2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Emergency Use of EVUSHELD

Initial Dosing
The initial dosage of EVUSHELD in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) is **300 mg of tixagevimab and 300 mg of cilgavimab** administered as two separate consecutive intramuscular (IM) injections *[see Clinical Pharmacology (12.3)]*. Refer to Table 1 below.

Dosing for Individuals Who Initially Received 150 mg of Tixagevimab and 150 mg of Cilgavimab
Individuals who have already received the previously authorized initial dose (150 mg of tixagevimab and 150 mg of cilgavimab) **should receive an additional EVUSHELD dose as soon as possible, with the dose based on the following criteria:**

- If the patient received their initial dose ≤ 3 months ago, the patient should receive a dose of 150 mg of tixagevimab and 150 mg of cilgavimab, refer to Table 2 below.
- If the patient received their initial dose > 3 months ago, the patient should receive a dose of 300 mg of tixagevimab and 300 mg of cilgavimab, refer to Table 1 below.

Repeat Dosing
The repeat dosage of EVUSHELD in adults and pediatric individuals (12 years of age and older weighing at least 40 kg) is **300 mg of tixagevimab and 300 mg of cilgavimab** administered every 6 months, refer to Table 1 below. Repeat dosing should be timed from the date of the most recent EVUSHELD dose.

The recommendations for dosing are based on the totality of the scientific evidence including clinical pharmacology data, antiviral activity data, and clinical trial data *[see Clinical Pharmacology (12.3), Microbiology (12.4), and Clinical Studies (14)]*. EVUSHELD has only been studied for the prophylaxis of COVID-19 at the EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) dose. There are no data available in a prophylaxis setting for the EVUSHELD (300 mg of tixagevimab and 300 mg of cilgavimab) dose. The clinical safety of the EVUSHELD (300 mg of tixagevimab and 300 mg of cilgavimab) dose is supported by safety data from a treatment study in subjects with mild to moderate COVID-19 *[see Adverse Reactions (6.1)]*. There are limited safety and no efficacy data available with repeat dosing.

To access the most recent EVUSHELD Fact Sheets, please visit http://www.evusheld.com or scan the QR code:

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)]*.

Administration of EVUSHELD should be done under the supervision of a healthcare provider with appropriate medical support to manage severe hypersensitivity reactions. 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.

5.3 Risk for COVID-19 Due to SARS-CoV-2 Viral Variants Not Neutralized by EVUSHELD

Certain SARS-CoV-2 viral variants may not be neutralized by monoclonal antibodies such as tixagevimab and cilgavimab, the components of EVUSHELD. EVUSHELD may not be effective at preventing COVID-19 caused by these SARS-CoV-2 viral variants. The *in-vitro* neutralization activity of EVUSHELD against SARS-CoV-2 viral variants is shown in Table 6 *[see Microbiology (12.4)]*.

Inform individuals of the increased risk, compared to other variants, for COVID-19 due to SARS-CoV-2 viral variants not neutralized by EVUSHELD. If signs or symptoms of COVID-19 occur, advise individuals to test for COVID-19 and seek medical attention, including starting treatment for COVID-19 as appropriate. Symptoms of COVID-19 may include: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, or diarrhea[1].

5.4 Clinically Significant Bleeding Disorders

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

5.5 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

[1] For additional information on the symptoms of COVID-19, please see https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.

- 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 responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of EVUSHELD.

*Serious adverse events are defined as:

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

6.5 Other Reporting Requirements

Healthcare facilities and providers will report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

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, STORM CHASER and TACKLE *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

8.5 Geriatric Use

Of the 2,555 subjects in the pooled pharmacokinetics (PK) analysis (Phase I and Phase III studies), 21% (N= 533) were 65 years of age or older and 3% (N= 81) 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 (300 mg of tixagevimab and 300 mg of cilgavimab) intramuscular dose is provided in Table 5.

Table 5 Summary of PK Parameters and Properties of Tixagevimab and Cilgavimab Following a Single EVUSHELD (300 mg Tixagevimab and 300 mg Cilgavimab) Intramuscular Dose

PK Parameters	Tixagevimab	Cilgavimab
C_{max} (µg/mL)*	21.9 (61.7)	20.3 (63.6)
T_{max} (day)†	14.9 (1.1 – 86)	15.0 (1.1 – 85)
C_2 (µg/mL)‡	9.5 (77)	9.1 (80)
C_{84} (µg/mL)§	15 (48)	14 (51)
$AUC_{0\text{-}84}$ (day•µg/mL)*	1408 (54)	1307 (58)
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 2 day after dosing
§ Observed geomean (geometric %CV) concentration 84 days after dosing
# Arithmetic mean (SD)
¶ Based on a single EVUSHELD (150 mg tixagevimab and 150 mg cilgavimab)

