Report on the Deliberation Results

August 29, 2022
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Evusheld Intramuscular Injection Set
Non-proprietary Name	Tixagevimab (Genetical Recombination) (JAN*) and Cilgavimab (Genetical Recombination) (JAN*)
Applicant	AstraZeneca K.K.
Date of Application	June 9, 2022

Results of Deliberation

Under the current pandemic of disease caused by a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), the applicant has submitted an application for approval of the product on the understanding that the product is qualified for approval based on Article 14-3, Paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960, hereinafter referred to as the "Pharmaceuticals and Medical Devices Act").

In its meeting held on August 29, 2022, the Second Committee on New Drugs discussed whether the product was qualified for Special Approval for Emergency under Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. The Committee concluded that the product may be approved with the conditions listed below, and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product. The re-examination period is 8 years. Neither the drug products nor their drug substances are classified as poisonous or powerful drugs.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. In case where there is a concern that a new variant may be in circulation, the applicant is required to promptly investigate the neutralization activity of the product against the variant and submit the results of investigation to the Ministry of Health, Labour and Welfare.
3. If a variant with potentially reduced susceptibility to the product is circulating, in view of the neutralization activity of the product against the new variant and the circulation of the new variant by region, the applicant is required to take necessary actions to ensure the proper use of the product, for example, by instructing physicians to use the product in eligible patients.

**Japanese Accepted Name (modified INN)*

Report on Special Approval for Emergency

August 18, 2022
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product[1)] submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Evusheld Intramuscular Injection Set
Non-proprietary Name	Tixagevimab (Genetical Recombination) and Cilgavimab (Genetical Recombination)
Applicant	AstraZeneca K.K.
Date of Application	June 9, 2022
Dosage Form/Strength	Injection: Each vial of tixagevimab contains 150 mg of tixagevimab (genetical recombination) in 1.5 mL and each vial of cilgavimab contains 150 mg of cilgavimab (genetical recombination) in 1.5 mL.
Application Classification	Prescription drug, (1) Drug(s) with a new active ingredient
Definition	Tixagevimab is a recombinant anti-SARS-CoV-2 spike protein monoclonal antibody derived from human IgG1. In the H-chain, amino acid residues at positions 240, 241, 258, 260, 262 and 337 are substituted by Phe, Glu, Tyr, Thr, Glu and Ser, respectively. Tixagevimab is produced in Chinese hamster ovary cells. Tixagevimab is a glycoprotein (molecular weight: ca. 149,000) composed of 2 H-chains (γ1-chains) consisting of 461 amino acid residues each and 2 L-chains (κ-chains) consisting of 216 amino acid residues each. Cilgavimab is a recombinant anti-SARS-CoV-2 spike protein monoclonal antibody derived from human IgG1. In the H-chain, amino acid residues at positions 248, 249, 266, 268, 270 and 345 are substituted by Phe, Glu, Tyr, Thr, Glu and Ser, respectively. Cilgavimab is produced in Chinese hamster ovary cells. Cilgavimab is a glycoprotein (molecular weight: ca. 152,000) composed of 2 H-chains (γ1-chains) consisting of 461 amino acid

1) For the convenience of preparation of the data for submission, the applicant separately submitted applications for marketing approval of Evusheld with the indications of "Prevention of disease caused by SARS-CoV-2 infection (COVID-19)" and "Treatment of disease caused by SARS-CoV-2 infection (COVID-19)." As the result of the review, the 2 indications were collectively addressed in this report on the Special Approval for Emergency.

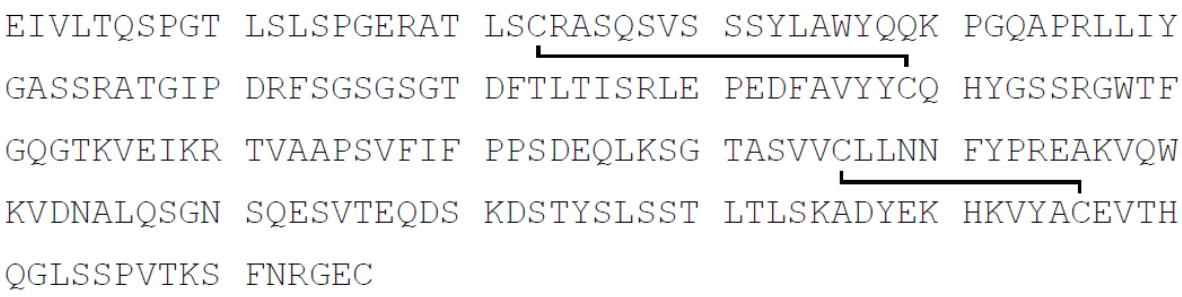
residues each and 2 L-chains (κ-chains) consisting of 219 amino acid residues each.

Structure

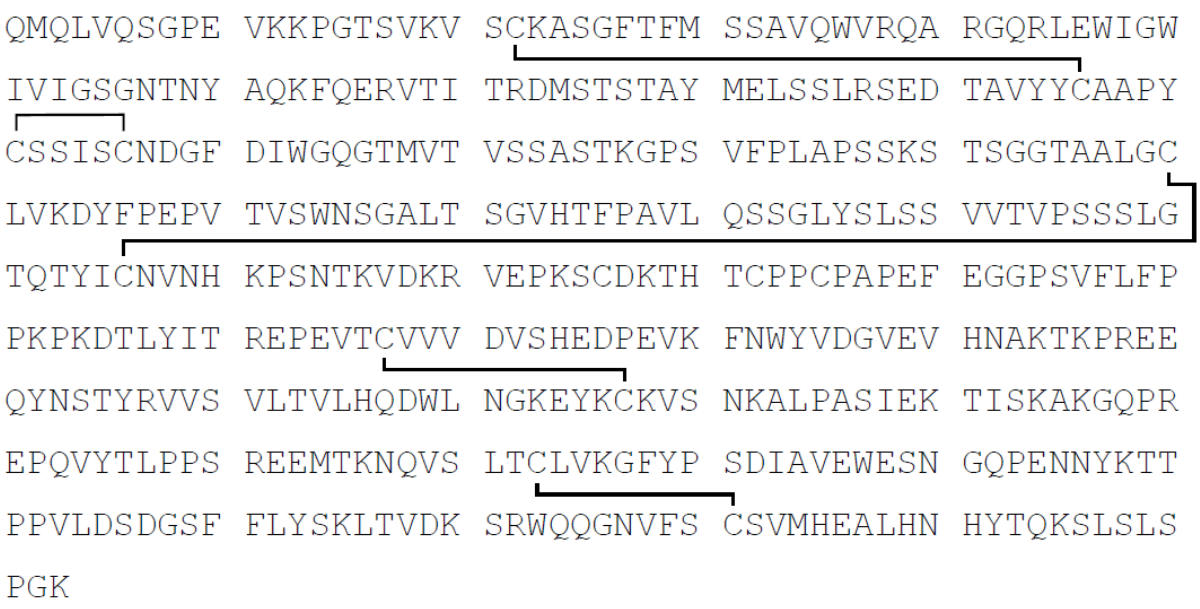
Tixagevimab (Genetical Recombination)

Amino acid sequences:

L-chain



H-chain



Intrachain disulfide bonds: Shown in solid lines.

