PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

EVUSHELD™

tixagevimab and cilgavimab injection

solution, 100 mg/mL (tixagevimab) and 100 mg/mL (cilgavimab), intramuscular use

Anti-SARS-CoV-2 spike protein monoclonal antibodies

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RECENT MAJOR LABEL CHANGES

Not Applicable.

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

EVUSHELD (tixagevimab and cilgavimab) is indicated for the pre-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in adults and adolescents (≥12 years of age weighing at least 40 kg), who have not had a known recent exposure to an individual infected with SARS-CoV-2 and:

- Who are immune compromised and unlikely to mount an adequate immune response to COVID-19 vaccination **or**
- For whom COVID-19 vaccination is not recommended.

Pre-exposure prophylaxis with EVUSHELD is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended.

Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies. Healthcare professionals should routinely review the Antiviral Resistance information in 15 MICROBIOLOGY, in conjunction with literature and local guidelines, for details regarding specific variants and resistance, which may be updated regularly.

1.1 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of EVUSHELD in children <18 years of age has not been established. No data are available. See 4.2 Recommended Dose and Dosage Adjustment. However, the recommended dose (see 4.2 Recommended Dose and Dosage Adjustment) is expected to result in comparable serum exposures of tixagevimab and cilgavimab in adolescents ≥12 years of age and weighing at least 40 kg as observed in adults based on an allometric scaling approach (which accounted for the effect of body weight changes associated with age on clearance and volume of distribution). See 10.2 Pharmacodynamics and 10.3 Pharmacokinetics. Close observation in adolescents is highly recommended.

1.2 Geriatrics

Geriatrics (≥65 years of age): Of the participants in the pooled pharmacokinetic (PK) analysis, 21% (N=534) were ≥65 years of age and 4.2% (N=107) were ≥75 years of age. There is no clinically meaningful difference in the PK of tixagevimab and cilgavimab in geriatric subjects (≥65 years) compared to younger individuals. See 10.2 Pharmacodynamics and 10.3 Pharmacokinetics.

2 CONTRAINDICATIONS

EVUSHELD is contraindicated in individuals who have a history of severe hypersensitivity reactions, including anaphylaxis, to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

The recommended dose is 300 mg of EVUSHELD, administered as two separate 1.5 mL, sequential, injections of:

- 150 mg of tixagevimab
- 150 mg of cilgavimab

Due to decreased *in vitro* neutralization activity of EVUSHELD against the Omicron subvariants BA.1 (12 to 183-fold) and BA.1.1 (176 to 424-fold) compared to the reference strain, it is unknown whether the 300 mg dose is protective against these subvariants clinically. Consideration should be given to increase the dose to 600 mg in regions where BA.1 and BA.1.1 are circulating (see 15 MICROBIOLOGY). For further information regarding the *in vitro* neutralization susceptibility data of EVUSHELD against SARS-CoV-2 variants see 15 MICROBIOLOGY.

EVUSHELD has only been studied in single-dose studies. There are no safety and efficacy data available on repeat dosing.

Pediatrics (<18 years of age): The safety and efficacy of EVUSHELD in children <18 years of age have not been established.

4.4 Administration

For intramuscular injection

Tixagevimab and cilgavimab must be administered by a qualified healthcare provider using aseptic technique.

Visually inspect the vials for particulate matter and discolouration. Both tixagevimab and cilgavimab are clear to opalescent, colourless to slightly yellow solutions. Discard the vials if the solution is cloudy, discoloured or visible particles are observed. Do not shake the vials.

Withdraw the appropriate amount of tixagevimab solution and the appropriate amount of cilgavimab solution into separate syringes. Discard unused portion in vials.

Administer tixagevimab and cilgavimab as separate, sequential intramuscular injections at different injection sites, preferably one in each of the gluteal muscles.

Each carton of EVUSHELD contains two vials:

- tixagevimab solution for injection (dark grey vial cap)
- cilgavimab solution for injection (white vial cap)

Each vial contains an overfill to allow the withdrawal of 150 mg (1.5 mL).

Indication	EVUSHELD dose (tixagevimab and cilgavimab)	Antibody dose	Number of vials needed	Volume to withdraw from vial
Pre-exposure prophylaxis of COVID-19	300 mg (1 carton)	tixagevimab 150 mg	1 vial	1.5 mL
		cilgavimab 150 mg	1 vial	1.5 mL
	600 mg[A] (2 cartons)	tixagevimab 300 mg	2 vials	3.0 mL
		cilgavimab 300 mg	2 vials	3.0 mL

[A] Consideration should be given to increase the dose to 600 mg in regions where Omicron BA.1 and Omicron BA.1.1 subvariants are circulating (see 4.2 Recommended Dose and Dosage Adjustment and 15 MICROBIOLOGY).

The tixagevimab and cilgavimab solutions for injection are 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 should not exceed 4 hours, either:

- in a refrigerator at 2ºC to 8ºC or
- at room temperature up to 25ºC.

Any unused solution should be discarded.