In the PROVENT repeat dose sub-study, following a second IM dose of EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) administered 10 to 14 months after the initial IM dose of EVUSHELD (150 mg of tixagevimab and 150 mg of cilgavimab) (N= 53), the geometric mean serum concentration was 26.4 µg/mL on post-administration Day 29. This serum concentration was similar

to the geometric mean drug concentration on post-administration Day 29 (23.3 µg/mL) following the initial IM EVUSHELD dose (150 mg of tixagevimab and 150 mg of cilgavimab) in the PROVENT parent study.

The primary analysis in the clinical efficacy study PROVENT was conducted prior to the emergence of the Omicron variant; the dominant variants in circulation at that time were Alpha, Beta, Gamma, and Delta. Pharmacokinetic and pharmacodynamic modeling using cell-based EC_{50} values of EVUSHELD against the currently circulating variants in the U.S. suggest in vivo activity against these variants may be retained at drug concentrations achieved following a single EVUSHELD initial dose of 300 mg tixagevimab and 300 mg cilgavimab for 6 months *[see Dosage and Administration (2.1)]*.

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. Tixagevimab selected a variant expressing F486S in the spike protein with a >800-fold reduction in susceptibility to tixagevimab. Cilgavimab selected variants that expressed spike protein amino acid substitutions R346G, R346I, K444E, K444N, K444Q, K444R, K444T or N450D were each associated with a >200-fold reduction in susceptibility to cilgavimab. No escape variants to 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; Zeta, 7.3-fold). Similar results were observed, where data were available, in neutralization assays using authentic SARS-CoV-2 variant strains.

VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BA.1 or BA.1.1 (BA.1+R346K) showed reduced susceptibility to tixagevimab (>600- to >1,000-fold or 460-fold, respectively) and to cilgavimab (>700- to >1,000-fold or >500-fold, respectively). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BA.2 or BA.2.12.1 showed reduced susceptibility to tixagevimab (>1,000-fold or >500-fold, respectively) but not to cilgavimab (1.9-fold or 2-fold, respectively). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BA.2.75 or BA.2.75.2 showed reduced susceptibility to tixagevimab (7- to 53-fold or >3,333- to >10,000-fold, respectively) and to cilgavimab (6- to 40-fold or >769- to >5,000-fold, respectively). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BA.3 showed reduced susceptibility to tixagevimab (>5,000-fold) but not to cilgavimab (4-fold). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BA.4/BA.5 showed reduced susceptibility to tixagevimab (>10,000-fold) and cilgavimab (7.5- to 9-fold). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BA.4.6 showed reduced susceptibility to tixagevimab (>1,000-fold) and to cilgavimab (>1,000-fold). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BF.7 or BJ.1 showed reduced susceptibility to tixagevimab (>3,333- to >10,000-fold or 85- to 172-fold, respectively) and to cilgavimab (>769- to >5,000-fold or >769- to >5,000-fold, respectively). VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BQ.1 or BQ.1.1 showed reduced susceptibility to tixagevimab (>1,250- to >10,000-fold) and to cilgavimab (>667- to >5,000-fold). The effects of the individual substitutions in Omicron spike glycoproteins on neutralization susceptibility are being investigated.

The neutralizing activity of tixagevimab and cilgavimab in combination was tested 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), Delta (B.1.617.2, 0.6- to 1.2-fold), and Delta [+K417N] (AY.1/ AY.2, 1.0-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 was also tested 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 6).

Preliminary data for the neutralizing activities of tixagevimab and cilgavimab in combination against circulating Omicron subvariants are available. VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BA.1 or BA.1.1 (BA.1+R346K) showed reduced neutralizing activity (132- to 183-fold or 424-fold, respectively), Omicron BA.2 showed no change in neutralizing activity (3.2-fold). VLPs pseudotyped with the spike of Omicron BA.2.12.1, BA.2.75, BA.2.75.2, BA.3, BA.4/BA.5, or BA.4.6 showed 5-fold, 2.4- to 15-fold, >5,000- to >10,000-fold, 16-fold, 33- to 65-fold, or >1,000-fold reductions in neutralizing activity, respectively. VLPs pseudotyped with the spike of Omicron BF.7, BJ.1, BQ.1 or BQ.1.1 showed >5,000- to >10,000-fold, 228- to 424-fold, >2,000- to >10,000-fold or

>2,000- to >10,000-fold reductions in neutralizing activity, respectively. Authentic Omicron BA.1, BA.1.1, BA.2, or BA.5 viruses showed 12- to 30-fold, 176-fold, 5.4-fold, or 2.8- to 16-fold reductions in susceptibility, respectively.