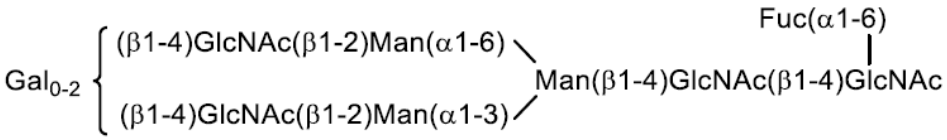
Interchain disulfide bonds: C216 (L-chain)-C226 (H-chain), C232 (H-chain)-C232 (H-chain), C235 (H-chain)-C235 (H-chain)

Pyroglutamate formation (partial): Q1 in H-chain

Glycosylation site: N303 in H-chain

Partial processing: K453 in H-chain

Putative structure of main carbohydrate chain



Gal, galactose; GlcNAc, *N*-acetylglucosamine; Man, mannose; Fuc, fucose

Molecular formula: $C_{6488}H_{10034}N_{1746}O_{2038}S_{50}$ (protein portion composed of 4 chains)
Molecular weight: Approx. 149,000

Cilgavimab (Genetical Recombination)
Amino acid sequences:

L-chain

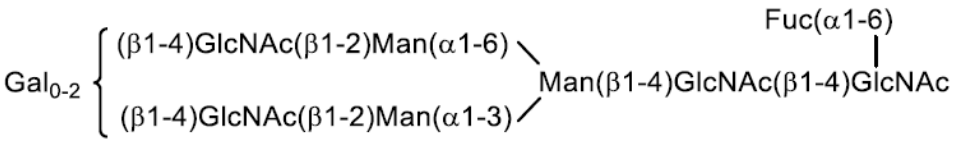
DIVMTQSPDS LAVSLGERAT INCKSSQSVL YSSNNKNYLA WYQQKPGQPP
KLLMYWASTR ESGVPDRFSG SGSGAEFTLT ISSLQAEDVA IYYCQQYYST
LTFGGGTKVE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK
VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE
VTHQGLSSPV TKSFNRGEC

H-chain

EVQLVESGGG LVKPGGSLRL SCAASGFTFR DVWMSWVRQA PGKGLEWVGR
IKSKIDGGTT DYAAPVKGRF TISRDDSKNT LYLQMNSLKT EDTAVYYCTT
AGSYYYDTVG PGLPEGKFDY WGQGTLVTVS SASTKGPSVF PLAPSSKSTS
GGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV
TVPSSSLGTQ TYICNVNHKP SNTKVDKRVE PKSCDKTHTC PPCPAPEFEG
GPSVFLFPPK PKDTLYITRE PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN
AKTKPREEQY NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK ALPASIEKTI
SKAKGQPREP QVYTLPPSRE EMTKNQVSLT CLVKGFYPSD IAVEWESNGQ
PENNYKTTPP VLDSDGSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY
TQKSLSLSPG K

Intrachain disulfide bonds: Shown in solid lines.
Interchain disulfide bonds: C219 (L-chain)-C234 (H-chain), C240 (H-chain)-C240 (H-chain), C243 (H-chain)-C243 (H-chain)
Glycosylation site: N311 in H-chain
Partial processing: K461 in H-chain

Putative structure of main carbohydrate chain



Gal, galactose; GlcNAc, *N*-acetylglucosamine; Man, mannose; Fuc, fucose

Molecular formula: $C_{6623}H_{10218}N_{1750}O_{2078}S_{44}$ (protein portion composed of 4 chains)
Molecular weight: Approx. 152,000

Items Warranting Special Mention	The product is handled as a product that requires approval from the Minister of Health, Labour and Welfare prescribed in Article 14, Paragraph 1 of the Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 1 of the Act (PSEHB/PED Notification 0608-4, dated June 8, 2022, issued by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare). Priority Review based on "Policy on regulatory review of drugs, etc. against disease caused by novel coronavirus 2019 (COVID-19) (No. 2)" (PSEHB/PED Notification No. 0617-9 and PSEHB/MDED Notification No. 0617-1, dated June 17, 2021)
Reviewing Office	Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment and prevention of disease caused by SARS-CoV-2 infection (COVID-19), and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below, with the following approval conditions.

Indications

Treatment and prevention of disease caused by SARS-CoV-2 infection (COVID-19)

Dosage and Administration

Treatment of COVID-19

The usual dosage in adults and pediatric individuals (≥12 years of age weighing ≥40 kg) is 300 mg of tixagevimab (genetical recombination) and 300 mg of cilgavimab (genetical recombination) administered as two separate sequential intramuscular injections.

Prevention of COVID-19

The usual dosage in adults and pediatric individuals (≥12 years of age weighing ≥40 kg) is 150 mg of tixagevimab (genetical recombination) and 150 mg of cilgavimab (genetical recombination) administered as two separate sequential intramuscular injections. Depending on the prevalence of circulating SARS-CoV-2 variants, 300 mg of tixagevimab (genetical recombination) and 300 mg of cilgavimab (genetical recombination) may be re-administered as two separate sequential intramuscular injections.

Approval Conditions

1. The applicant is obliged to fulfill the following duties set forth in each Item of Article 28, Paragraph 3 of the Cabinet Order for Enforcement of Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.
   (1) Matters related to Item 1
   The applicant is required to conduct a use-results survey of the product and report the result.
   (2) Matters related to Item 2
   When learning about diseases, disorders, or death suspected to be caused by the product, the applicant is required to report them promptly.
   (3) Matters related to Item 3
   The applicant is required to take necessary actions to ensure that healthcare professionals who use the product can understand, and appropriately explain to patients (or their legally acceptable representatives), that the product has been granted Special Approval for Emergency and the objectives of said approval.
   (4) Matters related to Item 4
   The applicant is required to report the quantity of the product sold or provided, as necessary.