5 OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre.

There is no specific treatment for overdose with EVUSHELD. Treatment of overdose should consist of general supportive measures, including monitoring of vital signs and observation of the clinical status of the patient.

In clinical trials, doses up to 600 mg intramuscular (300 mg each of tixagevimab and cilgavimab) and 3000 mg intravenously (1500 mg each of tixagevimab and cilgavimab) have been administered without dose-limiting toxicity.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Intramuscular use	Solution for injection • 100 mg/mL / 150 mg of tixagevimab • 100 mg/mL / 150 mg of cilgavimab	L-Histidine L-Histidine hydrochloride monohydrate Polysorbate 80 Sucrose Water for injection

Each carton of EVUSHELD contains two vials:

- **Tixagevimab**
  1.5 mL of solution for injection in a clear glass vial closed by chlorobutyl elastomeric stopper sealed with a dark-grey aluminium flip-off top.

- **Cilgavimab**
  1.5 mL of solution for injection in a clear glass vial closed by chlorobutyl elastomeric stopper sealed with a white aluminium flip-off top.

7 WARNINGS AND PRECAUTIONS

Cardiovascular

Cardiac adverse events
In PROVENT, a higher proportion of subjects who received EVUSHELD versus placebo reported serious cardiovascular events (0.7% versus 0.3%) notably myocardial infarction and cardiac failure. A smaller imbalance was observed for serious thromboembolic events (0.5% versus 0.2%). Most subjects 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 or thromboembolic events, and advise individuals to seek immediate medical attention if they experience any signs or symptoms suggestive of a cardiovascular or thromboembolic event.

Hematologic

Clinically significant bleeding disorders
As with any other intramuscular injections, EVUSHELD should be given with caution to patients with thrombocytopenia or any coagulation disorder.

Immune

Hypersensitivity and Anaphylaxis
Serious hypersensitivity reactions, including anaphylaxis, have been observed rarely with other IgG1 monoclonal antibodies. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medicinal products and/or supportive therapy.

Reproductive Health: Female and Male Potential

- **Fertility**
  There are no data on the effects of tixagevimab and cilgavimab on human fertility.

Sensitivity/Resistance
Potential Risk of Prophylaxis Failure due to Antiviral Resistance
Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies such as EVUSHELD. Healthcare professionals should routinely review the Antiviral Resistance information in 15 MICROBIOLOGY, in conjunction with literature and local guidelines, for details regarding specific variants and resistance, which may be updated regularly.

7.1 Special Populations

7.1.1 Pregnant Women

There are insufficient data from the use of tixagevimab and cilgavimab in pregnant women. Non-clinical reproductive toxicity studies have not been performed with tixagevimab and cilgavimab. In a tissue cross reactivity study with tixagevimab and cilgavimab using human fetal tissues, no binding of clinical concern was detected. 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.

EVUSHELD should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

7.1.2 Breast-feeding

There are no data available on whether tixagevimab and cilgavimab are excreted in human milk. Exposure to the breast-fed child cannot be excluded.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for EVUSHELD and any potential adverse effects on the breast-fed child from EVUSHELD or from the underlying maternal condition.

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of EVUSHELD in children <18 years of age has not been established. No data are available. However, the recommended adult dose is expected to result in comparable serum exposures of tixagevimab and cilgavimab in children ≥12 years of age and weighing at least 40 kg. EVUSHELD is not authorized for use in pediatrics under 12 years of age or weighing less than 40 kg. See 10.2 Pharmacodynamics and 10.3 Pharmacokinetics.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): Of the participants in the pooled PK analysis, 21% (N=534) were ≥65 years of age and 4.2% (N=107) were ≥75 years of age. There is no clinically

meaningful difference in the PK of tixagevimab and cilgavimab in geriatric subjects (≥65 years) compared to younger individuals. See 10.2 Pharmacodynamics and 10.3 Pharmacokinetics.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of EVUSHELD 300 mg is based on a total of 4210 adult participants who received 150 mg of tixagevimab and 150 mg of cilgavimab via intramuscular injection, in the Phase III prophylaxis studies PROVENT, D8850C00002 (a double-blind, placebo-controlled clinical trial for the pre-exposure prophylaxis of COVID-19) and STORM CHASER, D8850C00003 (a double-blind, placebo-controlled clinical trial for the post-exposure prophylaxis of COVID-19, an indication for which EVUSHELD is not approved). The median duration for safety follow-up was 137 days for PROVENT and 121 days for STORM CHASER.

The most frequently reported adverse reaction in the pooled analysis of PROVENT and STORM CHASER was injection site reaction (1.3%).

In PROVENT, adverse events were reported in 1417 (41%) subjects receiving EVUSHELD and 698 (40%) receiving placebo. Serious adverse events were reported in 92 (3%) subjects receiving EVUSHELD and 42 (2%) receiving placebo. Of the participants with at least one adverse event, the majority were mild (23%) or moderate (14%) in intensity and balanced between treatment arms.

