▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Evusheld 150 mg / 150 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each carton of Evusheld contains two vials:

Each vial of tixagevimab contains 150 mg of tixagevimab in 1.5 mL (100 mg/mL).
Each vial of cilgavimab contains 150 mg of cilgavimab in 1.5 mL (100 mg/mL).

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Clear to opalescent, colourless to slightly yellow, pH 6.0 solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pre-exposure prophylaxis
Evusheld is indicated for the pre-exposure prophylaxis of COVID-19 in adults 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 are unlikely to mount an adequate immune response to COVID-19 vaccination

or

- For whom COVID-19 vaccination is not recommended.

Treatment
EVUSHELD is indicated for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 (see sections 4.2, 5.1 and 5.2).

The use of Evusheld should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

Preparation and administration of Evusheld should be initiated and observed by a qualified healthcare provider using aseptic technique. Administration should be under conditions where management of

severe hypersensitivity reactions, such as anaphylaxis, is possible. Individuals should be observed at least for one 1 hour after injection.

Pre-exposure prophylaxis
The recommended dosage is 300 mg of Evusheld, as 150 mg of tixagevimab and 150 mg of cilgavimab (Table 1), administered as separate sequential intramuscular injections.

A higher dose of 600 mg of Evusheld, as 300 mg of tixagevimab and 300 mg of cilgavimab (Table 1), may be more appropriate for some SARS-CoV-2 variants (for example, Omicron BA.1, Omicron BA.1.1) based on *in vitro* neutralisation susceptibility data which show reduced susceptibility for Evusheld (see section 4.8 and 5.1).

Available data indicate that Evusheld may be effective for pre-exposure prophylaxis for six months post administration for non-Omicron SARS-CoV-2 variants prevalent during the study (see section 5.1). The duration of protection for other variants, such as Omicron BA.1 and BA.1.1, is currently not known. Evusheld has only been studied in single-dose studies. There are no safety and efficacy data available with repeat dosing.

Treatment
The recommended dose in adults is 600 mg of Evusheld, as 300 mg of tixagevimab and 300 mg of cilgavimab (Table 1), administered as two separate sequential intramuscular injections.

EVUSHELD should be given within 7 days of the onset of symptoms of COVID-19 (see section 5.1).

Special populations

Elderly
No dose adjustment is required for elderly patients ≥65 years (see section 5.2).

Renal and hepatic impairment
No dose adjustment is required for patients with renal or hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of Evusheld in children aged <18 years of age have not yet been established. No data are available.

Method of administration

Evusheld is for intramuscular injection only.

Each carton contains two vials:
- tixagevimab solution for injection (dark grey vial cap);
- cilgavimab solution for injection (white vial cap).

Table 1 Dosage of tixagevimab and cilgavimab

Indication	**Evusheld dose** tixagevimab and cilgavimab	**Antibody dose**	**Number of vials needed**†	**Volume to withdraw from vial(s)**
Pre-exposure prophylaxis of COVID-19	300 mg (1 EVUSHELD carton)	tixagevimab 150 mg	1 vial	1.5 mL
		cilgavimab 150 mg	1 vial	1.5 mL
	600 mg‡	tixagevimab 300 mg	2 vials	3.0 mL

	(2 EVUSHELD cartons)	cilgavimab 300 mg	2 vials	3.0 mL
Treatment of COVID-19	600 mg (2 EVUSHELD cartons)	tixagevimab 300 mg	2 vials	3.0 mL
		cilgavimab 300 mg	2 vials	3.0 mL

† Each vial contains an overfill to allow the withdrawal of 150 mg (1.5 mL).
‡ A higher dose of 600 mg of Evusheld, as 300 mg of tixagevimab and 300 mg of cilgavimab, may be more appropriate for some SARS-CoV-2 variants (for example, Omicron BA.1, Omicron BA.1.1) based on *in vitro* neutralisation susceptibility data which show reduced susceptibility for Evusheld.

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.

Tixagevimab and cilgavimab must be given as separate sequential intramuscular injections at different injection sites in two different muscles, preferably in the gluteal muscles. The order in which the two products are administered does not matter.

The solutions for injection do not contain a preservative. Any unused solution should be discarded.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity including Anaphylaxis

Serious hypersensitivity reactions, including anaphylaxis, have been observed with other IgG1 monoclonal antibodies such as Evusheld. 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.

Clinically significant bleeding disorders

As with any other intramuscular injections, Evusheld should be given with caution to patients with thrombocytopenia or any coagulation disorder.

Breakthrough infection or treatment failure due to antiviral resistance

Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies such as tixagevimab and cilgavimab. The *in-vitro* neutralisation activity of Evusheld against SARS-CoV-2 viral variants are shown in Table 5 (see section 5.1). As seen from the results, Evusheld does not neutralise BA.4.6 and is unlikely to be active against this variant. Due to the observed decrease in *in-vitro* neutralisation activity against the Omicron subvariants BA.1, BA.1.1, BA.4 and BA.5, the duration of protection of Evusheld for these subvariants is currently not known.

Patients who receive Evusheld prophylactically should be informed of the potential for breakthrough infections to occur. Patients should be instructed to promptly seek medical advice if signs or symptoms of COVID-19 occur (the most common symptoms include fever, cough, tiredness and loss

of taste or smell; the most serious symptoms include difficulty breathing or shortness of breath, loss of speech or mobility, or confusion and chest pain).

Decisions regarding the use of Evusheld for the treatment of COVID-19 should take into consideration what is known about the characteristics of the circulating SARS-CoV-2 viral variants, including geographical prevalence and local guidelines.

Cardiovascular and Thromboembolic Events

In PROVENT a higher proportion of subjects who received Evusheld versus placebo reported myocardial infarction and cardiac failure serious adverse events (SAEs), including one fatal SAE (Table 2). 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.

In PROVENT a higher proportion of subjects who received Evusheld versus placebo reported thromboembolic SAEs (Table 3).

In TACKLE (N= 903, data cut off 21 August 2021) 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.