2. The product is approved with the following conditions, based on the provisions of Article 79, Paragraph 1 of the Pharmaceuticals and Medical Devices Act:
   (1) The applicant is required to develop and appropriately implement a risk management plan.
   (2) In case where there is a concern that a new variant may be in circulation, the applicant is required to promptly investigate the neutralization activity of the product against the variant and submit the results of investigation to the Ministry of Health, Labour and Welfare.
   (3) If a variant with potentially reduced susceptibility to the product is circulating, in view of the neutralization activity of the product against the new variant and circulation of the new variant by region, the applicant is required to take necessary actions to ensure the proper use of the product, for example, by instructing physicians to use the product in eligible patients.

3. The product is approved based on Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. The approval may be withdrawn in accordance with the provision in Article 75-3 of the Act in a case where (1) the product does not conform to one or more Item of Article 14-3, Paragraph 1 of the Act or (2) the withdrawal is necessary to prevent the emergence or expansion of public health risks.

Attachment

Report on Special Approval for Emergency (1)

July 6, 2022

The following is an outline of the data submitted by the applicant[2)] and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Evusheld Intramuscular Injection Set
Non-proprietary Name	Tixagevimab (Genetical Recombination) and Cilgavimab (Genetical Recombination)
Applicant	AstraZeneca K.K.
Date of Application	June 9, 2022
Dosage Form/Strength	Injection: Each vial of tixagevimab contains 150 mg of tixagevimab (genetical recombination) in 1.5 mL and each vial of cilgavimab contains 150 mg of cilgavimab (genetical recombination) in 1.5 mL.

Proposed Indications

Treatment and prevention of disease caused by SARS-CoV-2 infection (COVID-19)

Proposed Dosage and Administration

Treatment of COVID-19

The usual dosage in adults and pediatric individuals (≥12 years of age weighing ≥40 kg) is 300 mg of tixagevimab (genetical recombination) and 300 mg of cilgavimab (genetical recombination) administered as two separate sequential intramuscular injections.

Prevention of COVID-19

The usual dosage in adults and pediatric individuals (≥12 years of age weighing ≥40 kg) is 150 mg of tixagevimab (genetical recombination) and 150 mg of cilgavimab (genetical recombination) administered as two separate sequential intramuscular injections.

2) For the convenience of preparation of the data for submission, the applicant separately submitted applications for marketing approval of Evusheld with the indications of "Prevention of disease caused by SARS-CoV-2 infection (COVID-19)" and "Treatment of disease caused by SARS-CoV-2 infection (COVID-19)." As the result of the review, the 2 indications were collectively addressed in this report on the Special Approval for Emergency.

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List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Coronavirus disease 2019 (COVID-19) is a disease caused by SARS-CoV-2 infection. The most common symptoms at the onset of the disease are fever, respiratory symptoms, malaise, headache, gastrointestinal symptom, nasal discharge, taste abnormality, dysosmia, arthralgia, and myalgia in the descending order. In contrast, people infected with the Omicron variant experienced common-cold-like symptoms such as nasal discharge, headache, malaise, and pharyngodynia more frequently while having olfaction dysfunction and taste disorder less frequently, compared with those infected with the preceding variants (*Guidelines for Diagnosis and Treatment of COVID-19*, ver. 7.2., May 9, 2022). In Japan, as of July 5, 2022, a total of 9,398,984 people have been confirmed to have infection with SARS-CoV-2 (those who tested positive on a polymerase chain reaction [PCR] test). Of them, 177,200 are in hospital (including 60 with severe COVID-19), and 9,175,603 were discharged from hospital or released from isolation, with a death toll of 31,324.[3)]

Tixagevimab (Genetical Recombination; hereinafter referred to as "tixagevimab") and Cilgavimab (Genetical Recombination; hereinafter referred to as "cilgavimab"), the two components of Evusheld, which were both discovered by AstraZeneca PLC in the United Kingdom (UK), are recombinant human monoclonal immunoglobulin G (IgG)1 antibodies targeting the receptor binding domain (RBD) of SARS-CoV-2 spike protein (S-protein). The two monoclonal antibodies bind non-overlapping epitopes on the RBD and block the binding of RBD to angiotensin converting enzyme 2 (ACE2), thereby preventing the entry of SARS-CoV-2 into host cells.

In response to the Emergency Use Authorization for pre-exposure prophylaxis of COVID-19 granted to Evusheld by the Food and Drug Administration (FDA) in the United States (US) and based on the results from a foreign phase III study in individuals who had an increased risk for inadequate response to SARS-CoV-2 vaccines or were intolerant of vaccine or who had an increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 (PROVENT study), and from a global phase III study (TACKLE study), the applicant submitted an application for Special Approval for Emergency of Evusheld Intramuscular Injection Set (hereinafter referred to as "Evusheld") for the treatment and prevention of disease caused by SARS-CoV-2 infection, on the understanding that Evusheld is qualified for approval under Article 14, Paragraph 1 of the Pharmaceuticals and Medical Devices Act, pursuant to Article 14-3, Paragraph 1 of the Act. Evusheld consists of two monoclonal antibodies that bind non-overlapping epitopes on the RBD of SARS-CoV-2 S-protein, and both antibodies must be co-administered. Given that Evusheld is qualified as an application for Special Approval for Emergency, the applicant submitted an application for approval of the two monoclonal antibody preparations as a single product, in order to ensure that the 2 components are distributed in a single package. This report contains the results of the review conducted based on the data submitted by the applicant, in accordance with the "Handling of drugs intended to be submitted for Special Approval for Emergency (Request)" (PSEHB/PED Notification 0608-4, dated June 8, 2022).

3) Ministry of Health, Labour and Welfare: https://www.mhlw.go.jp/stf/covid-19/kokunainohasseijoukyou.html (last accessed on July 5, 2022)

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substances

2.1.1 Generation and control of cell substrates

Memory B-cells from donors previously infected with SARS-CoV-2[4)] were screened for a single B-cell producing an antibody that binds to the S-protein of SARS-CoV-2. Two lead antibodies were selected from antibodies produced by the identified B-cells on the basis of their binding capacities to SARS-CoV-2 S-protein and ACE2-specific RBD as well as SARS-CoV-2 neutralization assay (*Science.* 2020;367:1260-3). The gene sequences for the heavy and light chains (H- and L-chains, respectively) of each of the lead antibodies were inserted into expression vectors to obtain the gene expression constructs of tixagevimab and cilgavimab. The Fc region is modified by inserting YTE substitutions (M252Y, S254T, and T256E) for extended plasma half-life and TM substitutions (L324F, L235E, and P331S) for reduced binding capacity to Fc gamma receptor (FcγR) and complement component 1q (C1q). These gene expression constructs were then introduced separately into different CHO cells. Optimal clones for manufacturing tixagevimab and cilgavimab drug substances were selected from the transfected CHO cells to establish master cell banks (MCBs) and working cell banks (WCBs) for tixagevimab and cilgavimab.