In STORM CHASER, adverse events were reported in 229 (31%) subjects receiving EVUSHELD and 150 (40%) receiving placebo. Serious Adverse Events (SAEs) were reported in 9 (1%) subjects receiving EVUSHELD and 7 (2%) receiving placebo. Of the participants with at least one adverse event, the majority were mild (EVUSHELD 19% versus placebo 25%) or moderate (EVUSHELD 10% versus placebo 12%) in intensity.

The safety of EVUSHELD 600 mg is based on a total of 452 non-hospitalized adult patients with mild to moderate COVID-19 who received 300 mg of tixagevimab and 300 mg of cilgavimab, via intramuscular injection (within ≤7 days of symptom onset), in the Phase III treatment study, TACKLE (D8851C00001). TACKLE is a Phase III, double-blind, placebo-controlled clinical trial for the treatment of adult patients with mild to moderate COVID-19 (an indication for which EVUSHELD is not approved). The median duration for safety follow-up was 84 days.

In TACKLE, four subjects reported cardiac SAEs. Acute myocardial infarction was reported for two subjects who received EVUSHELD (one of whom also experienced cardiac failure leading to death) and sudden cardiac death was reported for one subject who received EVUSHELD. One subject who received placebo reported arrhythmia. All subjects who experienced cardiac SAEs had cardiac risk factors and/or a prior history of cardiovascular disease at baseline.

The overall safety profile in patients who received 600 mg IM EVUSHELD was generally similar to that reported in participants who received 300 mg IM EVUSHELD. The most frequently reported adverse reaction in TACKLE was injection site reaction (2.4%). Adverse events were reported in 132 (29%) subjects receiving EVUSHELD and 163 (36%) receiving placebo. Serious adverse events were reported in 33 (7%) subjects receiving EVUSHELD and 54 (12%) receiving placebo. There were no reports of anaphylaxis or serious hypersensitivity reactions.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adverse Reactions organized by MedDRA System Organ Class (SOC) is summarised in **Table 2** below.

Table 2 – Adverse Reactions (Pooled PROVENT and STORM CHASER studies, Safety Analysis Set, and TACKLE)

MedDRA SOC	Preferred Term	EVUSHELD 300 mg (PROVENT and STORM CHASER)		EVUSHELD 600 mg (TACKLE)	
		EVUSHELD (N = 4210)	Placebo (N = 2108)	EVUSHELD (N = 452)	Placebo (N = 451)
Immune system disorders	Hypersensitivity[A]	1.0%	0.9%	0.4%	0.7%
Injury, poisoning and procedural complications	Injection site reaction[A]	1.3%	1.2%	2.4%	2.4%

[A] Grouped terms: Hypersensitivity (including Rash and Urticaria); Injection site reaction (including Injection site pain, Injection site erythema, Injection site pruritus, Injection site reaction and Injection site induration).

8.2.1 Clinical Trials adverse reactions: Pediatrics

No data are available for pediatric individuals <18 years old. See 4.2 Recommended Dose and Dosage Adjustment and 10.3 Pharmacokinetics.

8.3 Less Common Clinical Trial Adverse Reactions

Less common clinical trial adverse reactions organized by MedDRA System Organ Class (SOC) are summarized below:

General disorders and administration site conditions: injection-related reaction

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No interaction studies have been conducted with EVUSHELD.

EVUSHELD is not expected to undergo metabolism by hepatic enzymes or renal elimination. See 10.3 Pharmacokinetics.

An interaction with COVID-19 vaccinations has not been studied and can therefore not be excluded. Healthcare professionals should refer to local guidance regarding the timing of COVID-19 vaccination prior to or following administration of EVUSHELD.

9.4 Drug-Drug Interactions

Tixagevimab and cilgavimab are not renally excreted or metabolised by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

Based on PK modelling, COVID-19 vaccination following EVUSHELD administration had no clinically relevant impact on the clearance of EVUSHELD.

In the absence of compatibility studies, EVUSHELD should not be mixed with other medicinal products.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Tixagevimab and cilgavimab, two SARS-CoV-2 spike protein-directed attachment inhibitors, are two recombinant human IgG1κ monoclonal antibodies, with amino acid substitutions to extend antibody half-life (YTE) and to reduce antibody effector function and potential risk of antibody-dependent enhancement of disease (TM). Tixagevimab and cilgavimab bind to non-overlapping regions of the spike protein receptor binding domain (RBD) of SARS-CoV-2. Tixagevimab, cilgavimab and their combination bind to the spike protein RBD with equilibrium dissociation constants of K_D = 2.76 pM, 13.0 pM and 13.7 pM, respectively, blocking its interaction with the human ACE2 receptor, the SARS-CoV-2 receptor, required for virus attachment. Tixagevimab, cilgavimab and their combination blocked RBD binding to the human ACE2 receptor 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.

10.2 Pharmacodynamics

See 15 MICROBIOLOGY.

In a Phase I study, following a single 300 mg IM dose of EVUSHELD in healthy volunteers (N= 10) neutralizing antibodies geometric mean titers (GMT) were evaluated using an authentic virus neutralization assay (PRNT80) at 7, 30, 60, 90, 150, 210 and 270 days post-dose. GMT results were 689.2, 852.8, 656.8, 533.7, 290.1, 297.5 and 98.6 respectively.