In TACKLE in the Evusheld group, four subjects reported thromboembolic SAEs, including two events of acute myocardial infarction, one event of pulmonary embolism and one event of peripheral artery thrombosis. In the placebo group, two subjects reported SAEs of portal vein thrombosis and superior sagittal sinus thrombosis.

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.

Table 2 Exposure Adjusted Incidence Rate (EAIR) of Cardiac SAEs Regardless of Causality in PROVENT using the Median 6.5 Month Data Cut-off Date*

System Organ Class Preferred term	**Evusheld 300 mg IM** **N = 3461** **Events (EAIR† (person years))**	**Placebo** **N = 1736** **Events (EAIR† (person years))**
Cardiac disorders‡	23 (1.2)	5 (0.5)
Acute myocardial infarction	4 (0.2)	2 (0.2)
Myocardial infarction	5 (0.3)	0
Acute left ventricular failure	0	1 (0.1)
Paroxysmal atrioventricular block	1 (0.1)	0
Cardiac failure congestive	4 (0.2)	0
Atrial fibrillation	1 (0.1)	2 (0.2)
Angina pectoris	1 (0.1)	0
Arrhythmia	1 (0.1)	0
Arteriosclerosis coronary artery	1 (0.1)	0
Cardiac failure	1 (0.1)	0

Cardiac failure acute	1 (0.1)	0
Cardio-respiratory arrest	1 (0.1)	0
Cardiomegaly	1 (0.1)	0
Cardiomyopathy	1 (0.1)	0
Coronary artery disease	1 (0.1)	0

* Date Cut Off date: 29 August 2021

† EAIR is calculated by the number of participants with the events divided by the duration of exposure (in years) x 100. Exposure time is calculated from the first dose date to the end of study date or data cut-off if the participant is ongoing at the time of the data cut-off. Exposure time is converted to patient years by dividing the number of days with 365.25.

‡ One Evusheld recipient had two cardiac SAEs

Table 3 Exposure Adjusted Incidence Rate (EAIR) of thromboembolic event SAEs Regardless of Causality in PROVENT Using the Median 6.5 Month Data Cut-off Date*

System Organ Class Preferred term	**Evusheld 300 mg IM** **N = 3461** **Events (EAIR† (person years))**	**Placebo** **N = 1736** **Events (EAIR† (person years))**
Thromboembolic SAEs	**17 (0.9)**	**4 (0.4)**
Cardiac disorders		
Acute myocardial infarction	4 (0.2)	2 (0.2)
Myocardial infarction	5 (0.3)	0
Gastrointestinal disorders		
Mesenteric artery thrombosis	1 (0.1)	0
Nervous system disorders		
Cerebral infarction	1 (0.1)	0
Transient ischaemic attack	2 (0.1)	0
Lacunar infarction	0	1 (0.1)
Cerebrovascular accident	2 (0.1)	1 (0.1)
Respiratory, thoracic and mediastinal disorders		
Pulmonary embolism	2 (0.1)	0

* Date Cut Off date: 29 August 2021

† EAIR is calculated by the number of participants with the events divided by the duration of exposure (in years) x 100. Exposure time is calculated from the first dose date to the end of study date or data cut-off if the participant is ongoing at the time of the data cut-off. Exposure time is converted to patient years by dividing the number of days with 365.25

COVID-19 vaccines

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Evusheld is not renally excreted or metabolised by cytochrome P450 (CYP) enzymes; therefore, interactions with concomitant therapies that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely (see Section 5.2).

COVID-19 vaccines

Interaction studies with COVID-19 vaccines have not been performed. Refer to current vaccination guidelines with respect to timing of vaccination pre- or post-treatment with anti-SARS-CoV-2 monoclonal antibodies.

Limited data are available from the PROVENT and TACKLE clinical trial where subjects were permitted, on request to unblind, to receive COVID-19 vaccination. No safety concerns were identified. Based on PK modelling, COVID-19 vaccination following Evusheld administration had no clinically relevant impact on the clearance of Evusheld.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of tixagevimab and cilgavimab in pregnant women. Since tixagevimab and cilgavimab are both human immunoglobulins G (IgG), animal studies have not been evaluated with respect to reproductive toxicity (see section 5.3). No off-target binding was detected in a cross-reactive binding assay using a protein array enriched for human embryofetal proteins. Since tixagevimab and cilgavimab are both human immunoglobulins G (IgG), they have the potential for placental transfer from the mother to the developing foetus.

The potential prophylactic benefit or risk of placental transfer of tixagevimab and cilgavimab to the developing fetus is not known.

Evusheld may be used during pregnancy where the expected benefit to the mother justifies the potential risk to the fetus.

Breast-feeding

There are no data on the excretion of tixagevimab and cilgavimab in human milk. The potential prophylactic benefit or risk to the newborn or infants via breastfeeding is not known.

Decisions on whether to breastfeed during treatment or to abstain from Evusheld therapy should take into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effects of tixagevimab and cilgavimab on human male or female fertility. Effects on male and female fertility have not been evaluated in animal studies.

4.7 Effects on ability to drive and use machines

Evusheld has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

A total of 4210 adult participants have received 300 mg Evusheld, via intramuscular injections, in the Phase III prophylaxis studies, PROVENT (a double-blind, placebo-controlled clinical trial for the pre-exposure prophylaxis of COVID-19) and STORM CHASER (a double-blind, placebo-controlled clinical trial for the post-exposure prophylaxis of COVID-19, an indication for which Evusheld is not approved).

The most frequently reported adverse reactions (≥ 1%) in the pooled analysis of PROVENT and STORMCHASER were injection site reactions (1.3%) and hypersensitivity (1.0%).

TACKLE is a Phase III, double-blind, placebo-controlled clinical trial for the treatment of adult patients with COVID-19. TACKLE enrolled non-hospitalised adults (with the exception of those hospitalised for isolation purposes) with COVID-19 (within ≤7 days of symptom onset). Four-hundred and fifty two (452) patients have received 600 mg IM Evusheld in TACKLE. The median duration for safety follow-up was 84 days.

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 (≥ 1%) in TACKLE was injection site reaction (2.4%).

