vaccination.

Justification for Emergency Use of Drugs During the COVID-19 Pandemic

There is currently an outbreak of COVID-19 caused by SARS-CoV-2, a novel coronavirus. The Secretary of HHS has declared that:

- A public health emergency related to COVID-19 has existed since January 27, 2020.
- Circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic (March 27, 2020 declaration).

An EUA is a FDA authorization for the emergency use of an unapproved product or unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain circumstances including, but not limited to, when the Secretary of HHS declares that there is a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

- The biological agent(s) can cause a serious or life-threatening disease or condition;
- Based on the totality of the available scientific evidence (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that
    - The product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition; and
    - The known and potential benefits of the product - when used to diagnose, prevent, or treat such disease or condition - outweigh the known and potential risks of the product, taking into consideration the material threat posed by the biological agent(s);
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition.

Information Regarding Available Alternatives for the EUA Authorized Use

There are no adequate, approved and available alternatives to EVUSHELD for the pre-exposure prophylaxis of COVID-19 in individuals who may not mount an adequate immune response to COVID-19 vaccination or for whom COVID-19 vaccination is not recommended due to a history of severe adverse reaction to a COVID-19 vaccine or its components.

For information on clinical studies of EVUSHELD and other therapies for the prophylaxis of COVID-19, see www.clinicaltrials.gov.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Emergency Use of EVUSHELD

The dosage of EVUSHELD in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) is 150 mg of tixagevimab and 150 mg of cilgavimab administered as two separate consecutive intramuscular (IM) injections.

Repeat Dosing
Longer term data from the study PROVENT indicate that EVUSHELD may be effective for pre-exposure prophylaxis for 6 months post-administration *[see Clinical Studies (14)]*. While SARS-CoV-2 remains in circulation, individuals who qualify for EVUSHELD, per the conditions of the EUA, can be redosed every 6 months.

EVUSHELD has only been studied in single-dose studies. There are no safety and efficacy data available with repeat dosing. The recommendation for repeat dosing is based on the totality of the scientific evidence including clinical pharmacology data and clinical trial data *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

2.2 Dosage Adjustment in Specific Populations

No dosage adjustment is recommended in pregnant or lactating individuals, in geriatrics, and in individuals with renal impairment *[see Use in Specific Populations (8)]*.

2.3 Dose Preparation and Administration

Each EVUSHELD carton contains two vials; one of each antibody. Each vial contains an overfill to allow the withdrawal of 150 mg (1.5 mL).

Table 1. Dosage of Tixagevimab and Cilgavimab

EVUSHELD* (tixagevimab co-packaged with cilgavimab)	**Antibody dose**	**Number of vials needed**	**Volume to withdraw from vial(s)**
	tixagevimab 150 mg	1 vial (dark grey vial cap)	1.5 mL
	cilgavimab 150 mg	1 vial (white vial cap)	1.5 mL

* 150 mg of tixagevimab and 150 mg of cilgavimab are to be administered as separate, consecutive intramuscular injections

Preparation

- Tixagevimab and cilgavimab must be prepared by a qualified healthcare provider.
- Tixagevimab and cilgavimab are each supplied in individual single-dose vials. Do not shake the vials.
- Visually inspect the vials for particulate matter and discoloration. Tixagevimab and cilgavimab are clear to opalescent, colorless to slightly yellow solutions. Discard the vials if the solution is cloudy, discolored or visible particles are observed.
- Withdraw 1.5 mL of tixagevimab solution and 1.5 mL of cilgavimab solution into TWO separate syringes (see Table 1). Discard unused portion in vials.

- This product is preservative-free and therefore, the prepared syringes should be administered immediately. If immediate administration is not possible, and the prepared tixagevimab and cilgavimab syringes need to be stored, the total time from vial puncture to administration must not exceed 4 hours:
    - in a refrigerator at 2ºC to 8ºC (36ºF to 46ºF), or
    - at room temperature up to 25ºC (77ºF).

Administration

- Tixagevimab and cilgavimab must be administered by a qualified healthcare provider.
- Administer the two components of EVUSHELD consecutively.
- Administer the IM injections at different injection sites, preferably one in each of the gluteal muscles, one after the other.
- Clinically monitor individuals after injections and observe for at least 1 hour *[see Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

EVUSHELD is available as an individual single-dose vial of tixagevimab as a clear to opalescent, colorless to slightly yellow solution co-packaged with an individual single-dose vial of cilgavimab as a clear to opalescent, colorless to slightly yellow solution as:

- Injection: 150 mg/1.5 mL (100 mg/mL) of tixagevimab
- Injection: 150 mg/1.5 mL (100 mg/mL) of cilgavimab

4 CONTRAINDICATIONS

EVUSHELD is contraindicated in individuals with previous severe hypersensitivity reactions, including anaphylaxis, to any component of EVUSHELD *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

There are limited clinical data available for EVUSHELD. Serious and unexpected adverse events may occur that have not been previously reported with EVUSHELD use.

5.1 Hypersensitivity Including Anaphylaxis

Serious hypersensitivity reactions, including anaphylaxis, have been observed with Human immunoglobulin G1 (IgG1) monoclonal antibodies like EVUSHELD *[see Adverse Reactions (6.1)]*. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur while taking EVUSHELD, immediately discontinue administration and initiate appropriate medications and/or supportive care. Clinically monitor individuals after injections and observe for at least 1 hour.

5.2 Clinically Significant Bleeding Disorders

As with any other intramuscular injection, EVUSHELD should be given with caution to individuals with thrombocytopenia or any coagulation disorder.

5.3 Cardiovascular Events

In PROVENT there was a higher rate of cardiovascular serious adverse events (SAEs), including myocardial infarction (one fatal SAE) and cardiac failure, in subjects who received EVUSHELD compared to placebo *[see Adverse Reactions (6.1)]*. All subjects who experienced cardiac SAEs had cardiac risk factors and/or a prior history of cardiovascular disease, and there was no clear temporal pattern. A causal relationship between EVUSHELD and these events has not been established. There was no signal for cardiac toxicity or thrombotic events identified in the nonclinical studies.

Consider the risks and benefits prior to initiating EVUSHELD in individuals at high risk for cardiovascular events, and advise individuals to seek immediate medical attention if they experience any signs or symptoms suggestive of a cardiovascular event.

6 ADVERSE REACTIONS

6.1 Adverse Reactions from Clinical Studies

The following adverse events have been observed in the clinical studies of EVUSHELD that supported the EUA. The adverse event rates observed in these clinical studies cannot be directly compared to rates in the clinical studies of other products and may not reflect the rates observed in clinical practice. Additional adverse events associated with EVUSHELD may become apparent with more widespread use.

Approximately 4,220 subjects have been exposed to EVUSHELD (tixagevimab 150 mg and cilgavimab 150 mg) in clinical trials.

The safety of EVUSHELD is based on analyses from two ongoing Phase III trials, PROVENT and STORM CHASER. In both studies, adults received EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) administered as two separate consecutive IM injections or placebo *[see Clinical Studies (14)]*.