In PROVENT, following a single 300 mg IM dose of EVUSHELD, neutralizing antibody GMT at 7, 28, 57, and 91 days post-dose were similar to those observed in the Phase I healthy volunteer study and were 16, 22, 17 and 12-fold higher, respectively, than the GMT measured in convalescent plasma from COVID-19 patients (GMT= 30.8).

10.3 Pharmacokinetics

The pharmacokinetics of tixagevimab and cilgavimab are comparable, linear, and dose-proportional between 300 to 600 mg following a single IM administration.

Absorption:
After a single 300 mg IM dose (150 mg each antibody) in healthy volunteers, the mean (%CV) maximum concentration (C_{max}) was 16.5 (35.6%) and 15.3 (38.5%) µg/mL for tixagevimab and cilgavimab respectively which was reached at a median T_{max} of 14 days. The estimated absolute bioavailability after a single 150 mg IM dose was 68.5% for tixagevimab and 65.8% for cilgavimab.

Distribution:
Based on PK modelling, the central volume of distribution was 2.72 L for tixagevimab and 2.48 L for cilgavimab. The peripheral volume of distribution was 2.64 L for tixagevimab and 2.57 L for cilgavimab.

Metabolism:
Tixagevimab and cilgavimab are expected to be degraded into small peptides and component amino acids via catabolic pathways in the same manner as endogenous IgG antibodies.

Elimination:
The clearance (CL) was 0.041 L/day for tixagevimab and 0.041 L/day for cilgavimab with between subject variability of 21% and 29% respectively. The estimated population median terminal elimination half-life was 89 days for tixagevimab and 84 days for cilgavimab.

In PROVENT, following a single 300 mg IM dose of EVUSHELD, the mean serum concentration was 26.7 µg/mL (SD: 11.2) on Day 29.

Special Populations and Conditions

- **Pediatrics (12 years of age and older weighing at least 40 kg):** The recommended dosing regimen is expected to result in comparable serum exposures of tixagevimab and cilgavimab in adolescents 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 Trial D8850C00002 (PROVENT).

- **Geriatrics:** Of the participants in the pooled PK analysis, 21% (N= 534) were 65 years of age or older and 4.2% (N= 107) 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 individuals.

- **Hepatic Insufficiency:** 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 has not been established and it is

unknown whether a dose adjustment is needed in these individuals.

- **Renal Insufficiency:** No specific studies have been conducted to examine the effects of renal impairment on the pharmacokinetics of tixagevimab and cilgavimab.

  Tixagevimab and cilgavimab are not eliminated intact in the urine, since monoclonal antibodies with molecular weight >69 kDa do not undergo renal elimination, thus renal impairment is not expected to significantly affect the exposure of tixagevimab and cilgavimab. Similarly, dialysis is not expected to impact the PK of tixagevimab and cilgavimab.

  Based on population PK analysis, there is no difference in the clearance of tixagevimab and cilgavimab in patients with mild (N= 978) or moderate (N= 174) renal impairment compared to patients with normal renal function. In the population PK model there were insufficient participants with severe renal impairment (N= 21) to draw conclusions.

- **Other Special Populations:** The PK profile of tixagevimab and cilgavimab were not affected by sex, age, race or ethnicity. Bodyweight had no clinically relevant effect on the PK of tixagevimab and cilgavimab in adults over the range of 36 kg to 177 kg.

11 STORAGE, STABILITY AND DISPOSAL

Store in a refrigerator (2°C to 8°C). See 4.4 Administration.

Do not freeze. Do not shake.

Keep the vials in the original carton to protect from light.

Any unused product or waste material should be disposed of in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance
Proper name: tixagevimab and cilgavimab injection

Chemical name: tixagevimab and cilgavimab

Molecular formula and molecular mass: tixagevimab: 149 kDa, cilgavimab: 152 kDa

Physicochemical properties: Both tixagevimab and cilgavimab are clear to opalescent, colourless to slightly yellow, pH 6.0 solutions.

Product Characteristics: Tixagevimab and cilgavimab are produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Pre-Exposure Prophylaxis of COVID-19

Trial Design and Study Demographics

Table 3 – Summary of patient demographics: PROVENT for pre-exposure prophylaxis of COVID-19

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
D8850C00002 (PROVENT)	Phase III randomized (2:1), double-blind, placebo-controlled, multicenter study to determine the safety and efficacy of EVUSHELD for the pre-exposure prophylaxis of COVID-19 in adults ≥18 years of age	Single dose (administered as two intramuscular injections) of EVUSHELD 300 mg (150 mg of tixagevimab and 150 mg of cilgavimab administered separately) or saline placebo	EVUSHELD: 3441 Placebo: 1731	53.5 (18-99) years	Male: 54% Female: 46%