Tabulated list of adverse reactions

The table below presents the adverse reactions from the pooled analysis of PROVENT and STORM CHASER and from TACKLE. Adverse reactions (Table 4) are organised by MedDRA System Organ Class (SOC). Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000) and not known (cannot be estimated from available data).

Table 4 Adverse reactions

MedDRA SOC	**PROVENT and STORM CHASER (300 mg)**		**TACKLE (600 mg)**	
	Frequency†	**Adverse Drug Reaction**	**Frequency**†	**Adverse Drug Reaction**
Immune system disorders	Common	Hypersensitivity*	Uncommon	Hypersensitivity‡
General disorders and administration site conditions	Uncommon	Injection related reaction	Not observed	Not observed
Injury, poisoning and procedural complications	Common	Injection site reaction*	Common	Injection site reaction*

* 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).

† Frequencies are based on exposure to 300 mg Evusheld in the pooled data from the prophylaxis studies.

‡ Grouped terms: Hypersensitivity (including Rash)

Paediatric population

No data are available for paediatric patients <18 years old (see Section 4.2 and 5.2).

Elderly

In PROVENT 817 (24%) of patients who received treatment with Evusheld were ≥65 years old. The safety profile of these patients was similar to that in adult patients <65 years old.

In TACKLE 57 (12.6%) of patients who received EVUSHELD were >65 years old. The safety profile in these patients was acceptable.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Coronavirus Yellow Card Reporting Site at: https://coronavirus-yellowcard.mhra.gov.uk or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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 injections (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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiviral monoclonal antibodies, ATC code: J06BD03

Mechanism of action

Tixagevimab and cilgavimab are two recombinant human IgG1k monoclonal antibodies, with amino acid substitutions in the Fc regions 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 can simultaneously bind to non-overlapping regions of the spike protein receptor binding domain (RBD) of SARS-CoV-2. Tixagevimab, cilgavimab and their combination bind to spike 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, which is 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.

In-vitro antiviral activity

In a SARS-CoV-2 virus neutralisation assay on Vero E6 cells, tixagevimab, cilgavimab and their combination neutralised 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.

The neutralising activity of tixagevimab, cilgavimab alone and tixagevimab, cilgavimab together was assessed against S protein variants, including known Variants of Concern/Interest, variants identified from in vitro escape studies, and variants from publicly available SARS-CoV-2 genome data obtained from the Global Initiative on Sharing All Influenza Data (GISAID). These data are presented as mean fold change in IC_{50} (half maximal inhibitory concentration) values relative to the reference virus (Table 5).

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

Table 5 **Pseudovirus and Authentic SARS-CoV-2 Neutralisation Data for SARS-CoV-2 Variant Substitutions with Tixagevimab and Cilgavimab alone and the combination of Tixagevimab and Cilgavimab together**

Pango Lineage with Spike Protein Substitutions	Characteristic RBD Substitutions Tested	Susceptibility Reduction Factor[a] (IC_{50} (ng/mL))					
		Tixagevimab		Cilgavimab		Tixagevimab + Cilgavimab	
		Pseudovirus[b]	Authentic virus[c]	Pseudovirus[b]	Authentic virus[c]	Pseudovirus[b]	Authentic virus[c]
B.1.1.7 (Alpha, UK)	N501Y	2.2-5.6 (2.4-3.8)	0.1-4.2 (5-21.0)	0.95-3.4 (4.6-11.9)	0.5-1 (10-56)	1.3-4.2 (2.7-9.0)	0.5-1.4 (4-39.5)
B.1.1.7 (Alpha, UK)	N501Y+ (L455F, E484K, F490S, Q493R, and/or S494P)[b]	0.9-18.4 (1.1-21.6)	ND	0.57-1.5 (2.9-3.0)	ND	1-5.2 (1.1-5.9)	ND
B.1.351 (Beta, South Africa)	K417N+E484K+ N501Y	3.6-15.4 (4.6-10)	1.8-8.9 (10.3-414)	1.1-1.7 (3.6-7.3)	0.3-3.9 (14-247)	2.5-5.5 (5.6-11.4)	0.9-3.8 (6.5-256)
P.1 (Gamma, Brazil)	K417T+E484K+ N501Y	0.9-2.3 (1.1-2.3)	8-11.5 (30-46)	0.4-0.9 (1.7-3.4)	0.3-0.8 (7-10)	0.8-1.7 (1.8-2.7)	0.4-2.0 (3.2-8)
B.1.617.2 (Delta, India)	L452R+T478K	0.6-1.0 (1-1.2)	0.5-2.3 (2-8.2)	2.5-6.8 (9.4-25.2)	1.5-3.8 (38-48.3)	1-1.2 (1.9-2.2)	0.6-1 (3-7.5)
AY.1/AY.2 (Delta [+K417N], India)	K417N+L452R+ T478K	0.6 (1.2)	ND	2.5 (9.4)	ND	1.0 (1.9)	ND
B.1.1.529 Omicron, BA.1 (Botswana)	G339D+S371L+ S373P+S375F+ K417N+N440K+ G446S+S477N+ T478K+E484A+ Q493R+G496S+ Q489R+N501Y+ Y505H	>600- >1000 (269- >1600)	152-230 (913-1152)	> 700- >1000 (381- >5000)	12-268 (301-3488)	132-183 (51-277)	12-30 (147-278)
Omicron BA.1.1 (Multiple country)	G339D+R346K+ S371L+S373P+ S375F+K417N+ N440K+G446S+ S477N+T478K+ E484A+Q493R+ G496S+Q489R+ N501Y+ Y505H	460 (552)	128 (686)	> 500 (> 1000)	>1000 (>10000)	424 (466)	176 (1147)
Omicron BA.2 (Multiple country)	G339D+S371F+ S373P+S375F+ T376A+D405N+ R408S+K417N+ N440K+S477N+ T478K+E484A+ Q493R+Q498R+ N501Y+Y505H+ H655Y+N679K+ P681H+N764K	>1000 (>1000)	68 (365)	1.9 (11.1)	0.9 (28)	3.2 (9.8)	5.4 (35)
Omicron BA.2.12.1 (United States)	G339D:S371F: S373P:S375F:T376A: D405N:R408S:	>500 (648)	ND	2 (7.4)	ND	5 (10.7)	ND