The primary safety analysis was based on data through to an event driven efficacy data cut-off, such that individual subjects had variable follow-up times *[see Clinical Studies (14)]*, with a median (range) of follow-up of 83 days (3-166 days) for PROVENT and 49 days (5-115 days) for STORM CHASER. An additional data cut-off was conducted to provide updated analyses with a median (range) of follow-up of 6.5 months (3-282 days) for PROVENT and approximately 6 months (5-249 days) for STORM CHASER. The median and range of follow-up times were similar between EVUSHELD and placebo recipients in each trial.

PROVENT
PROVENT enrolled adults ≥18 years of age who were either ≥60 years of age, had pre-specified co-morbidities *[see Clinical Studies (14)]*, or were at increased risk of SARS-CoV-2 infection due to their living situation or occupation. Subjects could not have previously received a COVID-19 vaccine or have known prior or current SARS-CoV-2 infection. Subjects received a single dose of EVUSHELD (N= 3,461) or placebo (N= 1,736).

Adverse events were reported in 1,221 (35%) subjects receiving EVUSHELD and 593 (34%) receiving placebo. SAEs were reported in 50 (1%) subjects receiving EVUSHELD and 23 (1%) receiving placebo. There was 1 adverse event reported as anaphylaxis among subjects who received

EVUSHELD. The event began within minutes of EVUSHELD administration and was treated with epinephrine. The event resolved.

Of the reported adverse events (N= 4,507), the majority were mild (73%) or moderate (24%) in severity. All adverse events, occurring in at least 1% of subjects, were reported at similar incidence rates among subjects receiving EVUSHELD compared to those receiving placebo (difference <1%). The most common treatment-emergent adverse events, occurring in at least 3% of subjects receiving EVUSHELD or placebo are shown in Table 2.

Table 2 Adverse Events (All Grades) Regardless of Causality Occurring in at Least 3% of Subjects Receiving EVUSHELD or Placebo in Primary Safety Analysis

	EVUSHELD N= 3,461	**Placebo N= 1,736**
Headache	6%	5%
Fatigue	4%	3%
Cough	3%	3%

At the additional data cut-off (median follow-up 6.5 months), the overall adverse event profile for subjects who received EVUSHELD remained similar to events displayed in Table 2.

Cardiac Serious Adverse Events

Through the additional data cut-off in PROVENT, a higher proportion of subjects who received EVUSHELD versus placebo in PROVENT reported myocardial infarction SAEs, one of which resulted in death, and cardiac failure SAEs (see Table 3 below). All subjects who experienced cardiac SAEs had cardiac risk factors and/or a prior history of cardiovascular disease at baseline. There was no clear temporal pattern, with events reported from several hours after EVUSHELD receipt through the end of the follow-up period.

Table 3 Cardiac SAEs Regardless of Causality in PROVENT with Onset Prior to Day 183 Using the Median 6-Month Data Cut-off Date

	EVUSHELD N= 3,461	**Placebo N= 1,736**
Subjects with any cardiac SAE*	22 (0.6%)	3 (0.2%)
SAEs related to coronary artery disease or myocardial ischemia†	10 (0.3%)	2 (0.1%)
Myocardial infarctions‡	8 (0.2%)	1 (0.1%)
SAEs related to cardiac failure§α	6 (0.2%)	1 (0.1%)
SAEs related to an arrhythmia¶	4 (0.1%)	1 (0.1%)
Other (cardiomegaly, cardiomyopathy, and cardio-respiratory arrest)	3 (0.1%)	0

* One EVUSHELD recipient and one placebo recipient had two cardiac SAEs each.
† Includes the preferred terms angina pectoris, coronary artery disease, arteriosclerosis, troponin increased, acute myocardial infarction, and myocardial infarction.
‡ Includes the preferred terms acute myocardial infarction, myocardial infarction, and troponin increased (with a discharge diagnosis of myocardial infarction).
§ Includes the preferred terms cardiac failure congestive, acute left ventricular failure, cardiac failure, and cardiac failure acute.
¶ Includes the preferred terms atrial fibrillation, arrhythmia, paroxysmal atrioventricular block, and heart rate irregular.

STORM CHASER

STORM CHASER enrolled adults ≥18 years of age following potential exposure (within 8 days) to an identified individual with a laboratory-confirmed SARS-CoV-2 infection (symptomatic or asymptomatic). Subjects could not have previously received a COVID-19 vaccine, have symptoms consistent with COVID-19, or have a known prior SARS-CoV-2 infection. Subjects received a single dose of EVUSHELD (N= 749) or placebo (N= 372).

Adverse events were reported in 162 (22%) subjects receiving EVUSHELD and 111 (30%) receiving placebo. SAEs were reported in 5 (<1%) subjects receiving EVUSHELD and 3 (<1%) receiving placebo. Of the reported adverse events (N= 777), the majority were mild (75%) or moderate (23%) in severity.

At the additional data cut-off (median follow-up approximately 6 months), the overall adverse event profile for subjects who received EVUSHELD remained similar to earlier results. EVUSHELD is not authorized for post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2 *[see Emergency Use Authorization (1)]*.

Cardiac Serious Adverse Events

In STORM CHASER (N= 1,121) no cardiac SAEs were reported (median follow-up approximately 6 months). Compared to PROVENT, the subjects in STORM CHASER were younger (median age 48 versus 57 years) and had fewer baseline cardiac risk factors (24% versus 36% with hypertension, 11% versus 14% with diabetes, and 3% versus 8% with cardiovascular disease in STORM CHASER versus PROVENT, respectively).

6.4 Required Reporting for Serious Adverse Events and Medication Errors

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory reporting of all serious adverse events* and medication errors potentially related to EVUSHELD within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 3500 (for information on how to access this form, see below). The FDA recommends that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race)
- A statement "EVUSHELD use for COVID-19 under Emergency Use Authorization (EUA)" under the "**Describe Event, Problem, or Product Use/Medication Error"** heading
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes)
- Patient's preexisting medical conditions and use of concomitant products
- Information about the product (e.g., dosage, route of administration, NDC #)

Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm

- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax to 1-800-FDA-0178, or
- Call 1-800-FDA-1088 to request a reporting form

In addition, please provide a copy of all FDA MedWatch forms to AstraZeneca:

- Fax 1-866-742-7984

and to report adverse events please:

- Visit https://contactazmedical.astrazeneca.com, or
- Call AstraZeneca at 1-800-236-9933.

The prescribing healthcare provider and/or the provider's designee is/are to provide mandatory responses to requests from FDA for information about adverse events and medication errors associated with EVUSHELD.

*Serious adverse events are defined as:

- Death or a life-threatening adverse event;
- A medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
- A congenital anomaly/birth defect.

7 DRUG INTERACTIONS

Drug-drug interaction studies have not been performed.

Tixagevimab and cilgavimab are not renally excreted or metabolized by cytochrome P450 (CYP) enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. EVUSHELD should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

Nonclinical reproductive toxicity studies have not been conducted with tixagevimab and cilgavimab. In a tissue cross-reactivity study assessing off-target binding of tixagevimab and cilgavimab to human fetal tissues no binding of clinical concern was observed. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, tixagevimab and cilgavimab have the

potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of tixagevimab and cilgavimab provides any treatment benefit or risk to the developing fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

8.2 Lactation

Risk Summary

There are no available data on the presence of tixagevimab or cilgavimab in human milk or animal milk, the effects on the breastfed infant, or the effects of the drug on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EVUSHELD and any potential adverse effects on the breastfed infant from EVUSHELD.