PROVENT
In PROVENT, all participants were individuals considered to be at increased risk for inadequate response to active immunisation (due to age ≥60 years, co-morbidity, pre-existing chronic illness, immunocompromised, or intolerant of vaccination) or at increased risk of SARS-CoV-2 infection (due to their location or circumstances at time of enrolment). Subjects could not have previously received a COVID-19 vaccine. Participants received either a single dose (administered as two intramuscular injections) of EVUSHELD 300 mg (150 mg of tixagevimab

and 150 mg of cilgavimab administered separately) or placebo. The study excluded participants with a history of laboratory-confirmed SARS-CoV-2 infection or SARS-CoV-2 antibody positivity at screening. 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 well balanced across the EVUSHELD and placebo arms (Table 3). The median age was 57 years (with 43% of participants aged 60 years or older), 46% of participants were female, 73% were White, 3.3% were Asian, 17% were Black/African American, and 15% were Hispanic/Latino. Of the 5197 participants, 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%).

Study Results

PROVENT

The primary endpoint was a COVID-19 case defined as SARS-CoV-2 RT-PCR-positive symptomatic illness occurring between EVUSHELD administration and Day 183. The primary analysis included 5172 participants who were SARS-CoV-2 RT-PCR-negative at baseline, of which 3441 received EVUSHELD and 1731 received placebo. Only events that occurred prior to unblinding or vaccine receipt were included. The results of the primary endpoint are shown in Table 4. The median follow-up time post-administration was 83 days.

Table 4 – Incidence of COVID-19 (Full Pre-Exposure Analysis Set)

	N	Number of events[a], n (%)	Relative Risk Reduction, % (95% CI)
EVUSHELD 300 mg[b]	3441	8 (0.2%)	77% (46 - 90) p-value <0.001
Placebo	1731	17 (1.0%)	

CI = Confidence Interval, N = number of participants in analysis.

[a] Primary endpoint, a participant 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.

[b] 300 mg (150 mg tixagevimab and 150 mg cilgavimab).

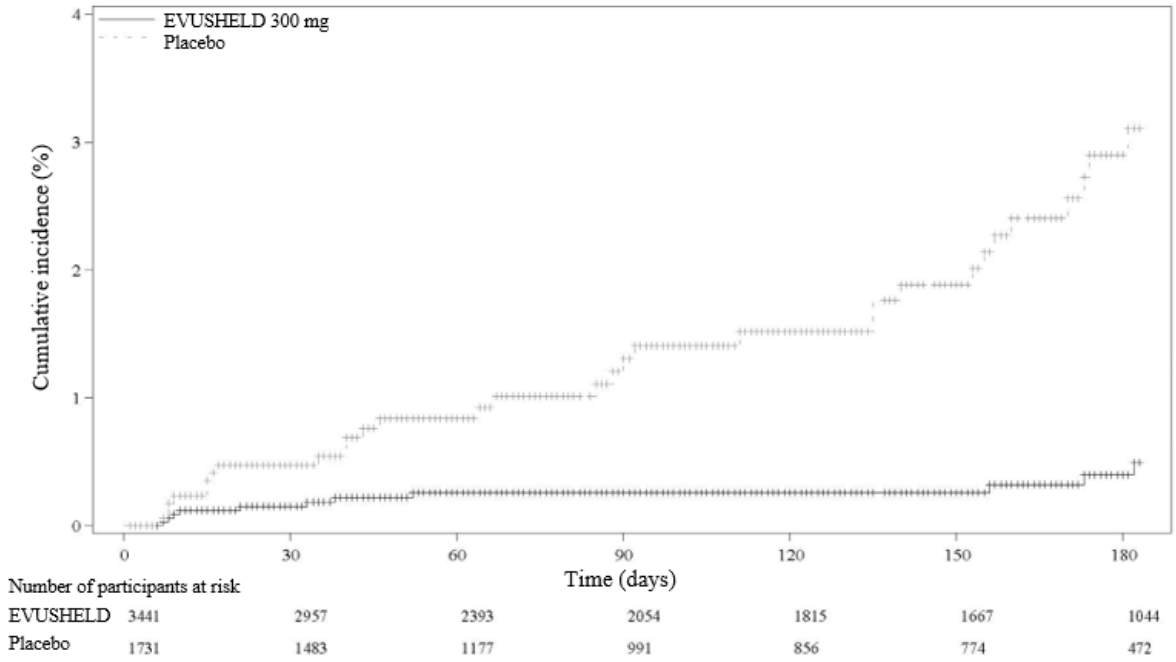
In a supportive analysis of the incidence of SARS-CoV-2 RT-PCR-positive symptomatic illness or death from any cause for participants who had received EVUSHELD (12/3441) compared with placebo (19/1731), the relative risk reduction was 69% (95% CI: 36, 85).

Among participants who received EVUSHELD there were no severe/critical COVID-19 events (defined as SARS-CoV-2 RT-PCR-positive symptomatic illness characterised by a minimum of either pneumonia [fever, cough, tachypnea 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 participants who received placebo.