MCBs, WCBs, end of production cell banks (EOPCBs), and limit of *in vitro* cell age (LIVCA) of tixagevimab and cilgavimab were subjected to characterization and purity test according to the ICH Q5A (R1), Q5B, and Q5D Guidelines. Results confirmed the genetic stability of both tixagevimab and cilgavimab during the manufacturing. None of the tests performed detected viral or nonviral adventitious agents, except endogenous retrovirus-like particles commonly observed in cell lines of rodent origin.

MCBs and WCBs are stored in [redacted]. MCBs [redacted], and WCBs [redacted].

2.1.2 Manufacturing process

The manufacturing processes for tixagevimab and cilgavimab drug substances consist of the following steps: cell thawing, expansion culture, production culture, harvesting, [redacted] chromatography, low pH viral inactivation, anion exchange chromatography, cation exchange chromatography, virus removal filtration, [redacted], [redacted], filling, storage, and testing.

[redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] were identified as critical steps for both drug substances. In addition, [redacted] is controlled as a critical intermediate.

The manufacturing processes for both tixagevimab and cilgavimab drug substances were subjected to process validation at a commercial scale.

4) The viral strain was not identified.

2.1.3 Safety evaluation of adventitious agents

No raw materials of biological origin except CHO cells as the host cells, are used in the manufacturing processes for tixagevimab and cilgavimab drug substances.

Purity tests were performed on the MCBs, WCBs, EOPCBs, and LIVCA of tixagevimab and cilgavimab [see Section 2.1.1]. The pre-harvest unprocessed bulk at a commercial scale was tested for bioburden, mycoplasma, and *in vitro* viruses, and subjected to transmission electron microscopy. None of the tests performed detected contamination with either viral or nonviral adventitious agents. All the tests on the pre-harvest unprocessed bulk except for transmission electron microscopy are in-process control tests.

Viral clearance studies using model viruses were performed to assess the purification process. The studies showed a certain viral clearance capacity of the purification process (Table 1).

Table 1. Results of viral clearance studies

Manufacturing process	Viral reduction factor (log10)							
	Tixagevimab drug substance				Cilgavimab drug substance			
	Xenotropic murine leukemia virus	Pseudorabies virus	Reovirus type 3	Minute virus of mice	Xenotropic murine leukemia virus	Pseudorabies virus	Reovirus type 3	Minute virus of mice
Low pH viral inactivation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anion exchange chromatography	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cation exchange chromatography	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Virus removal filtration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total viral reduction factor	>18.30	>16.74	9.21	>8.94	>20.49	>16.82	>10.49	>8.68

[redacted] for the virus removal filtration.

The applicant's explanation: When [redacted], [redacted] for [redacted], [redacted] and [redacted] are [redacted] in the manufacturing process for tixagevimab drug substance and [redacted] in the manufacturing process for cilgavimab drug substance.

2.1.4 Manufacturing process development

Several changes were made to the manufacturing process during the development of tixagevimab and cilgavimab drug substances (Process 1, Process 2, Process 3 and proposed commercial process). Major changes are shown below. Non-clinical studies used drug products formulated with the drug substances manufactured by Process 1, foreign phase I study (Study D8850C00001) and foreign phase III study (STORM CHASER study) used ones with the drug substances manufactured by Process 2, foreign phase III study (PROVENT study) used ones with the drug substances manufactured by Process 2 or Process 3, and Japanese phase I study (Study D8850C00005) and global phase III study (TACKLE study) used ones with the drug substances manufactured by Process 3.

- Process 1 → Process 2: Changes of [redacted], [redacted], formulation, [redacted], and [redacted]
- Process 2 → Process 3: Introduction of [redacted] and [redacted], and [redacted]
- Process 3 → proposed commercial process: Changes of [redacted], [redacted], and [redacted]

When the above process changes were made, the quality attributes of the pre- and post-change drug substances were evaluated and shown to be comparable.

2.1.5 Characterization

2.1.5.1 Structure and characteristics

Tixagevimab and cilgavimab were subjected to characterization tests described in Table 2.

Table 2. Parameters evaluated in characterization of tixagevimab and cilgavimab drug substances

Primary structure/ higher order structure	Amino acid sequence, posttranslational modification (, oxidation, deamidation, , pyroglutamylation of N-terminal glutamic acid residue, C-terminal lysine clipping,), disulfide bonds, free thiol groups, secondary structure, tertiary structure
Physicochemical properties	Molecular weight, , size variant, charge variant,
Carbohydrate structure	N-linked glycosylation profile
Biological properties	Binding activity to SARS-CoV-2 S-protein
	Binding affinity for FcγRIIIa, binding activity to FcRn
	SARS-CoV-2 neutralization activity, pseudotyped virus neutralization activity

Biological properties were investigated as described below.

- Binding activity to SARS-CoV-2 S-protein was determined by .
- Binding affinity for FcγRIIIa was determined by , and binding activity to neonatal Fc receptor (FcRn) was determined by .
- SARS-CoV-2 neutralization activity was determined based on viral infection in cells incubated with tixagevimab or cilgavimab and SARS-CoV-2 (GenBank MT020880.1).
- Pseudotyped virus neutralization activity was determined by using S-protein-expressing lentivirus particles (pseudotyped virus-like particles) and ACE2-overexpressing cells.

2.1.5.2 Product-related substances/product-related impurities

Based on the results of characterization presented in Section 2.1.5.1, , , , , , (except for), , and were identified as product-related substances. For tixagevimab, molecular species with oxidation in the variable region (, , and) were also identified as product-related substances. In addition, high-molecular-weight species, low-molecular-weight species, Impurity A, oxidized forms (Impurity B of tixagevimab and Impurity C of cilgavimab) as well as foreign insoluble matters and insoluble particulate matters were identified as product-related impurities. For cilgavimab, Impurity D was also identified as a product-related impurity. Among the product-related impurities, and are controlled by the specifications for the drug substances and drug products, and foreign insoluble matters and insoluble particulate matters by the specifications for the drug products. Impurity A, oxidized forms, and Impurity D are not subject to routine control because their contents have been consistently low in the past manufacturing experience.