8.4 Pediatric Use

EVUSHELD is not authorized for use in pediatric individuals under 12 years of age or weighing less than 40 kg. The safety and effectiveness of EVUSHELD have not been established in pediatric individuals. The dosing regimen is expected to result in comparable serum exposures of tixagevimab and cilgavimab in individuals 12 years of age and older and weighing at least 40 kg as observed in adults, since adults with similar body weight have been included in the trials PROVENT and STORM CHASER *[see Adverse Reactions (6.1) and Clinical Studies (14)].*

8.5 Geriatric Use

Of the 2,029 subjects in the pooled pharmacokinetics (PK) analysis (Phase I and Phase III studies), 23% (N= 461) were 65 years of age or older and 3.3% (N= 67) were 75 years of age or older. There is no clinically meaningful difference in the PK of tixagevimab and cilgavimab in geriatric subjects (≥65 years) compared to younger subjects.

8.6 Renal Impairment

Tixagevimab and cilgavimab are not eliminated intact in the urine, renal impairment is not expected to affect the exposure of tixagevimab and cilgavimab. Similarly, dialysis is not expected to impact the PK of tixagevimab and cilgavimab.

8.7 Hepatic Impairment

The effect of hepatic impairment on the PK of tixagevimab and cilgavimab is unknown.

8.8 Other Specific Populations

Based on a population PK analysis, the PK profile of tixagevimab and cilgavimab was not affected by sex, age, race, or ethnicity. Population PK model-based simulations suggest that body weight had no

clinically relevant effect on the PK of tixagevimab and cilgavimab in healthy adults over the range of 36 kg to 177 kg.

10 OVERDOSAGE

Treatment of overdose with EVUSHELD should consist of general supportive measures including the monitoring of the clinical status of the individual. There is no specific treatment for overdose with EVUSHELD.

11 DESCRIPTION

Tixagevimab, a SARS-CoV-2 spike protein-directed attachment inhibitor, is a human immunoglobulin G1 (IgG1κ) monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. The molecular weight is approximately 149 kDa.

Tixagevimab injection is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow solution supplied in a single-dose vial for intramuscular use. The vial stoppers are not made with natural rubber latex. Each 1.5 mL contains 150 mg tixagevimab, L- histidine (2.4 mg), L- histidine hydrochloride monohydrate (3.0 mg), polysorbate 80 (0.6 mg), sucrose (123.2 mg), and Water for Injection, USP. The pH is 6.0.

Cilgavimab, a SARS-CoV-2 spike protein-directed attachment inhibitor, is a human IgG1κ monoclonal antibody produced in CHO cells by recombinant DNA technology. The molecular weight is approximately 152 kDa.

Cilgavimab injection is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow solution supplied in a single-dose vial for intramuscular use. The vial stoppers are not made with natural rubber latex. Each 1.5 mL contains 150 mg cilgavimab, L- histidine (2.4 mg), L- histidine hydrochloride monohydrate (3.0 mg), polysorbate 80 (0.6 mg), sucrose (123.2 mg), and Water for Injection, USP. The pH is 6.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tixagevimab and cilgavimab are two recombinant human IgG1κ monoclonal antibodies with amino acid substitutions to extend antibody half-life (YTE), reduce antibody effector function, and minimize the potential risk of antibody-dependent enhancement of disease (TM). Tixagevimab and cilgavimab can simultaneously bind to non-overlapping regions of the receptor binding domain (RBD) of SARS-CoV-2 spike protein. Tixagevimab, cilgavimab, and their combination bind to spike protein with equilibrium dissociation constants of K_D = 2.76 pM, 13.0 pM and 13.7 pM, respectively, blocking its interaction with human ACE2, the SARS-CoV-2 receptor, which is required for virus attachment. Tixagevimab, cilgavimab, and their combination blocked RBD binding to human ACE2 with IC_{50} values of 0.32 nM (48 ng/mL), 0.53 nM (80 ng/mL), and 0.43 nM (65 ng/mL), respectively.

12.3 Pharmacokinetics

A summary of PK parameters and properties of tixagevimab and cilgavimab following administration of a single EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) intramuscular dose is provided in Table 4.

Table 4 Summary of PK Parameters and Properties of Tixagevimab and Cilgavimab Following a Single EVUSHELD Intramuscular Dose

PK Parameters	Tixagevimab	Cilgavimab
C_{max} (µg/mL)*	16.5 (35.6)	15.3 (38.5)
T_{max} (day)†	14.0 (3.1 – 30)	14.0 (3.1 – 60)
C_1 (µg/mL)‡	4.4 (92.2)	3.9 (94.4)
C_{150} (µg/mL)§	6.6 (25.6)	5.5 (35.2)
C_{210} (µg/mL)¶	4.0 (31.6)	3.9 (37.1)
AUC_{inf} (day•µg/mL)	2529 (30.2)	2133 (31.7)
Absorption		
Bioavailability#	68.5	65.8
Distribution		
Apparent Volume of Distribution (L)#	7.7 (1.97)	8.7 (2.73)
Elimination		
Half-life (days)#	87.9 (13.9)	82.9 (12.3)
Apparent Clearance (L/day)#	0.062 (0.019)	0.074 (0.028)
Metabolism	Catabolic pathways; Same manner as endogenous IgG	
Excretion	Not likely to undergo renal excretion	

* Geomean (geometric %CV)
† Median (range)
‡ Observed geomean (geometric %CV) concentration 1 day after dosing
§ Observed geomean (geometric %CV) concentration 150 days after dosing
¶ Observed geomean (geometric %CV) concentration 210 days after dosing
# Arithmetic mean (SD)

For repeat dose pre-exposure prophylaxis, it is expected that 6-month repeat EVUSHELD dosing will result in steady-state serum tixagevimab and cilgavimab trough concentrations greater than or equal to Day 183 tixagevimab and cilgavimab serum concentrations following a single EVUSHELD dose. Predicted steady-state serum tixagevimab and cilgavimab trough concentrations after 6-month repeat EVUSHELD dosing are in the range of the observed mean Day 150 and mean Day 210 concentration in serum (Table 4) following a single EVUSHELD dose.

Specific Populations

The PK profile of tixagevimab and cilgavimab were not affected by sex, age, race or ethnicity. Body weight had no clinically relevant effect on the PK of tixagevimab and cilgavimab in adults over the range of 36 kg to 177 kg.

Pediatric Population

The PK of tixagevimab and cilgavimab in pediatric individuals have not been evaluated.

The dosing regimen is expected to result in comparable plasma exposures of tixagevimab and cilgavimab in pediatric individuals ages 12 years of age or older who weigh at least 40 kg as observed in adult individuals *[see Use in Specific Populations (8.4)]*.

Renal impairment
Tixagevimab and cilgavimab are not eliminated intact in the urine.

Renal impairment is not expected to impact the PK of tixagevimab and cilgavimab, since monoclonal antibodies with molecular weight >69 kDa are known not to undergo renal elimination. Similarly, dialysis is not expected to impact the PK of tixagevimab and cilgavimab.