An additional data cut-off was conducted to provide post-hoc updated safety and efficacy analyses; the median follow-up was 6.5 months for participants in both the EVUSHELD and

placebo arms. The relative risk reduction of SARS-CoV-2 RT-PCR-positive symptomatic illness was 83% (95% CI 66-91), with 11/3441 [0.3%] events in the EVUSHELD arm and 31/1731 [1.8%] events in the placebo arm (see **Figure 1**).

Figure 1 – Kaplan Meier: Cumulative Incidence of Symptomatic COVID-19



14.4 Immunogenicity

In PROVENT through Day 183, treatment-emergent anti-tixagevimab, anti-cilgavimab and anti-EVUSHELD antibodies were detected in 0.8% (6/716), 1.1% (7/644) and 1.3% (10/743) ADA-evaluable participants who received EVUSHELD. No evidence of an association of ADA with any impact on efficacy or safety has been observed.

15 MICROBIOLOGY

Antiviral activity
In a SARS-CoV-2 virus 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 the tixagevimab and cilgavimab combination showed reduced or no antibody-dependent cellular phagocytosis (ADCP) antibody-dependent cell-mediated cytotoxicity (ADCC) or antibody-dependent natural killer cell activation (ADNKA) in cell culture studies. Tixagevimab, cilgavimab and the tixagevimab and cilgavimab combination did not mediate 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 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 pseudovirus into these cells.

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, and lung injury and pathology based on histology measurements). No evidence of enhancement of disease was observed at any dose evaluated, including sub-neutralizing doses down to 0.04 mg/kg.

Antiviral resistance

There is a risk of resistance to monoclonal antibodies such as EVUSHELD due to the development of viral variants that are resistant to tixagevimab and cilgavimab. Prescribing healthcare professionals should consider the prevalence of SARS-CoV-2 variants in their area, in combination with antiviral resistance information, literature, and local guidelines when considering pre-exposure prophylaxis with EVUSHELD.

SARS-CoV-2 or recombinant vesicular stomatitis virus encoding SARS-CoV-2 spike protein were serially passaged in cell cultures in the presence of cilgavimab or tixagevimab individually, or tixagevimab and cilgavimab in combination. Escape variants were identified following passage with cilgavimab, but not with tixagevimab or tixagevimab and cilgavimab in combination. Variants which showed reduced susceptibility to cilgavimab alone included spike protein amino acid substitutions R346I (>200-fold), K444E (>200-fold), and K444R (>200-fold). All variants maintained susceptibility to tixagevimab alone, and tixagevimab and cilgavimab in combination.

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

In neutralization assays using recombinant SARS-CoV-2 pseudoviruses harbouring individual spike substitutions identified in circulating SARS-CoV-2, variants with reduced susceptibility to tixagevimab alone included those with F486S (>600-fold) and F486V (121- to 149-fold); variants with reduced susceptibility to cilgavimab alone included those with R346I (>200-fold), K444E (>200-fold), K444Q (>200-fold), K444R (>200-fold), and V445A (21- to 51-fold).

Tixagevimab and cilgavimab in combination retained full to nearly full neutralization activity against pseudovirus and/or live virus SARS-CoV-2 variant strains harbouring all spike substitutions identified in Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), Delta [+K417N] (AY.1/AY.2), and Omicron (BA.2) variants of concern.

Pseudotyped VLPs expressing spike protein and authentic SARS-CoV-2 Omicron BA.1 variant (B.1.1.529) and Omicron BA.1.1 (B.1.1.529 [+R346K]) showed reduced susceptibility to tixagevimab and cilgavimab in combination (Table 5).

Pseudovirus SARS-CoV-2 spike variant strains with moderate reduced susceptibility to tixagevimab alone included those harbouring E484K (Alpha, 18.5-fold; Beta, 3.5- to 15-fold) and variants with moderate reduced susceptibility to cilgavimab alone included those with R346K:E484K:N501Y (Mu, 21-fold), as indicated above. Similar results were observed, where data was available, in neutralization assays using authentic SARS-CoV-2 variants strains.

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

Table 5 – Pseudovirus and Authentic SARS-CoV-2 Neutralization Data for SARS-CoV-2 Variant Substitutions with Tixagevimab and Cilgavimab Together

Lineage with Spike Protein Substitutions		Characteristic RBD Substitutions Tested	Fold Reduction in Susceptibility[a]		IC_{50} (ng/mL)	
Pango Lineage	WHO Label		Pseudo virus[b]	Authentic SARS-CoV-2[c]	Pseudo virus[b]	Authentic SARS-CoV-2[c]
Variants of Concern						
B.1.1.7	Alpha	N501Y	1.0-5.2	0.5-1.4	1.1-9.0	4-39.5
B.1.351	Beta	K417N:E484K: N501Y	2.5-5.5	0.9-3.8	5.6-11.4	6.5-256
P.1	Gamma	K417T:E484K: N501Y	0.8-1.7	0.4-2.0	1.8-2.7	3.2-8
B.1.617.2	Delta	L452R:T478K	1.0-1.2	0.6-1.0	1.9-2.2	3-7.5
AY.1/AY.2	Delta [+K417N]	K417N:L452R: T478K	1.0	ND	1.9	ND
B.1.1.529	Omicron BA.1	A67V, H69-, V70-, T95I, G142D, V143- ,Y144-, Y145-, N211-,L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F.	132- to 183-fold	12- to 30-fold	51-277	147–278
BA.1.1	Omicron BA.1.1	G339D:R346K: S371L:S373P: S375F:K417N: N440K:G446S: S477N:T478K: E484A:Q493R: G496S:Q489R: N501Y:Y505H	424	176	466	1147
BA.2	Omicron BA.2	G339D:S371F: S373P:S375F:	3.2	5.4	9.8	35