2.1.5.3 Process-related impurities

For both tixagevimab and cilgavimab, host cell deoxyribonucleic acid (DNA), host cell protein (HCP), protein A, Impurity E, Impurity F, Impurity G, Impurity H, Impurity I, and Impurity J were identified as process-related impurities. Host cell DNA, HCP, [redacted], and Impurity E have been demonstrated to be adequately removed by the manufacturing process. Impurity F, Impurity G, Impurity H, Impurity I and Impurity J were subjected to risk assessment and considered to pose only a low risk. Host cell DNA, HCP, and [redacted] are controlled by the specifications for the drug substances.

2.1.6 Control of drug substance

The proposed specifications for tixagevimab and cilgavimab drug substances include content, description, identification (peptide mapping), pH, purity (capillary gel electrophoresis-sodium dodecyl sulfate [CE-SDS] [redacted], high performance size exclusion chromatography [HPSEC]), capillary isoelectric focusing (cIEF), host cell DNA, HCP, [redacted], bacterial endotoxins, microbial limits, biological activity (enzyme-linked immunosorbent assay [ELISA]), [redacted], and assay (ultraviolet visible spectroscopy) [see Sections 2.R.1 and 2.R.2].

2.1.7 Stability of drug substances

Table 3 shows the main stability studies on tixagevimab and cilgavimab drug substances.

Table 3. Summary of the main stability studies on tixagevimab and cilgavimab drug substances

Study type	Number of batches[a)]	Storage condition	Study duration	Storage package
Long-term	6	[redacted]°C	12 months[b)]	[redacted]
Accelerated	6	[redacted]°C/[redacted]%RH	6 months	[redacted] bag
Stress	6	[redacted]°C/[redacted]%RH	3 months	[redacted] bottle

Tixagevimab and cilgavimab drug substances were subjected to the same stability studies.
a) Drug substance manufactured by the proposed commercial process
b) The stability studies (ongoing) are continued for up to [redacted] months.

The long-term study of tixagevimab drug substance showed no clear changes in quality attributes throughout the study period. The long-term study of cilgavimab drug substance showed a trend toward a decrease in [redacted] in [redacted] and a trend toward an increase in [redacted].

The accelerated study of tixagevimab drug substance showed a trend toward a decrease in [redacted] in [redacted], a trend toward a decrease in [redacted] and a trend toward an increase in [redacted] in [redacted], as well as a decrease in [redacted] and an increase in [redacted] in [redacted]. The stress study showed a trend toward a decrease in [redacted], in addition to changes observed in the accelerated study.

The accelerated study of cilgavimab drug substance showed a trend toward a decreasing in [redacted] in [redacted], a trend toward a decrease in [redacted] and a trend toward an increase in [redacted] in [redacted], as well as a trend toward a decrease in [redacted] and a trend toward an increase in [redacted] in [redacted]. The stress study showed a decrease in [redacted], in addition to changes observed in the accelerated study.

The applicant has proposed a shelf life of 12 months for tixagevimab and cilgavimab drug substances when stored in a [redacted] bag at [redacted] to [redacted]°C.

2.2 Drug products

2.2.1 Description and composition of drug products and formulation development

Tixagevimab drug product is supplied in a glass vial (13.5 mL) containing tixagevimab 150 mg per 1.5 mL of solution (aqueous injection), and cilgavimab durg product supplied in a glass vial (13.5 mL) containing cilgavimab 150 mg per 1.5 mL of solution (aqueous injection). Both vials are co-packaged in a carton. Both tixagevimab and cilgavimab drug products contain the following excipients: L-histidine, L-histidine monohydrochloride monohydrate, sucrose, polysorbate 80, and water for injection.

2.2.2 Manufacturing process

Manufacturing processes for both tixagevimab and cilgavimab drug products consist of [redacted], bioburden reduction filtration/storage, mixing, sterile filtration, aseptic filling/stoppering/capping, visual inspection, and storage/testing. The tixagevimab drug product and cilgavimab drug product are co-packaged in the same carton during the labeling/packaging/storage/testing step to produce Evusheld.

[redacted] and [redacted] steps in the manufacturing processes of both tixagevimab and cilgavimab drug products were identified as critical steps.

The manufacturing processes were subjected to process validation at a commercial scale.

2.2.3 Manufacturing process development

Several changes were made to the manufacturing process during the development for tixagevimab and cilgavimab drug products. Major changes are as shown below (Process I, Process II, and proposed commercial process). The foreign phase I study (Study D8850C00001) used the drug products manufactured by Process I, and the Japanese phase I study (Study D8850C00005), foreign phase III study (PROVENT study), foreign phase III study (STORM CHASER study), and global phase III study (TACKLE study) used ones manufactured by Process II.

- Process I → Process II: Change from lyophilized powder to liquid form and Changes of [redacted] and [redacted]
- Process II → proposed commercial process: Changes of [redacted], [redacted], and [redacted]

When the above process changes were made, the quality attributes of the pre- and post-change drug products were evaluated and shown to be comparable.

2.2.4 Control of drug products

The proposed specifications for tixagevimab and cilgavimab drug products include strength, description, identification (lateral flow method), osmolality, pH, purity (CE-SDS [redacted], HPSEC), cIEF, bacterial endotoxins, extractable volume, foreign insoluble matters, insoluble particulate matters, sterility, biological activity (ELISA), and assay (ultraviolet visible spectroscopy) [see Sections 2.R.1 and 2.R.2].

2.2.5 Stability of drug products

Table 4 shows the main stability studies for the drug products.

Table 4. Summary of the main stability studies on tixagevimab and cilgavimab drug products

Study type	Number of batches	Storage condition	Study duration	Storage package
Long-term	3[a)]	5 ± 3°C	12 months[c)]	Glass vial with an ETFE-laminated chlorobutyl rubber stopper
	3[b)]		18 months[d)]	
Accelerated	3[a)]	25 ± 2°C/60 ± 5%RH	6 months	
Stress	3[a)]	40 ± 2°C/75 ± 5%RH	3 months	

Tixagevimab and cilgavimab drug products were subjected to the same stability studies.

a) Drug product manufactured by the proposed commercial process, using the drug substance manufactured by the proposed commercial process
b) Drug product manufactured by Process II, using the drug substance manufactured by Process 1 or Process 2
c) The stability studies (ongoing) are continued for up to [redacted] months.
d) The stability studies (ongoing) are continued for up to [redacted] months.

The long-term studies showed no clear changes in the quality attributes of either drug product throughout the study period.

The accelerated study of tixagevimab drug product showed a trend toward a decrease in [redacted], a trend toward a decrease in [redacted] and a trend toward in an increase in [redacted] in [redacted], and a trend toward a decrease in [redacted] and a trend toward an increase in [redacted] in [redacted]. These changes were greater in the stress study.