Data collection is ongoing to better understand how the reductions in activity seen in pseudotyped VLP assays or authentic SARS-CoV-2 assays may correlate with clinical outcomes.

Table 6 EVUSHELD Pseudotyped Virus-Like Particles and Authentic SARS-CoV-2 Neutralization Data for SARS-CoV-2 Variants

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§
BA.1	Botswana	Omicron (BA.1)	G339D+S371L+S373P+ S375F+K417N+N440K+ G446S+S477N+T478K+ E484A+Q493R+G496S+ Q489R+N501Y+Y505H	132- to 183-fold#	12- to 30-fold
BA.1.1	Multiple country origin	Omicron (BA.1.1) [+R346K]	BA.1+R346K	424-fold	176-fold
BA.2	Multiple country origin	Omicron (BA.2)	G339D+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ S477N+T478K+E484A+ Q493R+Q498R+N501Y+ Y505H	No Change§	5.4-fold
BA.2.12.1	United States	Omicron (BA.2.12.1)	BA.2+L452Q	5-fold	ND
BA.2.75	India	Omicron (BA.2.75)	G339H+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ G446S+N460K+S477N+ T478K+E484A+Q498R+ N501Y+ Y505H	2.4- to 15-fold	ND
BA.2.75.2	India	Omicron (BA.2.75.2)	BA.2.75+R346T+F486S	>5000-foldÞ	ND
BA.3	Multiple country origin	Omicron (BA.3)	G339D+S371F+S373P+ S375F+D405N+K417N+ N440K+G446S+S477N+ T478K+E484A+Q493R+ Q498R+N501Y+Y505H	16-fold	ND
BA.4	Multiple country origin	Omicron (BA.4)	G339D+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ L452R+S477N+T478K+ E484A+F486V+Q498R+ N501Y+Y505H	33- to 65-fold	ND
BA.4.6	United States	Omicron (BA.4.6)	BA.4+R346T	>1000-foldÞ	ND

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‡)
BA.5	Multiple country origin	Omicron (BA.5)	G339D+S371F+S373P+ S375F+T376A+D405N+ R408S+K417N+N440K+ L452R+S477N+T478K+ E484A+F486V+Q498R+ N501Y+Y505H	33- to 65-fold	2.8- to 16-fold
BF.7	United States/Belgium	Omicron (BF.7)	BA.4+R346T	>5000-fold[Þ]	ND
BJ.1	Multiple country origin	Omicron (BJ.1)	G339H+R346T+L368I+ S371F+S373+S375F+ T376A+D405N+R408S+ K417N+N440K+V445P+ G446S+S477N+T478K+ V483A+E484A+F490V+ Q493R+Q498R+N501Y+ Y505H	228- to 424-fold	ND
BQ.1	Nigeria	Omicron (BQ.1)	BA.5+K444T+N460K	>2000-fold[Þ]	ND
BQ.1.1	Multiple country origin	Omicron (BQ.1.1)	BA.5+R346T+K444T+ N460K	>2000-fold[Þ]	ND
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	Colombia	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
C.36.3	Multiple country origin	-	R346S:L452R	No Change[§]	ND
B.1.214.2	Multiple country origin	-	Q414K:N450K	No Change[§]	ND
B.1.619.1	Multiple country origin	-	N440K:E484K	No Change[§]	ND
P.2	Brazil	Zeta	E484K	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 effective 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
# EC_{50} value = 1.13 – 1.83 nM (171 - 277 ng/mL)
Þ Tixagevimab and cilgavimab together are unlikely to be active against this variant.
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 who received tixagevimab and cilgavimab and 15 placebo). Fourteen 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 low frequency (between 3% and 24%) included V503F in the tixagevimab and cilgavimab group.

In STORM CHASER, illness visit sequencing data was available for 19 of 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.

12.6 Immunogenicity

There are no immunogenicity data available for the currently authorized dosing regimen (EVUSHELD [300 mg of tixagevimab and 300 mg cilgavimab] administered every 6 months).

There was no apparent clinically significant effect of anti-EVUSHELD antibodies (ADA) on the safety or effectiveness of EVUSHELD in PROVENT (EVUSHELD [150 mg of tixagevimab and 150 mg cilgavimab]), but data are limited at this time. There is up to a 26% decrease, on average, in serum concentrations of EVUSHELD over time through 183 days post-administration in subjects with

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 7). 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

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

18 MANUFACTURER INFORMATION

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