There is no difference in the clearance of tixagevimab and cilgavimab in individuals with mild or moderate renal impairment compared to individuals with normal renal function. There were insufficient subjects with severe renal impairment to draw conclusions *[see Use in Specific Populations (8.6)]*.

Hepatic impairment
No specific studies have been conducted to examine the effects of hepatic impairment on the PK of tixagevimab and cilgavimab. The impact of hepatic impairment on the PK of tixagevimab and cilgavimab is unknown *[see Use in Specific Populations (8.7)]*.

Drug Interaction Studies
Drug-drug interaction studies have not been performed. Based on key elimination pathways, tixagevimab and cilgavimab interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely *[see Drug Interactions (7)]*.

12.4 Microbiology

Antiviral Activity
In a neutralization assay on Vero E6 cells, tixagevimab, cilgavimab, and their combination neutralized SARS-CoV-2 (USA-WA1/2020 isolate) with EC_{50} values of 60.7 pM (9 ng/mL), 211.5 pM (32 ng/mL), and 65.9 pM (10 ng/mL), respectively.

Tixagevimab, cilgavimab, and their combination showed reduced or no antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), or antibody-dependent natural killer cell activation (ADNKA) in cell culture studies. Tixagevimab, cilgavimab, and their combination did not mediate antibody-dependent complement deposition (ADCD) activity with guinea pig complement proteins.

Antibody Dependent Enhancement (ADE) of Infection
The potential of tixagevimab and cilgavimab to mediate antibody-dependent viral entry was assessed in FcγRII-expressing Raji cells co-incubated with recombinant virus-like particles (VLPs) pseudotyped with SARS-CoV-2 spike protein, with antibody concentrations at a range of 6.6 nM (1 µg/mL) to 824 pM (125 ng/mL). Tixagevimab, cilgavimab, and their combination did not mediate entry of VLPs into these cells under the tested conditions.

The potential for ADE was also evaluated in a non-human primate model of SARS-CoV-2 using EVUSHELD. Intravascular administration prior to virus inoculation resulted in a dose-dependent improvement in all measured outcomes (total viral RNA in the lungs or nasal mucosae, infectious virus levels in the lungs based on $TCID_{50}$ measurements, or lung injury and pathology based on histology measurements). No evidence of enhancement of viral replication or disease was observed at any dose evaluated, including sub-neutralizing doses down to 0.04 mg/kg.

Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to tixagevimab and cilgavimab. Prescribing healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area, where data are available, when considering prophylactic treatment options.

Escape variants were identified following serial passage in cell culture of SARS-CoV-2 or replication competent recombinant vesicular stomatitis virus (VSV) expressing SARS-CoV-2 spike protein in the presence of tixagevimab or cilgavimab individually or in combination. Variants which showed reduced susceptibility to cilgavimab expressed spike protein amino acid substitutions R346I (>200-fold), K444E (>200-fold), and K444R (>200-fold). No escape variants to tixagevimab, or the tixagevimab and cilgavimab combination were selected.

In neutralization assays using recombinant VLPs pseudotyped with SARS-CoV-2 spike and harboring individual spike amino acid substitutions identified in circulating SARS-CoV-2, variants with reduced susceptibility to cilgavimab alone included those with R346I (>200-fold), K444E (>200-fold), K444Q (>200-fold), K444R (>200-fold), V445A (21- to 51-fold), G446V (4.2-fold), N450K (9.1-fold), or L452R (5.8-fold) substitutions. Variants with reduced susceptibility to tixagevimab alone included those with Q414R (4.6-fold), L455F (2.5- to 4.7-fold), G476S (3.3-fold), E484D (7.1-fold), E484K (6.2- to 12-fold), E484Q (3.0-fold), F486S (>600-fold), F486V (121- to 149-fold), Q493K (2.4- to 3.2-fold), Q493R (7.9-fold), E990A (6.1-fold), or T1009I (8.2-fold) substitutions. Variants harboring an E484K (2.4- to 5.4-fold), Q493R (3.4-fold), E990A (5.7-fold), or T1009I (4.5-fold) substitution exhibited low level reduced susceptibility to tixagevimab and cilgavimab in combination.

VLPs pseudotyped with the SARS-CoV-2 spike of variant strains with reduced susceptibility to cilgavimab included those with R346K:E484K:N501Y (Mu, 21-fold), and those with reduced susceptibility to tixagevimab included those harboring E484K (Alpha, 18.5-fold; Beta, 3.5- to 15-fold). Similar results were observed, where data was available, in neutralization assays using authentic SARS-CoV-2 variant strains.

Tixagevimab and cilgavimab in combination retained neutralization activity against pseudotyped VLPs and/or authentic SARS-CoV-2 variant strains harboring all spike substitutions identified in Alpha (B.1.1.7, 0.5- to 5.2-fold), Beta (B.1.351, 1.0- to 3.8-fold), Gamma (P.1, 0.4- to 2.0-fold) and Delta (B.1.617.2, 0.6- to 1.2-fold) variants of concern, and Eta (B.1.525, 3.1-fold), Iota (B.1.526, 0.3- to 3.4-fold), Kappa (B.1.617.1, 0.5- to 3.4-fold) Lambda (C.37, 0.7-fold), and Mu (B.1.621, 7.5-fold) variants of interest. Tixagevimab and cilgavimab in combination also retained neutralization activity against Epsilon (B.1.427 / B.1.429, 0.8- to 3.5-fold), R.1 (3.5-fold), B.1.1.519 (1.4-fold), C.36.3 (2.3-fold), B.1.214.2 (0.8-fold), and B.1.619.1 (3.3-fold) variant alerts for further monitoring and B.1.616 (0.5-fold), A.23.1 (0.4-fold), A.27 (0.8-fold), and AV.1 (5.9-fold) variants de-escalated from further monitoring (Table 5).

Table 5 Pseudotyped Virus-Like Particles and Authentic SARS-CoV-2 Neutralization Data for SARS-CoV-2 Variant Substitutions with EVUSHELD

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested	Fold Reduction in Susceptibility* (Pseudotyped VLPs†)	Fold Reduction in Susceptibility* (Authentic virus‡)
B.1.1.7	UK	Alpha	N501Y	0.5- to 5.2-fold	No Change§
B.1.351	South Africa	Beta	K417N+E484K +N501Y	No Change§	No Change§
P.1	Brazil	Gamma	K417T+E484K +N501Y	No Change§	No Change§
B.1.617.2	India	Delta	L452R+T478K	No Change§	No Change§
AY.1/ AY.2	India	Delta [+K417N]	K417N+L452R +T478K	No Change§	No Change§
B.1.525	Multiple country origin	Eta	E484K	No Change§	ND
B.1.526	United States	Iota	E484K	No Change§	No Change§
B.1.617.1	India	Kappa	L452R+E484Q	No Change§	No Change§
C.37	Peru	Lambda	L452Q+F490S	No Change§	ND
B.1.621	Columbia	Mu	R346K+E484K +N501Y	7.5-fold	ND
B.1.427 / B.1.429	United States	Epsilon	L452R	No Change§	No Change§
R.1	Multiple country origin	-	E484K	No Change§	ND
B.1.1.519	Multiple country origin	-	T478K	No Change§	ND
B.1.616	France	-	V483A	No Change§	ND
A.23.1	UK	-	V367F	No Change§	ND
A.27	Multiple country origin	-	L452R+N501Y	No Change§	ND
AV.1	Multiple country origin	-	N439K+E484K	5.9-fold	ND