The accelerated study of cilgavimab drug product showed a trend toward a decrease in [redacted], a trend toward a decrease in [redacted] and a trend toward an increase in [redacted] in [redacted], a trend toward a decrease in [redacted] and a trend toward an increase in [redacted] in [redacted], and a trend toward a decrease in [redacted]. These changes were greater in the stress study.

The photostability study showed that both tixagevimab and cilgavimab drug products were [redacted].

The applicant has proposed a shelf life of 18 months for the drug products when stored at 2°C to 8°C in a glass vial with an ethylenetetrafluoroethylene (ETFE)-laminated chlorobutyl rubber stopper (primary packaging container), placed in a carton, and protected from light.

2.3 Control strategy of quality

Based on the following investigations, a quality control strategy was developed by combining control of process parameters, in-process controls, and specifications [for control of product-related impurities and process-related impurities, see Sections 2.1.5.2 and 2.1.5.3].

- Identification of critical quality attributes (CQAs):

  The following CQAs were identified based on information obtained during the development of tixagevimab and cilgavimab and related findings.

  For both tixagevimab and cilgavimab drug substances: High-molecular-weight species, Impurity A, truncated form, higher order structure, foreign insoluble matters, insoluble particulate matters, primary structure, host cell DNA, HCP, [redacted], color, clarity, pH, content, [redacted], osmolality, extractable volume, container integrity, bioburden, sterility, bacterial endotoxins, viral safety, mycoplasma, identification, biological activity, and FcRn binding affinity

  Tixagevimab drug substance only: Impurity B

  Cilgavimab drug substance only: Impurity D and Impurity C in its oxidized form

- Characterization of process
  Based on risk assessment on each process parameter and characterization of the process,
  - process parameters with a critical impact on critical process parameters (CQAs) were identified, and
  - operational control ranges of the process parameters including the identified ones were investigated.

2.R Outline of the review conducted by PMDA

Because of the short development period of Evusheld, some data pointed out below are lacking. Nevertheless, based on the submitted data and the following review, PMDA concluded that the quality of the drug substances and the drug products was adequately controlled.

2.R.1 Control of biological activity

When bound to the RBD of SARS-CoV-2 S-protein recognizing ACE2 as a receptor, tixagevimab and cilgavimab inhibit SARS-CoV-2 from binding to ACE2, thereby preventing viral infection. Their neutralization activity against SARS-CoV-2 is thus a critical quality attribute of Evusheld. Considering that [redacted] with tixagevimab and cilgavimab would be critical factors in the mechanism of action, the applicant included [redacted] in the specifications for the drug substances and drug products and claimed that measurement of the neutralization activity was unnecessary. PMDA asked the applicant to consider performing a test for measuring SARS-CoV-2 or pseudotyped virus neutralization activity to reflect the mechanism of action of tixagevimab and cilgavimab more extensively, because [redacted] is a test evaluating only a part of the upstream process of the mechanism by which tixagevimab and cilgavimab inhibit infection with SARS-CoV-2.

The applicant's response:

They will include [redacted] in the specifications for the drug substances and drug products when the test system is established and qualified as the specifications.

PMDA's view:

Given the mechanism of action of tixagevimab and cilgavimab, a test for biological activity should have been able to measure viral neutralization activity. However, the applicant's policy for the test for biological activity of Evusheld is acceptable, because (i) Evusheld is a drug urgently needed by healthcare professionals; (ii) the applicant's quality control strategy has ensured that products with consistent quality are manufactured consistently; and (iii) the biological activity will be controlled by evaluating [redacted] until the test on neutralization activity is established.

2.R.2 Acceptance limits in specifications

Acceptance limits in the specifications for the drug substances and drug products were defined based on the limited manufacturing experience and stability data available at the time of submission. PMDA therefore requested the applicant to review the specifications [redacted] in the future and submit a partial change application where necessary.

The applicant responded that they would take appropriate actions, and PMDA accepted.

2.R.3 Novel excipients

The drug products contain L-histidine monohydrochloride monohydrate and sucrose (excipients) in amounts exceeding those present in the existing intramuscular formulations.

2.R.3.1 Specifications and stability

L-histidine monohydrochloride monohydrate and sucrose conform to the Japanese Pharmacopoeia. PMDA thus concluded the specifications and stability had no problems.

2.R.3.2 Safety

The applicant's explanation:

- L-histidine monohydrochloride monohydrate

Use of this excipient in an amount exceeding those used previously is unlikely to raise a safety concern based on the following aspects: (i) for its systemic effect, the maximum daily dose of L-histidine monohydrochloride monohydrate (6 mg for each drug product) used for intramuscular administration of Evusheld at the maximum clinical dose (tixagevimab 300 mg and cilgavimab 300 mg) is smaller than the amount of this pharmaceutical excipient (50 mg) used for intravenous administration of the existing formulations; and (ii) for its local effect at the intramuscular administration site, no findings suggestive of local tolerance of the excipient were observed at the administration site of cynomolgus monkeys in a single-dose systemic toxicity study of Evusheld [see Section 5.1].

- Sucrose

Use of this excipient in an amount exceeding those used previously is unlikely to raise a safety concern based on the following aspects: (i) for its systemic effect, the maximum daily dose of sucrose (246.4 mg for each drug product) used for intramuscular administration of Evusheld at the maximum clinical dose (tixagevimab 300 mg and cilgavimab 300 mg) is smaller than the amount of this pharmaceutical excipient (39,840 mg) used for intravenous administration of the existing formulations; and (ii) for its local effect at the intramuscular administration site, no findings suggestive of local tolerance of the excipient were observed at the administration site of cynomolgus monkeys in a single-dose systemic toxicity study of Evusheld [see Section 5.1].

PMDA's view:

In view of the above results of the study, L-histidine monohydrochloride monohydrate 6 mg and sucrose 246.4 mg contained in Evusheld administered intramuscularly are unlikely to raise a safety concern.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The applicant submitted non-clinical pharmacological data of tixagevimab and cilgavimab, in the form of results from primary pharmacodynamic and secondary pharmacodynamic studies. In addition to tixagevimab and cilgavimab, antibodies listed in Table 5 were used in these non-clinical pharmacology studies. Unless otherwise specified, doses for the combination of tixagevimab and cilgavimab and the

combination of other antibodies listed in Table 5 are expressed as the total amount of two antibodies at the molar ratio of 1:1. In this section, values are expressed as means.