Pango Lineage with Spike Protein Substitutions	Characteristic RBD Substitutions Tested	Susceptibility Reduction Factor[a] (IC_{50} (ng/mL))					
		Tixagevimab		Cilgavimab		Tixagevimab + Cilgavimab	
		Pseudovirus[b]	Authentic virus[c]	Pseudovirus[b]	Authentic virus[c]	Pseudovirus[b]	Authentic virus[c]
	K417N:N440K:L452Q:S477N:T478K:E484A:Q493R:Q498R:N501Y:Y505H						
BA.2.75 (India)	Omicron BA.2.75	7 - 53 (7 - 81)	ND	6 - 40 (31 - 83)	ND	2.4 to 15 (1.2 - 14)	ND
Omicron BA.3 (Multiple country)	G339D:S371F:S373P:S375F:D405N:K417N:N440K:G446S:S477N:T478K:E484A:Q493R:Q498R:N501Y:Y505H	>5,000 (>5,000)	ND	4 (16.8)	ND	16 (34.5)	ND
Omicron BA.4 (Multiple country)	G339D:S371F:S373P:S375F:T376A:D405N:R408S:K417N:N440K:L452R:S477N:T478K:E484A:F486V:Q498R:N501Y:Y505H	>10,000 (>10,000)	ND	7.5 – 9 (15 – 36.5)	ND	33 - 65 (65 – 69.4)	ND
BA.4.6 (United States)	G339D:R346T:S371F:S373P:S375F:T376A:D405N:R408S:K417N:N440K:L452R:S477N:T478K:E484A:F486V:Q498R:N501Y:Y505H	>1000 (>1000[d])	ND	>1000 (>1000[d])	ND	>1000 (>1000[d])	ND
BA.5 (Multiple country)	G339D:S371F:S373P:S375F:T376A:D405N:R408S:K417N:N440K:L452R:S477N:T478K:E484A:F486V:Q498R:N501Y:Y505H	>10,000 (>10,000)	>10,000 (>10,000)	7.5-9 (15 - 36.5)	1.2-4.2 (23.5 - 131)	33 to 65 (65 – 69.4)	2.8 to 16 (56.6 – 229)

Pango Lineage with Spike Protein Substitutions	Characteristic RBD Substitutions Tested	Susceptibility Reduction Factor[a] (IC_{50} (ng/mL))					
		Tixagevimab		Cilgavimab		Tixagevimab + Cilgavimab	
		Pseudovirus[b]	Authentic virus[c]	Pseudovirus[b]	Authentic virus[c]	Pseudovirus[b]	Authentic virus[c]
B.1.525 (Eta, Multiple country)	E484K	4.2-4.8 (4.6-9.9)	ND	0.9-1.4 (5.2-6.6)	ND	1.8-3.0 (5-9.5)	ND
B.1.526 (Iota, United States)	E484K	8.4-8.6 (1-11.2)	0.3-2.5 (1-10)	0.6-1.4 (3.2-4.3)	0.3-0.5 (8-13)	0.7-3.4 (1.8-5.2)	0.3-1.8 (1-7)
B.1.617.1 (Kappa, India)	L452R+E484Q	0.9-1.2 (1-2)	0.5-1.3 (2-5)	1.9-2.3 (8-33)	0.5-2.4 (14-62)	0.9-3.4 (2.5-5.1)	0.5-1.3 (2-5)
C.37 (Lambda, Peru)	L452Q+F490S	0.6 (0.4)	ND	8.3 (21)	ND	0.7 (1.1)	ND
B.1.621 (Mu, Colombia)	R346K+E484K+ N501Y	5.3 (7.0)	ND	20.6 (67.1)	ND	7.5 (17.3)	ND
B.1.427 / B.1.429 (Epsilon, United States)	L452R	0.3-5.8 (0.4-3.2)	1.2-2.7 (5-11)	1.4-4.3 (5.9-12.4)	2.1-2.7 (55-75)	0.8-2.9 (1.2-4.5)	1.3-3.5 (5-14)
R.1 (Multiple country)	E484K	6.1 (8.0)	ND	1.1 (2.3)	ND	3.5 (4.6)	ND
B.1.1.519 (Multiple country)	T478K	4.8 (0.8)	ND	1.3 (3.2)	ND	1.0 (2.3)	ND
C.36.3 (Multiple country)	R346S+L452R	0.5 (0.8)	ND	NA	ND	2.3 (3.9)	ND
B.1.214.2 (Multiple country)	Q414K+N450K	0.5 (0.6)	ND	6.8 (30)	ND	0.8 (1.6)	ND
B.1.619.1 (Multiple country)	N440K+E484K	5.6 (7.1)	ND	3.0 (8.4)	ND	3.3 (7.6)	ND
P.2 (Zeta, Brazil)	E484K	7.3 (11.8)	ND	1.1 (6.4)	ND	2.9 (10.4)	ND
B.1.616 (France)	V483A	0.5-0.7 (0.6-0.8)	ND	0.5-0.7 (2.2-2.7)	ND	0.4-0.5 (1.1-1.2)	ND
A.23.1 (UK)	V367F	0.5 (0.3)	ND	0.9 (2.4)	ND	0.4 (0.5)	ND
A.27 (Multiple country)	L452R+N501Y	0.6 (0.8)	ND	2.6 (8.8)	ND	0.8 (1.8)	ND
AV.1 (Multiple country)	N439K+E484K	6.8 (8.0)	ND	2.6 (9.6)	ND	5.9 (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 (IC50) 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.

[d] Tixagevimab and cilgavimab together are unlikely to be active against this variant.

ND, not determined

It is not known how pseudotyped VLP or authentic SARS-CoV-2 neutralisation susceptibility data correlate with clinical outcome. Data collection is ongoing to better understand how reductions in activity seen in authentic SARS-CoV-2 or pseudotyped VLP assays may correlate with clinical outcomes.