* Range of reduced potency across multiple variants of each lineage using research-grade pseudotyped VLP neutralization assays; mean fold change in half maximal inhibitory concentration (EC_{50}) of mAb required for a 50% reduction in infection compared to wild type reference strain

† Pseudotyped virus-like particles expressing the entire SARS-CoV-2 spike variant protein and individual characteristic spike substitutions except L452Q were tested including Alpha (+L455F, E484K, F490S, Q493R, and/or S494P), and Delta (+K417N) harboring additional indicated RBD substitutions that are no longer detected or detected at extremely low levels within these lineages

‡ Authentic SARS-CoV-2 expressing the entire variant spike protein were tested including Alpha (+E484K or S494P) harboring additional indicated RBD substitutions that are no longer detected or detected at extremely low levels within these lineages

§ No change: <5-fold reduction in susceptibility

ND, not determined; RBD, receptor binding domain

It is not known how pseudotyped VLPs or authentic SARS-CoV-2 neutralization susceptibility data correlate with clinical outcome.

In PROVENT, illness visit sequencing data were available for 21 of 33 subjects with SARS-CoV-2 infection (6 of 13 who received tixagevimab and cilgavimab and 15 of 20 placebo). At an allele

fraction ≥25%, 14 of 21 subjects were infected with variants of concern or variants of interest, including 8 subjects with Alpha (B.1.1.7) (8 who received placebo), 1 subject with Beta (B.1.351) (1 who received tixagevimab and cilgavimab), 3 subjects with Delta (B.1.617.2) (3 who received placebo), and 2 subjects with Epsilon (B.1.429) (2 who received tixagevimab and cilgavimab). Seven additional subjects were infected with B.1.375 (1 who received tixagevimab and cilgavimab) or the A_1 set of lineages containing a constellation of spike protein substitutions including D614G and P681H or Q677P (3 who received tixagevimab and cilgavimab and 3 placebo). Additional spike protein RBD substitutions detected at an allele fraction ≥3% included V503F in the tixagevimab and cilgavimab group.

In STORM CHASER, illness visit sequencing data was available for 19 subjects with SARS-CoV-2 infections (12 of 12 who received tixagevimab and cilgavimab and 7 of 7 placebo). At an allele fraction ≥25%, 12 of 19 subjects were infected with variants of concern or variants of interest, including 9 subjects with Alpha (B.1.1.7) (5 who received tixagevimab and cilgavimab and 4 placebo) and 3 subjects with Epsilon (B.1.427 / B.1.429) (2 who received tixagevimab and cilgavimab and 1 placebo). Seven additional subjects were infected with B.1.1.519 (1 who received tixagevimab and cilgavimab) or the A_1 set of lineages containing a constellation of spike protein substitutions including D614G and D138H, Q675H, Q677H, or V1176F (4 who received tixagevimab and cilgavimab and 2 placebo). Additional spike protein RBD substitutions detected at an allele fraction ≥3% included S325P, Del342, C361W, Del428, F429V, and F515C in the tixagevimab and cilgavimab group.

Evaluation of neutralization susceptibility of variants identified through global surveillance and in subjects who received tixagevimab and cilgavimab is ongoing.

It is possible that variants resistant to tixagevimab and cilgavimab could have cross-resistance to other monoclonal antibodies targeting the RBD of SARS-CoV-2. The combination of tixagevimab and cilgavimab retained activity against pseudotyped VLPs harboring individual SARS-CoV-2 spike substitutions (K417E/N, D420N, K444Q, V445A, Y453F, L455F, N460K/S/T, E484D/K/Q, F486V, F490S, Q493K/R, and S494P) identified in neutralization escape variants of other monoclonal antibodies targeting the RBD of SARS-CoV-2 spike protein.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, genotoxicity, and reproductive toxicology studies have not been conducted with tixagevimab and cilgavimab.

13.2 Animal Toxicology and Pharmacology

In a toxicology study in cynomolgus monkeys, tixagevimab and cilgavimab had no adverse effects when administered via IM injection.

In tissue cross-reactivity studies with tixagevimab and cilgavimab using human adult and fetal tissues no binding of clinical concern was detected.

Tixagevimab and cilgavimab have been assessed in rhesus macaque and cynomolgus macaque models of SARS-CoV-2 infection. Prophylactic administration of tixagevimab and cilgavimab (N= 4

rhesus macaque; N= 3 cynomolgus macaque) three days prior to infection prevented SARS-CoV-2 infection of the upper and lower respiratory tracts in dose-dependent manner. Prophylactic administration of 4 mg/kg tixagevimab and cilgavimab resulted in a 7-$\log_{10}$ reduction in viral sub-genomic messenger RNA (sgmRNA) in nasopharyngeal swabs and 5 to 6-$\log_{10}$ reduction in sgmRNA or infectious virus titer in bronchoalveolar lavage samples at Day 2 post-challenge in all animals relative to placebo-treated animals.

Compared to placebo, prophylactic administration of tixagevimab and cilgavimab (N= 3 cynomolgus macaque) reduced lung injury associated with SARS-CoV-2 infection.

The applicability of these findings to a clinical setting is not known.

14 CLINICAL STUDIES

The data supporting this EUA are based on analyses from the Phase III trials PROVENT (NCT04625725) and STORM CHASER (NCT04625972). Both trials are evaluating the safety and efficacy of EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) for the prophylaxis SARS-CoV-2 symptomatic illness (COVID-19).

Efficacy Data from PROVENT

PROVENT is an ongoing Phase III, randomized (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 subjects were either ≥60 years of age, had a pre-specified co-morbidity (obesity, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, immunocompromised state, or previous history of severe or serious adverse event after receiving any approved vaccine), or were at increased risk of SARS-CoV-2 infection due to their living situation or occupation. Subjects could not have previously received a COVID-19 vaccine. Subjects received a single dose (administered as two IM injections) of EVUSHELD or placebo. The study excluded subjects with a history of laboratory-confirmed SARS-CoV-2 infection or SARS-CoV-2 antibody positivity at screening. Once COVID-19 vaccines were locally available, subjects were permitted on request to unblind to make an informed decision on vaccine timing and to receive COVID-19 vaccination.

The baseline demographics were balanced across the EVUSHELD and placebo arms. The median age was 57 years (with 43% of subjects aged 60 years or older), 46% of subjects were female, 73% were White, 3% were Asian 17% were Black/African American, and 15% were Hispanic/Latino. Of the 5,197 subjects, 78% had baseline co-morbidities or characteristics associated with an increased risk for severe COVID-19, including obesity (42%), diabetes (14%), cardiovascular disease (8%), cancer, including a history of cancer (7%), chronic obstructive pulmonary disease (5%), chronic kidney disease (5%), chronic liver disease (5%), immunosuppressive medications (3%) and immunosuppressive disease (<1%).