Table 5. Antibodies used in non-clinical pharmacology studies

COV2-2196	Parental antibody of tixagevimab
COV2-2130	Parental antibody of cilgavimab
Tixagevimab-TM Cilgavimab-TM	Antibodies engineered to have the Fab region unchanged from that of tixagevimab or cilgavimab and the Fc region with TM substitutions (L234F, L235E, and P331S)[a)], but without YTE substitutions (M252Y, S254T, and T256E)[b)]
Tixagevimab-YTE Cilgavimab-YTE	Antibodies engineered to have the Fab region unchanged from that of tixagevimab or cilgavimab and the Fc region with YTE substitutions (M252Y, S254T, and T256E)[b)], but without TM substitutions (L234F, L235E, and P331S)[a)]
Tixagevimab-WT Cilgavimab-WT	Antibodies having unaltered Fab and Fc regions[c)]

a) This mutation is expected to decrease binding of the antibody to FcγR and C1q, thereby reducing the effector function (*Acta Crystallogr D Biol Crystallogr*. 2008;64:700-4).
b) This mutation is expected to increase antibody's binding affinity to FcRn at endosomal pH to enhance recycle of the antibody, thereby extending the plasma half-life (*Antimicrob agents chemother.* 2013;57:6147-53)
c) These antibodies are different from the parental antibodies COV2-2196 and COV2-2130 (generated at Vanderbilt University) because they are expressed using AstraZeneca's plasmid.

3.1 Primary pharmacodynamics

3.1.1 Binding characteristics to SARS-CoV-2

3.1.1.1 Binding affinity to S-protein and RBD as well as inhibition of RBD binding to ACE2 (CTD P 4.2.1.1.1)

Binding affinity of tixagevimab and cilgavimab to S-protein (trimer) and RBD was investigated by surface plasmon resonance (SPR) and ELISA. Table 6 shows the results.

Table 6. Binding affinity to S-protein and RBD of SARS-CoV-2

	SPR Equilibrium dissociation constant (K_D) (pmol/L)		ELISA EC_{50} (ng/mL)	
	S-protein (trimer)	RBD	S-protein (trimer)	RBD
Tixagevimab	2.76	2150	3.93	5.97
Cilgavimab	13.0	2180	5.17	15.0
Tixagevimab and cilgavimab	13.7	-	-	-

-: No results are available.

Tixagevimab- and cilgavimab-mediated inhibition of RBD binding to ACE2 was investigated by ELISA. Tixagevimab and cilgavimab (alone and in combination) inhibited RBD binding to ACE2 in a concentration-dependent manner, with 50% inhibitory concentrations (IC_{50}) being 318 pmol/L for tixagevimab, 531 pmol/L for cilgavimab, and 433 pmol/L for the combination of tixagevimab and cilgavimab.

3.1.1.2 Competition for binding to RBD and epitope mapping (CTD P 4.2.1.1.2, 4.2.1.1.12, reference CTD P 4.3, *Nature.* 2020;584:443-9)

Biolayer interferometry assay showed that tixagevimab and cilgavimab do not compete each other for binding to RBD. In addition, crystal structure analysis using cryoelectron microscope revealed that COV2-2196 and COV2-2130 simultaneously bound to RBD through their Fab regions.

The structure of a complex of the Fab region of tixagevimab or cilgavimab and the RBD was determined by X-ray crystallography to investigate epitopes. Table 7 shows the results. Tixagevimab and cilgavimab

both bind to the RBD residues E484 and Q493, but the antibodies interact with different atoms of these amino acid residues and thus do not share any of their points of contact with the RBD. In addition, the RBD sites bound by tixagevimab and cilgavimab were shown to overlap with the RBD sites involved in binding to ACE2.

Table 7. Interacting amino acid residues[a)] in binding of tixagevimab and cilgavimab to RBD

	Amino acid residues of RBD	Amino acid residues of antibody	
		H-chain	L-chain
Tixagevimab	A475	C106	-
	S477	D108	-
	T478	D108	-
	V483	-	Y33
	G485	W50	-
	F486	W50, P99, F110	Y33, Y92, W98
	N487	N107, D108	-
	Y489	V52	-
	Q493	S55	-
Cilgavimab	R346	D56, Y106	-
	S443	P111	-
	K444	Y104, Y105, Y106, D107, V109	-
	V445	Y104	-
	G446	-	Y55
	Y449	-	N34, K36
	N450	Y105	-
	E484	-	S32
	Q493	-	S33

-: Not applicable

a) Of RBD sites bound by tixagevimab and cilgavimab, amino acid residues that are shown to have biochemical interactions (hydrogen bond, π–π stacking) are only listed. In addition, the RBD amino acid residues that have at least 1 atom within a 5Å-radius from any of the Fab regions of tixagevimab and cilgavimab are as follows: L455, F456, K458, A475, G476, S477, T478, P479, C480, V483, E484, G485, F486, N487, C488, Y489, and Q493 of tixagevimab; and T345, R346, N439, N440, L441, S443, K444, V445, G446, G447, Y449, N450, L452, E484, F490, L492, Q493, S494, and P499 of cilgavimab).

Sequence conservation of RBD sites[5)] bound by tixagevimab and cilgavimab was investigated based on SARS-CoV-2 whole-genome consensus sequences (1,413,790 sequences; February 1 to April 30, 2022) obtained from the database of the Global Initiative on Sharing Avian Influenza Data (GISAID database). Of 17 amino acid residues of RBD bound by tixagevimab, 4 (S477 [4.50%], T478 [4.42%], E484 [4.49%], and Q493 [5.47%]) were shown to be conserved in <99% of the SARS-CoV-2 genome sequences, and of 19 RBD residues bound by cilgavimab, 6 (R346 [72.14%], N440 [13.90%], G446 [65.25%], L452 [98.95%], E484 [4.49%], and Q493 [5.47%]) were shown to be conserved in <99% of the SARS-CoV-2 genome sequences.

3.1.2 Effects of YTE and TM substitutions in Fc region (CTD P 4.2.1.1.5)

Tixagevimab and cilgavimab have the H-chain CH2 domain in the constant region or Fc region modified with YTE substitutions[6)] and TM substitutions.[7)]

Effects of YTE substitutions on the binding affinity of tixagevimab and cilgavimab to FcRn were investigated by SPR. At low pH (6.0), corresponding to cellular endosomal pH, tixagevimab and

5) Amino acid residues of RBD that have at least 1 atom within a 5Å-radius from any of the Fab regions of tixagevimab and cilgavimab

6) This mutation is expected to increase antibody's binding affinity to FcRn at endosomal pH to enhance recycle of the antibody, thereby extending the plasma half-life (*Antimicrobial agents and chemotherapy.* 2013;57:6147-53)

7) This mutation is expected to decrease binding of the antibody to FcγR and C1q, thereby reducing the effector function (*Acta Crystallogr D Biol Crystallogr*. 2008;64:700-4).

cilgavimab showed 5.8 to 8.8 times higher binding affinity to human and cynomolgus monkey FcRn than tixagevimab-TM and cilgavimab-TM. At neutral pH (7.4), none of the antibodies bound to FcRn.