Lineage with Spike Protein Substitutions		Characteristic RBD Substitutions Tested	Fold Reduction in Susceptibility[a]		IC_{50} (ng/mL)	
Pango Lineage	WHO Label		Pseudo virus[b]	Authentic SARS-CoV-2[c]	Pseudo virus[b]	Authentic SARS-CoV-2[c]
		T376A:D405N: R408S:K417N: N440K:S477N: T478K:E484A: Q493R:Q498R: N501Y:Y505H: H655Y:N679K: P681H:N764K				
Variants of Interest						
B.1.525	Eta	E484K	1.8-3.1	ND	5-9.5	ND
B.1.526	Iota	E484K	0.8-3.4	0.3-1.8	1.9-5.2	1.0-7.0
B.1.617.1	Kappa	L452R:E484Q	0.9-3.4	0.5-1.3	2.5-5.1	2.0-5.0
C.37	Lambda	L452Q:F490S	0.7	ND	1.1	ND
B.1.621	Mu	R346K:E484K: N501Y	7.5	ND	17.3	ND
B.1.427 / B.1.429	Epsilon	L452R	0.8-2.9	1.3-3.5	1.0-4.5	5.0-14.0
P.2	Zeta	E484K	2.9	ND	10.4	ND
Additional SARS-CoV-2 Variants						
R.1	-	E484K	3.5	ND	4.6	ND
B.1.1.519	-	T478K	1.0-1.4	ND	2.3	ND
C.36.3	-	R346S:L452R	2.3	ND	3.9	ND
B.1.214.2	-	Q414K:N450K	0.8	ND	1.6	ND
B.1.619.1	-	N440K:E484K	3.3	ND	7.6	ND
B.1.616	-	V483A	0.4-0.5	ND	1.1-1.2	ND
A.23.1	-	V367F	0.4	ND	0.5	ND
A.27	-	L452R:N501Y	0.8	ND	1.8	ND
AV.1	-	N439K:E484K	5.9	ND	13.0	ND

[a] Range of reduced *in vitro* potency across multiple sets of co-occurring substitutions and/or testing labs using research-grade assays; mean fold change in half maximal inhibitory concentration (IC_{50}) of monoclonal antibody required for a 50% reduction in infection compared to wild type reference strain.

[b] Pseudoviruses 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) harbouring additional indicated RBD substitutions that are no longer detected or detected at extremely low levels within these lineages.

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

ND, not determined; RBD, receptor binding domain.

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

In PROVENT, illness visit sequencing data was available for 21 participants with COVID-19 infection (6 who received tixagevimab and cilgavimab and 15 placebo). At an allele fraction ≥25%, 14 participants were infected with variants of concern or variants of interest, including 8 participants with Alpha (B.1.1.7) (8 placebo), 1 participant with Beta (B.1.351) (1 who received tixagevimab and cilgavimab), 3 participants with Delta (B.1.617.2) (3 placebo), and 2 participants with Epsilon (B.1.429) (2 who received tixagevimab and cilgavimab). Seven additional participants 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.

It is possible that resistance-associated variants to tixagevimab and cilgavimab together could have cross-resistance to other monoclonal antibodies targeting the RBD of SARS-CoV-2. Tixagevimab and cilgavimab together retained activity against pseudoviruses harbouring individual SARS-CoV-2 spike substitutions (E484D/K/Q, F490S, Q493R, S494P, K417E/N, D420N, K444Q, V445A, Y453F, L455F, N460K/S/T, F486V, and Q493K) identified in neutralization escape variants of other monoclonal antibodies targeting the RBD of SARS-CoV-2 spike protein.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: In a single-dose toxicology study in cynomolgus monkeys, EVUSHELD administered via an intramuscular injection of 150 mg/kg (75 mg/kg of each antibody) had no adverse effects.

In tissue cross-reactivity studies using human adult and fetal tissues no specific binding was detected.

Carcinogenicity: studies have not been conducted.
Genotoxicity: studies have not been conducted.
Reproductive and Developmental Toxicology: studies have not been conducted.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

℞EVUSHELD™
tixagevimab and cilgavimab injection, intramuscular use

Read this carefully before you start taking **EVUSHELD** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **EVUSHELD**.

What is EVUSHELD used for?