For the primary endpoint, a subject was defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurred after administration and prior to Day 183. The primary analysis included 5,172 subjects who were SARS-CoV-2 RT-PCR-negative at baseline, of which 3,441 received EVUSHELD and 1,731 received placebo. Only events that occurred prior to unblinding or vaccine receipt were included. EVUSHELD receipt resulted in a statistically significant (p-value <0.001) 77% reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness

(COVID-19) when compared to placebo (Table 6). At the time of analysis the median follow-up time post-administration was 83 days (range 3 to 166 days).

Similar results were observed for EVUSHELD recipients compared to placebo recipients in the reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness or death from any cause (12/3,441 versus 19/1,731, respectively) with relative risk reduction of 69% (95% CI: 36, 85; p-value= 0.002), and in the reduction in incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness regardless of unblinding or vaccine receipt (10/3,441 versus 22/1,731, respectively) with relative risk reduction of 77% (95% CI: 52, 89 ; p-value <0.001).

Table 6 Incidence of Symptomatic COVID-19 in Adults (PROVENT)

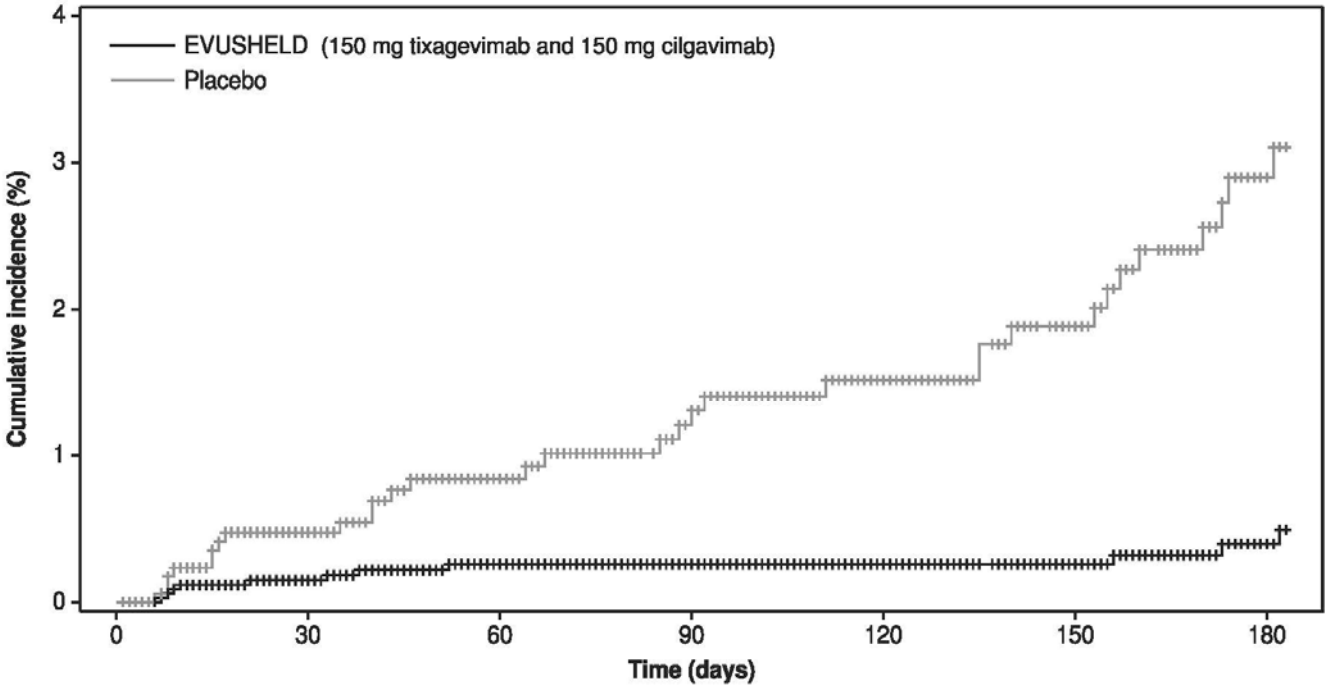
	N*	Number of events, n (%)	Relative Risk Reduction, % (95% CI)
EVUSHELD†	3,441	8 (0.2%)	77% (46, 90)
Placebo	1,731	17 (1.0%)	

N = number of subjects in analysis; CI = Confidence Interval
* subjects were censored after receiving the vaccine or being unblinded to consider the vaccine, whichever occurred earlier
† EVUSHELD dose (150 mg tixagevimab and 150 mg cilgavimab)

Among subjects who received EVUSHELD, there were no severe/critical COVID-19 events (defined as SARS-CoV-2 RT-PCR-positive symptomatic illness characterized by a minimum of either pneumonia [fever, cough, tachypnoea or dyspnea, and lung infiltrates] or hypoxemia [SpO_2 <90% in room air and/or severe respiratory distress] and a WHO Clinical Progression Scale score of 5 or higher) compared to one event (0.1%) among subjects who received placebo.

An additional data cut was conducted to provide post-hoc updated efficacy and safety analysis, the median follow-up was 6.5 months for subjects in both EVUSHELD and placebo arms. The relative risk reduction of SARS-CoV-2 RT-PCR-positive symptomatic illness was 83% (95% CI: 66, 91) with 11/3,441 (0.3%) events in the EVUSHELD arm and 31/1,731 (1.8%) events in the placebo arm, see Figure 1. These results are consistent with the duration of protection predicted by population PK modelling *[see Clinical Pharmacology (12.3)]*. Among subjects who received EVUSHELD there were no severe/critical COVID-19 events compared to five events among subjects who received placebo.

Figure 1 Kaplan Meier: Cumulative Incidence of Symptomatic COVID-19* (PROVENT)



Number of participants at risk							
EVUSHELD	3441	2957	2393	2054	1815	1667	1044
Placebo	1731	1483	1177	991	856	774	472

* Subjects who do not experience a primary endpoint event (and had not discontinued) are censored at Day 183. Subjects who were unblinded/vaccinated prior to an event are also censored at the earlier time of unblinding/vaccination.

Efficacy Data from STORM CHASER

STORM CHASER is an ongoing Phase III randomized (2:1), double-blind, placebo-controlled clinical trial of EVUSHELD for the post-exposure prophylaxis of COVID-19 in adults ≥18 years of age. Subjects who had not previously received a COVID-19 vaccine were enrolled following potential exposure (within 8 days) to an identified individual with a laboratory-confirmed SARS-CoV-2 infection (symptomatic or asymptomatic). Subjects received a single dose (administered as two IM injections) of EVUSHELD or placebo. The study excluded subjects with a history of laboratory-confirmed SARS-CoV-2 infection or SARS-CoV-2 antibody positivity at screening. Once COVID-19 vaccines were locally available, subjects were permitted on request to unblind to make an informed decision on vaccine timing and to receive COVID-19 vaccination.