For variants with reduced susceptibility official guidelines should be consulted before considering Evusheld in pre-exposure prophylaxis or treatment setting.

Antiviral resistance

There is a potential risk of a reduction in efficacy due to the development of viral variants that are less susceptible to tixagevimab and cilgavimab. Decisions regarding the use of Evusheld should take into consideration what is known about the characteristics of the circulating SARS-CoV-2 virus and the impact of the disease in different geographical areas and patient populations.

Escape variants were identified following serial passage in cell culture of SARS-CoV-2 (10 passages, with the antibodies held at low concentrations until cytopathic effect was observed) or replication-competent recombinant vesicular stomatitis virus encoding SARS-CoV-2 spike protein (pseudovirus; 2 passages) in the presence of cilgavimab or tixagevimab individually, or in combination. Variants which showed reduced susceptibility to cilgavimab included spike protein amino acid substitutions R346I (>200-fold increase in IC_{50}), K444E (>200-fold increase in IC_{50}), and K444R (>200-fold increase in IC_{50}). No escape variants to tixagevimab, or the tixagevimab and cilgavimab combination were selected.

In neutralization assays using recombinant SARS-CoV-2 pseudoviruses harboring 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) and variants with reduced susceptibility to cilgavimab alone included those with R346I (>200-fold), K444E (>200-fold), K444Q (>200-fold), and K444R (>200-fold).

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.

In the PROVENT clinical trial, spike protein RBD substitutions detected at an allele fraction ≥3% included V503F in the tixagevimab and cilgavimab group. The significance of this substitution regarding the activity of Evusheld is being determined.

In patients treated with EVUSHELD in the TACKLE clinical trial, treatment-emergent substitutions in the spike protein within the EVUSHELD binding site detected at an allele fraction ≥3% included K440N, L441R, V445I, G446V, L452R, L452P, L452Q, R452L, F456S, A475T, A475V, N477S, S477N, S477R/S, K/T478K, K478T, K/T478T, V483I, E484E/V, E484K, K484E, C488C/Y, C488R, C488F, and F490L. In an in vitro microneutralization assay with lentiviral pseudotyped SARS-CoV-2 spike, there was no change in susceptibility of EVUSHELD to: K440N, G446V, L452R, R452L, N477S, S477N, S477R/S, K/T478K, K478T, K/T478T, E484E/V, E484K, K484E, and F490L (IC50 values from 0.89-4.2 ng/ml). The effect of substitutions L441R, V445I, L452P, L452Q, F456S, A475T, A475V, V483I, C488C/Y, C488R, and C488F on the activity of EVUSHELD is being determined.

Clinical efficacy

Pre-exposure prophylaxis of COVID-19

PROVENT is an ongoing Phase III, randomised (2:1), double-blind, placebo-controlled clinical trial studying Evusheld for the pre-exposure prophylaxis of COVID-19 in adults ≥18 years of age.

The study included participants identified to 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 due to their living situation or occupation. Predicted poor responders to vaccines had at least one of the following: obesity (BMI ≥ 30) or pre-specified co-morbidity (congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, immunocompromised state) or age ≥60 years. The study excluded participants with a history of laboratory-confirmed SARS-CoV-2 infection or COVID-19 vaccination or SARS-CoV-2 antibody positivity at screening. Randomisation was stratified within each cohort (Cohort 1 included participants ≥60 years of age and Cohort 2 included participants <60 years of age). In Cohort 1 randomisation was stratified by residence in a long-term facility or not and in Cohort 2 randomisation was stratified by risk of infection to SARS-CoV-2. Participants received either a single dose (administered as two IM injections) of Evusheld 300 mg (150 mg of tixagevimab and 150 mg of cilgavimab administered separately) or placebo.

A total of 5254 participants were randomised to receive either Evusheld (N=3500) or placebo (N=1754). Of the 5197 participants (full analysis set all participants who were randomised and received at least one injection of the IMP), at baseline the median age was 57 years (range: 18-99), (4.2% were 75 years and older), 46% of participants were female, 73% were White, 3.3% were Asian, 17% were Black/African American, and 15% were Hispanic/Latino. The baseline co-morbidities or characteristics associated with an increased risk for severe COVID-19 included 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 (0.5%).

The primary endpoint was defined as the first case of SARS-CoV-2 RT-PCR (reverse transcriptase polymerase chain reaction) positive symptomatic illness occurs post-dose of Evusheld prior to Day 183. 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 (or not) COVID-19 vaccination. Only events that occurred prior to unblinding or receipt of COVID-19 vaccine or other COVID-19 preventative product were included in the primary analysis (i.e. participants were censored at the date of unblinding/receipt of COVID-19 vaccine or other COVID-19 preventative product, whichever is earlier). The analysis was conducted in the pre-exposure analysis set (all participants who were randomised and received at least one injection of Evusheld and who were SARS-CoV-2 RT-PCR negative at baseline).

The primary analysis included 5172 participants, of which 3441 received Evusheld and 1731 received placebo. Evusheld reduced the risk of SARS-CoV-2 RT-PCR-positive symptomatic illness (COVID-19) when compared to placebo with a relative risk reduction (RRR) of 77% (95% CI: 46-90; p<0.001), (Table 4). Estimate of the RRR (95% CI) of SARS-CoV-2 RT-PCR-positive symptomatic illness (COVID-19) compared to placebo, regardless of unblinding and/or receipt of COVID-19 preventative product was 77% (95% CI: 52-89); p<0.001. The median follow-up time from post-administration of Evusheld to primary analysis was 83 days (range 3-166 days). The absolute risk reduction was 0.75% (95% CI: 0.33%, 1.35%); p <0.001 and number needed to treat was 134 (95% CI: 75, 304).

Table 6 Incidence of COVID-19 (Full Pre-Exposure Analysis Set)

	N	Number of events[a], n (%)	Relative Risk Reduction[b], % (95% CI)	p-value
Evusheld 300 mg[c]	3441	8 (0.2%)	77 % (46 - 90)	<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. Only events that occurred prior to unblinding or vaccine receipt were included. Data cut-off, 05 May 2021.