- EVUSHELD is used for the pre-exposure prophylaxis (prevention) of Coronavirus Disease 2019 (COVID-19) illness in adults and adolescents (aged 12 years and older weighing at least 40 kg) who:
    - have a weaker immune system and are unlikely to be protected by a COVID-19 vaccine
    - or when vaccination is not recommended.

EVUSHELD is not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended.

How does EVUSHELD work?

EVUSHELD contains the active substances tixagevimab and cilgavimab. Tixagevimab and cilgavimab are types of protein called 'monoclonal antibodies'. EVUSHELD work specifically against the SARS-CoV-2 virus (the virus that causes COVID-19 illness) by preventing the virus from infecting healthy cells in your body. This can help prevent you from getting COVID-19 illness.

What are the ingredients in EVUSHELD?

Medicinal ingredients: tixagevimab and cilgavimab
Non-medicinal ingredients: L-histidine, L-histidine hydrochloride monohydrate, polysorbate 80, sucrose and water.

EVUSHELD comes in the following dosage forms:

A carton containing two clear glass vials:

- 1 vial of tixagevimab (100 mg/mL) solution for injection (dark grey vial cap)
- 1 vial of cilgavimab (100 mg/mL) solution for injection (white vial cap)

Both solutions are a clear to opalescent, colourless to slightly yellow solution.

Do not use EVUSHELD if:

- if you are allergic to tixagevimab, cilgavimab or any of the other ingredients of this medicine (see What are the ingredients in EVUSHELD).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take EVUSHELD. Talk about any health conditions or problems you may have, including if you:

- have low numbers of blood platelets (which help blood clotting), a bleeding disorder or are taking an anticoagulant medicine (to prevent blood clots).
- are pregnant, think you may be pregnant or are planning to have a baby, ask your healthcare professional for advice before receiving this medicine. There is not enough information to be sure that EVUSHELD is safe for use in pregnancy. EVUSHELD will only be given if the potential benefits of use outweigh the potential risks to you and your unborn child.
- are breast-feeding, ask your healthcare professional for advice before receiving this medicine. It is unknown if EVUSHELD or the COVID-19 virus pass into human breast milk. You will need to consider the potential benefits of use for you, compared with the health benefits and risks of breast-feeding for your baby.
- have a history of severe allergic reaction to this drug.
- have had a heart attack or stroke, have other heart problems, or are at high-risk of cardiac (heart) events.

Serious allergic reaction
Tell your healthcare professional or seek medical help right away if you notice any signs of serious allergic reaction during or following administration of EVUSHELD including: difficulty breathing or swallowing, swelling of the face, lips, tongue or throat, severe itching of the skin, with a red rash or raised bumps.

Other warnings you should know about:
EVUSHELD should not be given to children below 12 years of age or weighing less than 40 kg.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take EVUSHELD:
EVUSHELD will be given to you by a healthcare professional as two intramuscular injections, usually one into each of your buttocks.

Usual dose:
EVUSHELD consists of two medicines, tixagevimab and cilgavimab. You will receive 2 injections one after the other.

The recommended dose for pre-exposure prophylaxis (prevention) of COVID-19 is 300 milligrams (mg) given as two 1.5 mL injections:

- 150 mg of tixagevimab
- 150 mg of cilgavimab

The recommended dose for pre-exposure prophylaxis (prevention) of some variants of COVID-19 is 600 milligrams (mg), given as two 3.0 mL injections:

- 300 mg of tixagevimab
- 300 mg of cilgavimab

Your healthcare professional will decide which dose you need to receive.

Overdose:

If you think you, or a person you are caring for, have taken too much EVUSHELD, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using EVUSHELD?
These are not all the possible side effects you may have when taking EVUSHELD. If you experience any side effects not listed here, tell your healthcare professional.

Allergic reactions may be serious and occur during or following administration of monoclonal antibodies (see Serious allergic reaction above).

A higher percentage of people who received EVUSHELD compared to people who did not receive EVUSHELD reported serious cardiac adverse events in a clinical trial. It is not known if these events are related to EVUSHELD or underlying medical conditions. Contact your healthcare professional 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.

If you notice any side effects, please tell your healthcare professional right away:

Common: may affect up to 1 in 10 people

- hypersensitivity reaction (rash or hives - an itchy red rash or raised bumps)
- injection site reaction (pain, redness, itching, swelling where the injection was given)

Uncommon: may affect up to 1 in 100 people

- injection related reaction (examples of these include headache, chills and redness, discomfort or soreness near where the injection was given)

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
The following information about storage, expiry and use and handling is intended for the healthcare professional:

- Keep out of reach and sight of children.
- Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C to 8°C).
- Do not freeze. Do not shake.
- Store in the original package in order to protect from light.
- Prepared syringes should be used immediately. If necessary, store the prepared syringes for no more than 4 hours either: at 2°C to 8°C, or at room temperature up to 25°C.
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

If you want more information about EVUSHELD:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website: www.astrazeneca.ca, or by calling 1-800-668-6000.
- This Patient Medication Information is current at the time of printing. The most up-to-date version can be found at www.astrazeneca.ca.

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