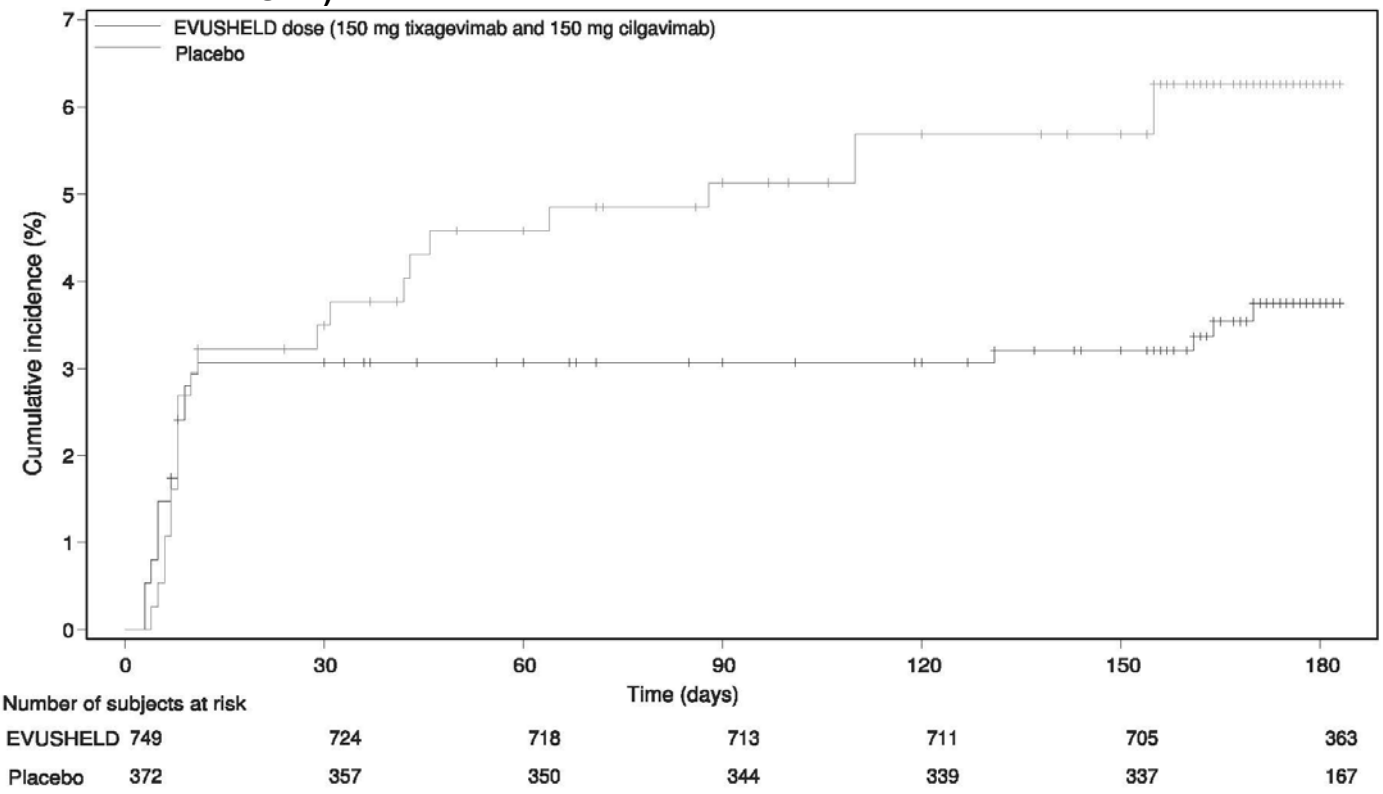
Of the 1,121 subjects who were randomized and received EVUSHELD (N= 749) or placebo (N= 372), 48 subjects were positive for SARS-CoV-2 (RT-PCR analysis of nasopharyngeal swabs) at baseline.

The primary efficacy analysis, comparison of the incidence of a subject's first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurring post-dose and before Day 183, did not demonstrate a statistically significant effect for EVUSHELD versus placebo with 23 cases of symptomatic COVID-19 in the EVUSHELD arm (3.1%) and 17 cases in the placebo arm (4.6%) (relative risk reduction of 33%, 95% CI: -26, 65). At the time of analysis the median follow-up time post-administration was 49 days (range 5 to 115 days).

The study did not demonstrate benefit for EVUSHELD in preventing symptomatic COVID-19 in the first 30 days after randomization, leading to the limitation of use for post-exposure prophylaxis *[see Emergency Use Authorization (1)]*. However, there was a higher proportion of symptomatic COVID-19

cases among placebo recipients after Day 29 (see Figure 2 below, data from the post-hoc updated efficacy analysis with a median follow-up time of 6.5 months). EVUSHELD is not authorized for post-exposure prophylaxis of COVID-19 in individuals who have been exposed to someone infected with SARS-CoV-2.

Figure 2 Kaplan Meier: Cumulative Incidence of Symptomatic COVID-19* (STORM CHASER)



* Subjects who do not experience a primary endpoint event (and had not discontinued) are censored at Day 183.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Each EVUSHELD co-packaged carton contains two vials (Table 7):

- 1 single-dose vial of tixagevimab injection as a sterile, preservative-free, clear to opalescent and colorless to slightly yellow solution.
- 1 single-dose vial of cilgavimab injection as a sterile, preservative-free, clear to opalescent and colorless to slightly yellow solution.

Table 7 EVUSHELD co-packaged carton contents

Carton (2 vials per pack)	Components	
	1 vial of Tixagevimab 150 mg/1.5 mL (100 mg/mL) **(dark grey cap)**	**1 vial of Cilgavimab** 150 mg/1.5 mL (100 mg/mL) **(white cap)**
NDC 0310-7442-02	NDC 0310-8895-01	NDC 0310-1061-01

Storage and Handling

Store unopened vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Discard any unused portion.

DO NOT FREEZE. DO NOT SHAKE.

17 PATIENT COUNSELING INFORMATION

As a prescribing healthcare practitioner, you must communicate to the patient, parent and caregiver information consistent with the "FACT SHEET FOR PATIENTS, PARENTS OR CAREGIVERS" and provide them with a copy of this Fact Sheet prior to administration of EVUSHELD.

Cardiovascular Events
Inform individuals that a higher proportion of subjects who received EVUSHELD versus placebo reported cardiovascular serious adverse events (myocardial infarctions and heart failure). Advise individuals to seek immediate medical attention if they experience any signs or symptoms suggestive of a cardiovascular event *[see Warnings and Precautions (5.3)]*.

For additional information, please visit the website or call the telephone number provided below.

To access the most recent EVUSHELD Fact Sheets, please scan the QR code provided below.

Website	Telephone number
http://www.evusheld.com	1-800-236-9933

18 MANUFACTURER INFORMATION

Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

Manufactured by: Samsung Biologics, 300 Songdo bio-daero, Yeonsu-gu, Incheon 21987, Republic of Korea

Fact Sheet for Patients, Parents And Caregivers Emergency Use Authorization (EUA) of EVUSHELD™ (tixagevimab co-packaged with cilgavimab) for Coronavirus Disease 2019 (COVID-19)

You are being given this Fact Sheet because your healthcare provider believes it is necessary to provide you with EVUSHELD (tixagevimab co-packaged with cilgavimab) for pre-exposure prophylaxis for prevention of coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus.

This Fact Sheet contains information to help you understand the potential risks and potential benefits of taking EVUSHELD, which you have received or may receive.

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to make EVUSHELD available during the COVID-19 pandemic (for more details about an EUA please see "**What is an Emergency Use Authorization?**" at the end of this document). EVUSHELD is not an FDA-approved medicine in the United States.

Read this Fact Sheet for information about EVUSHELD. Talk to your healthcare provider if you have any questions. It is your choice to receive or not receive EVUSHELD.