[b] Relative Risk Reduction = 100% x (1-relative risk)

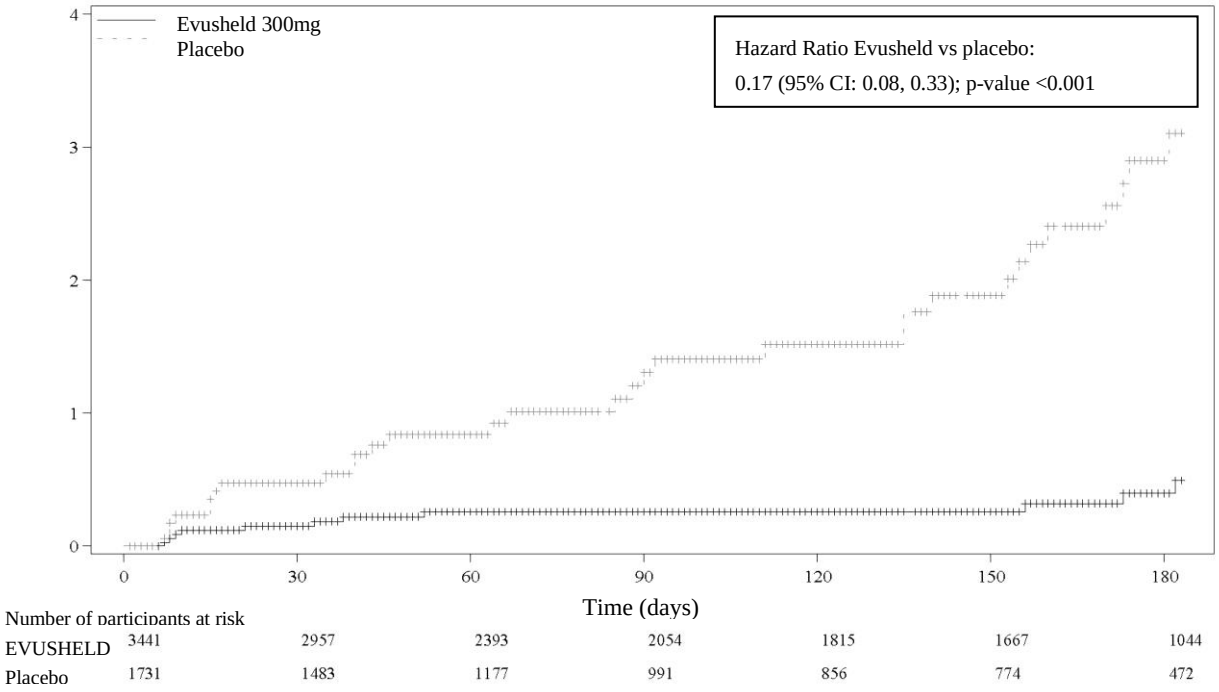
[c] 300 mg (150 mg tixagevimab and 150 mg cilgavimab).

Efficacy was consistent across pre-defined sub-groups including age, gender, ethnicity and baseline co-morbidities or characteristics associated with an increased risk for severe COVID-19.

Among participants who received Evusheld there were no severe/critical COVID-19 events compared to one event (0.1%) among participants who received placebo.

An additional data cut-off (29 August 2021) 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 (for the variants Alpha, Beta, Delta and Epsilon circulating at the time of the study). The relative risk reduction of SARS-CoV2 -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). Among participants who received Evusheld there were no severe/critical COVID-19 events compared to five events among participants who received placebo.

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



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).

Treatment of COVID-19

TACKLE is an ongoing Phase III, randomised (1:1), double-blind, placebo-controlled clinical trial studying EVUSHELD for the treatment of unvaccinated adult patients with COVID-19. The study enrolled individuals who were not hospitalised for COVID-19 treatment and had at least 1 or more COVID-19 symptom that was at least mild in severity. Treatment was initiated within 3 days of obtaining the sample for a positive SARS-CoV-2 viral infection and within ≤7 days of COVID-19 symptom onset. Patients received standard of care treatment and either 600 mg of Evusheld (300 mg of tixagevimab and 300 mg of cilgavimab) (N= 413) or placebo (N= 421), administered as two separate intramuscular injections. Participants were stratified by time from symptom onset (≤5 days versus >5 days) and risk of progression to severe COVID-19 (high risk versus low risk).

Demographics and disease characteristics were well balanced across the treatment and placebo groups. At baseline, the median age was 46 years (with 13% of subjects aged 65 years or older), 50% of the subjects were female, 62% were White, 5.6% were Asian, 4.0% were Black and 52% were Hispanic/Latino. The majority of participants (90%) were considered at higher risk of progressing severe COVID-19, defined as either individuals aged 65 years and older at randomisation or individuals aged < 65 years and having at least one medical condition or other factor that placed them at higher risk for progression to severe COVID-19. High risk co-morbidities included: obesity (BMI ≥ 30) (43%), smoking (current or former) (40%), hypertension (28%), chronic lung disease or moderate to severe asthma (12%), diabetes (12%), cardiovascular disease (including history of stroke) (9%), immunocompromised state (from solid organ transplant, blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of other immunosuppressive medicines) (5%), cancer (4%), chronic kidney disease (2%), chronic liver disease (2%), or sickle cell disease (0%).

At baseline, 88% of patients had WHO clinical progression scale of 2 and 12% had WHO clinical progression scale of 3 COVID-19, the median duration of symptoms prior to treatment was 5 days.

The primary efficacy endpoint was a composite of either severe COVID-19 or death from any cause by Day 29, in subjects who received treatment within 7 days from symptom onset and were not hospitalized (excluding for isolation purposes) at baseline. Severe COVID-19 was defined as characterised by either pneumonia (fever, cough, tachypnoea or dyspnoea, and lung infiltrates observed on chest X-ray or lung computed tomography scan) or hypoxemia (SpO_2 <90% in room air and/or severe respiratory distress) and a WHO Clinical Progression Scale score of 5 or higher. Primary endpoint events occurred in 18/407 (4.4%) of EVUSHELD-treated patients compared to 37/415 (8.9%) of patients randomised to placebo, demonstrating a statistically significant (p= 0.010) 50% (95% CI 15, 71) reduction in severe COVID-19 or death from any cause compared to placebo (Figure 2). Efficacy was generally consistent across pre-defined sub-groups.

Table 7 Incidence of severe COVID-19 or death from any cause through Day 29

	EVUSHELD [a]	**Placebo**

Non-hospitalised patients dosed ≤ 7 days from symptom onset (mFAS)		
Number of participants included in analysis	407	415
Number of events, n (%)	18 (4.4%)	37 (8.9%)
Number of severe COVID-19 events, n (%)	16 (3.9%)	37 (8.9%)
Number of deaths, n (%) [b]	2 (0.5%)	0
Relative risk reduction, % (95% CI)	50% (15, 71) p= 0.010 [c]	
All randomised participants, including hospitalised and non-hospitalised patients (FAS)		
Number of participants included in analysis	446	444
Number of events, n (%)	24 (5.4%)	41 (9.2%)
Number of severe COVID-19 events, n (%)	22 (4.9%)	41 (9.2%)
Number of deaths, n (%)	2 (0.4%)	0
Relative risk reduction, % (95% CI)	42% (5, 64) p= 0.028 [c]	

CI = Confidence Interval, mFAS= Modified full analysis set, FAS= Full analysis set.

a. 300 mg tixagevimab and 300 mg cilgavimab

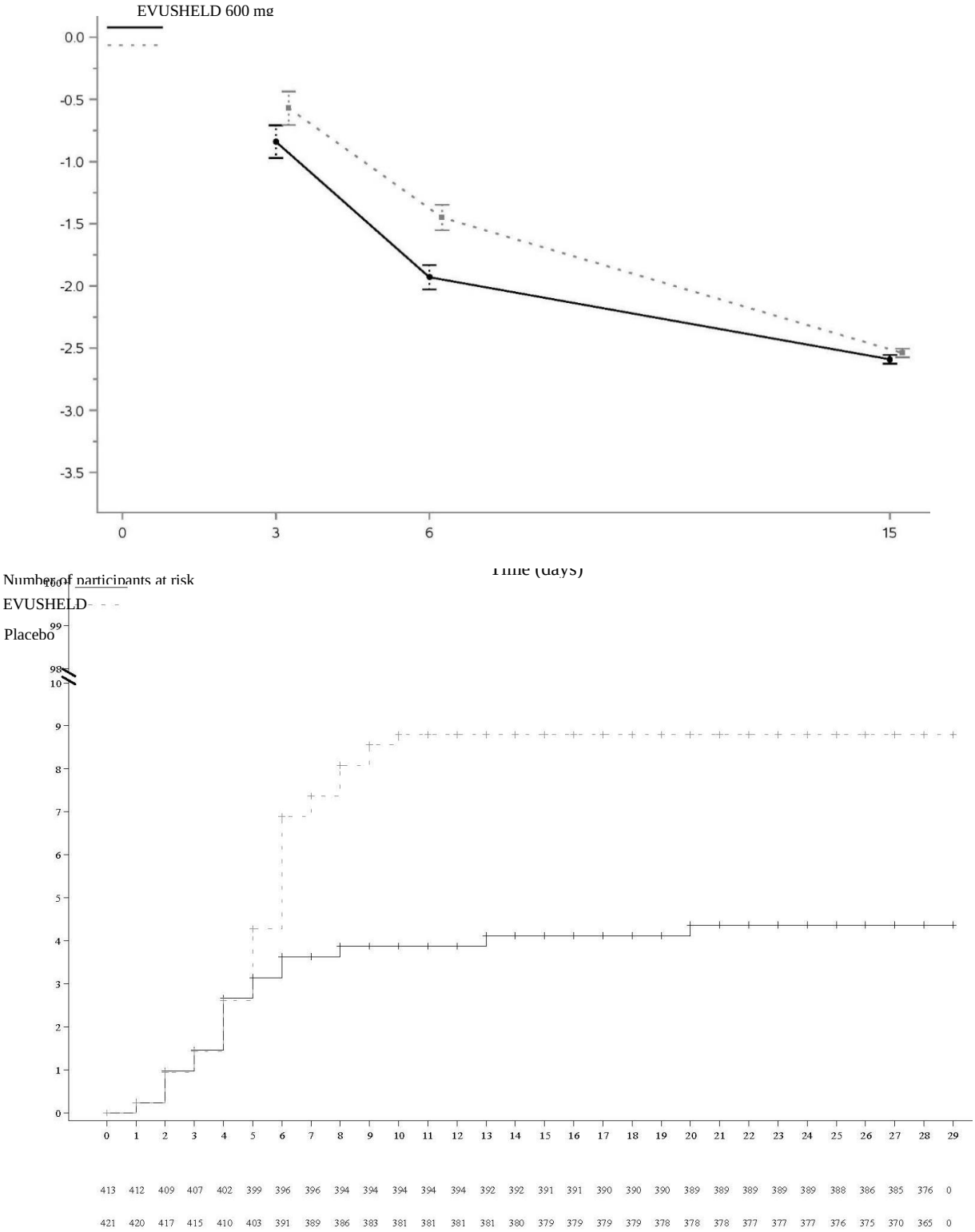
b. Participants who experience death without documented severe COVID-19.

c. Results from a CMH test stratified by time from symptom onset (≤ 5 vs. > 5 days), and risk of progression to severe COVID-19 (high vs. low).

Missing response data were not imputed.

Patients treated early in their disease course appeared to derive greater treatment benefit. The relative risk reduction of severe COVID-19 or death from any cause in patients in the mFAS who received treatment ≤ 5 days from symptom onset (early intervention analysis set) was 67% (95% CI 31, 84; p= 0.002), with 9/235 (3.6%) events in the EVUSHELD arm and 27/251 (11%) events in the placebo arm. In patients who received treatment ≤ 3 days from symptom onset (pre-specified subgroup analyses) the relative risk reduction was 88% (95% CI 9.4, 98) with 1/90 (1.1%) events in the EVUSHELD arm and 8/84 (9.5%) events in the placebo arm.