What is COVID-19?
COVID-19 is caused by a virus called a coronavirus. You can get COVID-19 through close contact with another person who has the virus.

COVID-19 illnesses have ranged from very mild (including some with no reported symptoms) to severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, serious illness can happen and may cause some of your other medical conditions to become worse. Older people and people of all ages with severe, long-lasting (chronic) medical conditions like heart disease, lung disease, and diabetes, for example, seem to be at higher risk of being hospitalized for COVID-19.

What is EVUSHELD (tixagevimab co-packaged with cilgavimab)?
EVUSHELD is an investigational medicine used in adults and adolescents (12 years of age and older who weigh at least 88 pounds [40 kg]) for pre-exposure prophylaxis for prevention of COVID-19 in persons who are:

- not currently infected with SARS-CoV-2 and who have not had recent known close contact with someone who is infected with SARS-CoV-2 **and**
    - Who have moderate to severe immune compromise due to a medical condition or have received immunosuppressive medicines or treatments **and** may not mount an adequate immune response to COVID-19 vaccination **or**

- For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction (such as severe allergic reaction) to a COVID-19 vaccine(s) or COVID-19 vaccine ingredient(s).

EVUSHELD is investigational because it is still being studied. There is limited information known about the safety and effectiveness of using EVUSHELD for pre-exposure prophylaxis for prevention of COVID-19. EVUSHELD is not authorized for post-exposure prophylaxis for prevention of COVID-19.

The FDA has authorized the emergency use of EVUSHELD for pre-exposure prophylaxis for prevention of COVID-19 under an Emergency Use Authorization (EUA).

What should I tell my healthcare provider before I receive EVUSHELD?
Tell your healthcare provider if you:

- Have any allergies
- Have low numbers of blood platelets (which help blood clotting), a bleeding disorder, or are taking anticoagulants (to prevent blood clots)
- Have had a heart attack or stroke, have other heart problems, or are at high-risk of cardiac (heart) events
- Are pregnant or plan to become pregnant
- Are breastfeeding a child
- Have any serious illness
- Are taking any medications (prescription, over-the-counter, vitamins, or herbal products)

How will I receive EVUSHELD?

- EVUSHELD consists of two investigational medicines, tixagevimab and cilgavimab.
- You will receive 1 dose of EVUSHELD, consisting of 2 separate injections (tixagevimab and cilgavimab).
- EVUSHELD will be given to you by your healthcare provider as 2 intramuscular injections. They are usually, given one after the other, 1 into each of your buttocks.

After the initial dose, if your healthcare provider determines that you need to receive additional doses of EVUSHELD for ongoing protection, the additional doses would be administered once every 6 months.

Who should generally not take EVUSHELD?
Do not take EVUSHELD if you have had a severe allergic reaction to EVUSHELD or any ingredient in EVUSHELD.

What are the important possible side effects of EVUSHELD?
Possible side effects of EVUSHELD are:

- **Allergic reactions**. Allergic reactions can happen during and after injection of EVUSHELD. Tell your healthcare provider right away if you get any of the following signs and symptoms of allergic reactions: fever, chills, nausea, headache, shortness of breath, low or high blood pressure, rapid or slow heart rate, chest discomfort or pain, weakness, confusion, feeling tired, wheezing, swelling of your lips, face, or throat, rash including hives, itching, muscle aches, dizziness and sweating. These reactions may be severe or life threatening.
- **Cardiac (heart) events**: Serious cardiac adverse events have happened, but were not common, in people who received EVUSHELD and also in people who did not receive EVUSHELD in the clinical trial studying pre-exposure prophylaxis for prevention of COVID-19. In people with risk factors for cardiac events (including a history of heart attack), more people who received EVUSHELD experienced serious cardiac events than people who did not receive EVUSHELD. It is not known if these events are related to EVUSHELD or underlying medical conditions. Contact your healthcare provider or get medical help right away if you get any symptoms of cardiac events, including pain, pressure, or discomfort in the chest, arms, neck, back, stomach or jaw, as well as shortness of breath, feeling tired or weak (fatigue), feeling sick (nausea), or swelling in your ankles or lower legs.

The side effects of getting any medicine by intramuscular injection may include pain, bruising of the skin, soreness, swelling, and possible bleeding or infection at the injection site.

These are not all the possible side effects of EVUSHELD. Not a lot of people have been given EVUSHELD. Serious and unexpected side effects may happen. EVUSHELD is still being studied so it is possible that all of the risks are not known at this time.

It is possible that EVUSHELD may reduce your body's immune response to a COVID-19 vaccine. If you have received a COVID-19 vaccine, you should wait to receive EVUSHELD until at least 2 weeks after COVID-19 vaccination.

What other prevention choices are there?
Vaccines to prevent COVID-19 are approved or available under Emergency Use Authorization. Use of EVUSHELD does not replace vaccination against COVID-19. For more information about other medicines authorized for treatment or prevention of COVID-19 go to https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization for more information.

It is your choice to receive or not receive EVUSHELD. Should you decide not to receive EVUSHELD, it will not change your standard medical care.

EVUSHELD is not authorized for post-exposure prophylaxis of COVID-19.

What if I am pregnant or breastfeeding?
If you are pregnant or breastfeeding, discuss your options and specific situation with your healthcare provider.

How do I report side effects with EVUSHELD?
Contact your healthcare provider if you have any side effects that bother you or do not go away. Report side effects to FDA MedWatch at www.fda.gov/medwatch or call 1-800-FDA-1088 or call AstraZeneca at 1-800-236-9933.

Additional Information
If you have questions, visit the website or call the telephone number provided below.

To access the most recent EVUSHELD Fact Sheets, please scan the QR code provided below.

Website	Telephone number
http://www.evusheld.com 	1-800-236-9933

How can I learn more about COVID-19?
- Ask your healthcare provider.
- Visit https://www.cdc.gov/COVID19
- Contact your local or state public health department.

What is an Emergency Use Authorization?
The United States FDA has made EVUSHELD (tixagevimab co-packaged with cilgavimab) available under an emergency access mechanism called an Emergency Use Authorization EUA. The EUA is supported by a Secretary of Health and Human Service (HHS) declaration that circumstances exist to justify the emergency use of drugs and biological products during the COVID-19 pandemic.

EVUSHELD for pre-exposure prophylaxis for prevention of coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus has not undergone the same type of review as an FDA-approved product. In issuing an EUA under the COVID-19 public health emergency, the FDA has determined, among other things, that based on the total amount of scientific evidence available including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective for diagnosing, treating, or preventing COVID-19, or a serious or life-threatening disease or condition caused by COVID-19; that the known and potential benefits of the product, when used to diagnose, treat, or prevent such disease or condition, outweigh the known and potential risks of such product; and that there are no adequate, approved and available alternatives.

All of these criteria must be met to allow for the product to be used in the treatment of patients during the COVID-19 pandemic. The EUA for EVUSHELD is in effect for the duration of the COVID-19 declaration justifying emergency use of EVUSHELD,

unless terminated or revoked (after which EVUSHELD may no longer be used under the EUA).

Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

Manufactured by: Samsung Biologics, 300 Songdo bio-daero, Yeonsu-gu, Incheon 21987, Republic of Korea

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/s/

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