Figure 2 Kaplan Meier: Cumulative Incidence of Severe COVID-19 or Death



The change from baseline for SARS-CoV-2 RNA (Log_{10} copies/ml) from nasal swabs specimens through Day 29 is shown in Figure 3. Treatment with EVUSHELD resulted in greater reductions in viral load at Days 3 and 6, when compared to placebo.

Figure 3 LS Mean Change from Baseline Over Time (mean ± SD)

In TACKLE, baseline visit sequencing data was available for 834 participants (413 who received tixagevimab and cilgavimab and 421 placebo). At an allele fraction ≥25%, the proportion of participants infected with variants of concern or variants of interest was balanced between treatment

group, including participants with Alpha (139 who received tixagevimab and cilgavimab and 119 placebo), Beta (0 who received tixagevimab and cilgavimab and 1 placebo), Gamma (37 who received tixagevimab and cilgavimab and 46 placebo), Delta (33 who received tixagevimab and cilgavimab and 33 placebo), Lambda (11 who received tixagevimab and cilgavimab and 9 placebo), and Mu (0 who received tixagevimab and cilgavimab and 2 placebo).

There are no clinical data regarding use of Evusheld against Omicron variant.

Paediatric population

The licensing authority has deferred the obligation to submit the results of studies with Evusheld in one or more subsets of the paediatric population in the prophylaxis of COVID-19 (see section 4.2).

Conditional approval

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. New information on this medicinal product will be reviewed at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetics of tixagevimab and cilgavimab are comparable, linear and dose-proportional between 300 mg and 3000 mg following a single IV administration and 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.

In participants in the PROVENT study, based on Population PK modelling, the mean (% CV) maximum concentration (C_{max}) was 13.1 (24.6%) and 11.7 (55.8%) µg/mL for tixagevimab and cilgavimab respectively which was reached at a median T_{max} of 20 days. The estimated absolute bioavailability in this population after a single 150 mg IM dose was 62% for tixagevimab and 59% for cilgavimab.

Based on pharmacokinetic/pharmacodynamic modelling, the time to achieve the minimum protective serum concentration for the original and Delta variant (2.2 µg/mL) is estimated to be 6 hours for a typical subject following 300 mg IM administration into the gluteal region.

After a single 600 mg IM dose (300 mg of each antibody) in participants with COVID-19 in TACKLE, the mean (%CV) C_{max} was 21.9 (61.7%) and 20.3 (63.6%) µg/mL for tixagevimab and cilgavimab respectively, which were reached at a median T_{max} of 15 days.

Distribution

The mean 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.

Biotransformation/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 (tixagevimab plus cilgavimab), the mean serum concentration was 26.7 µg/mL (SD: 11.2) on Day 29. Based on population PK modelling and the strong correlation between serum concentrations and neutralising antibody titer over time for the original and Delta variant, the duration of protection following prophylactic administration of a single 300 mg dose of Evusheld is estimated to be at least 6 months.

In TACKLE, following a single 600 mg IM dose of Evusheld (tixagevimab plus cilgavimab), the geometric mean serum concentration was 42.2 µg/mL on Day 29. Based on population PK modelling serum trough concentrations 9 months after a single intramuscular dose of 600 mg dose of Evusheld, are expected to be equal to serum concentrations at Day 183 following single 300 mg of Evusheld. COVID-19 infection did not affect the clearance of tixagevimab and cilgavimab.

Special populations

Renal impairment

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.

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.

Tixagevimab and cilgavimab are expected to be catabolised by multiple tissues through proteolytic degradation into amino acids and recycling into other proteins, therefore hepatic impairment is not expected to affect the exposure of tixagevimab and cilgavimab.

Elderly patients

Of the 2,560 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. There are limited pharmacokinetic clearance data available for individuals over 85 years of age. No recommendations for dose adjustment can be made at this time.

Paediatric population

The PK of tixagevimab and cilgavimab in individuals <18 years old have not been evaluated.

Other special populations
Based on a population PK analysis, sex, age, BMI (range 21-41), weight (range 36-177 kg) race, ethnicity, cardiovascular disease, diabetes and immunocompromise had no clinically relevant effect on the PK of tixagevimab and cilgavimab.

Drug-Drug Interaction

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, vaccination following Evusheld administration has no clinically relevant impact on the clearance of Evusheld.

5.3 Preclinical safety data

Non-clinical toxicity

Non-clinical data reveal no special hazards for humans based on studies of tissue binding and a single dose toxicity study in cynomolgus monkeys including assessment of safety pharmacology and local tolerance.

In a single-dose toxicology study in cynomolgus monkeys, Evusheld administered via IV infusion of 600 mg/kg (combination of 300 mg/kg of tixagevimab and 300 mg/kg of cilgavimab) or an IM injection of 150 mg/kg (75 mg/kg of each antibody) had no adverse effects.

Reproductive toxicology

Nonclinical reproductive and developmental toxicity studies have not been conducted with tixagevimab and cilgavimab in line with international regulatory guidelines for an antibody targeting a virus.

In tissue cross reactivity studies using human fetal tissues no binding was detected.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine hydrochloride monohydrate
Sucrose
Polysorbate 80
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

18 months

Storage of syringes for intramuscular administration

The solutions for injection do not contain a preservative. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not be longer than 4 hours at 2 to 8ºC or room temperature (up to 25ºC).

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Store in the original package in order to protect from light.
Do not freeze.
Do not shake.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

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

Pack size: each carton of Evusheld contains 1 vial each of tixagevimab and cilgavimab.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited,
600 Capability Green,
Luton,
LU1 3LU,
United Kingdom.

8. MARKETING AUTHORISATION NUMBER(S)

PLGB 17901/0360

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 March 2022

10. DATE OF REVISION OF THE TEXT

15 November 2022