Effects of TM substitutions on the binding affinity of tixagevimab and cilgavimab to FcγR and C1q were investigated by SPR. Tixagevimab and cilgavimab, compared with tixagevimab-WT and cilgavimab-WT, showed low or no binding affinity to FcγR and C1q (human FcγRI, human FcγRIIa, human FcγRIIIa [low affinity F158 variant and high affinity V158 variant], cynomolgus monkey FcγRI, mouse FcγRI, mouse FcγRIV, and human C1q).

3.1.3 *In vitro* antiviral activity

3.1.3.1 Neutralization activity against SARS-CoV-2 (CTD P 4.2.1.1.3)

SARS-CoV-2 (USA-WA1/2020 isolate) was treated with tixagevimab and cilgavimab (alone and in combination) followed by 24-hour incubation with Vero E6 cells, and their neutralization activity was determined by staining SARS-CoV-2 nucleocapsid in cells indicative of viral infection. pseudotyped virus-like particles[8)] expressing S-protein were treated with tixagevimab and cilgavimab (alone and in combination) followed by 48-hour incubation with Ad293-hACE2 cells, and their neutralization activity was determined by luciferase reporter assay that detected cells infected with the virus. Concentration-dependent neutralization profiles were obtained by both assays, and Table 8 shows the EC_{50} values.

Table 8. Neutralization activity of tixagevimab and cilgavimab against SARS-CoV-2 (EC_{50} [ng/mL])

	SARS-CoV-2 (USA-WA1/2020 isolate)	Pseudotyped virus-like particles	
		Wild-type [a)]	D614G variant
Tixagevimab	9	1.3	0.3
Cilgavimab	32	4.7	1.7
Tixagevimab and cilgavimab	10	5.6	0.7

a) Carrying SARS-CoV-2 (USA-WA1/2020 isolate) S-protein gene

Effects of YTE or TM substitutions on neutralization activity of tixagevimab and cilgavimab were investigated using virus-like particles pseudotyped with SARS-CoV-2 S-protein (USA-WA1/2020 isolate). Table 9 shows the results, and there was no clear difference in neutralization activity regardless of with or without YTE or TM substitutions.

Table 9. Effects of YTE or TM substitutions on neutralization activity

Antibody	EC_{50} (ng/mL)	Antibody	EC_{50} (ng/mL)
Tixagevimab	0.3	Cilgavimab	5.1
Tixagevimab-WT	0.8	Cilgavimab-WT	5.0
Tixagevimab-TM	0.3	Cilgavimab-TM	4.1
Tixagevimab-YTE	0.2	Cilgavimab-YTE	2.5

3.1.3.2 Effects of tixagevimab and cilgavimab in combination (CTD P 4.2.1.1.4)

Virus-like particles pseudotyped with SARS-CoV-2 S-protein were treated with tixagevimab (0-24 ng/mL) and cilgavimab (0-24 ng/mL) followed by 48-hour incubation with Ad293-hACE2 cells, and their neutralization activity[9)] was determined by luciferase reporter assay that detected cells infected with the virus. The results were used to investigate the effects of the monoclonal antibody combination

8) Lentivirus carrying SARS-CoV-2 S-protein gene and luciferase reporter gene in a lentivirus vector derived from the third-generation human immunodeficiency virus (HIV)

9) Tested using a synergy scoring model for excess of highest single agent (*Proc Natl Acad Sci USA.* 2003;100:7977-82).

on neutralization activity. The combination of tixagevimab and cilgavimab at suboptimal concentrations for neutralization activity of each individual monoclonal antibody exerted a synergistic effect, while the combination of the monoclonal antibodies at concentrations potentially leading to high neutralization activity with each individual monoclonal antibody did not exert any synergistic effect. These data suggested that tixagevimab and cilgavimab would not be antagonistic.

3.1.3.3 Neutralization activity against variants (CTD P 4.2.1.1.3, 4.2.1.1.12)

Virus particles pseudotyped with SARS-CoV-2 S-protein with major amino acid substitutions[10)] were treated with tixagevimab and cilgavimab (alone and in combination), followed by 48-hour incubation with Ad293-hACE2 cells, and their neutralization activity was determined by luciferase reporter assay that detected cells infected with the virus. Table 10 shows amino acid substitutions in pseudotyped virus particles that decreased neutralization activity to one-third of that against the reference strain (expressing S-protein derived from Wuhan-Hu-1/2019 isolate with D614G substitution).

Table 10. Neutralization activity against pseudotyped virus particles carrying major amino acid substitutions

	Fold change in neutralization activity [a)]		
Amino acid substitutions	Tixagevimab	Cilgavimab	Combination of tixagevimab and cilgavimab
R346I	-	> 200	-
R346K	-	25.9	-
Q414R	4.6	-	-
K444E	-	> 200	-
K444Q	-	> 200	-
K444R	-	> 200	-
V445A	-	21 - 51	-
G446V	-	4.2	-
N450K	-	9.1	-
L452R	-	5.6 - 5.8	-
L455F	2.5 - 4.7	-	-
G476S	3.3	-	-
E484D	7.1	-	-
E484K	6.2 - 12	-	2.1 - 5.4
E484Q	2.7 - 3.0	-	-
F486S	> 600	-	3.2
F486V	121 - 149	-	2.6 - 3.9
Q493K	2.4 - 3.2	-	-
Q493R	7.9	-	3.4
P499R	-	9.2	-
E990A	6.1	-	5.7
T1009I	8.2	-	4.5

-: Fold change <3

a) EC_{50} against the variant/EC_{50} against reference strain (expressing S-protein with D614G substitution derived from SARS-CoV-2 [Wuhan-Hu-1/2019 isolate])

10) Of amino acid substitutions in variants traced by the World Health Organization (WHO), ones identified in PROVENT, STORM CHASER, and TACKLE studies, ones within sites bound by tixagevimab and cilgavimab (in ≥1% or ≥5% of SARS-CoV-2 genome sequences for co-occurring substitutions according to GISAID database), and ones within RBD except for sites involved in binding (in ≥5% or ≥15% of SARS-CoV-2 genome sequences for co-occurring substitutions according to GISAID database), the following substitutions were investigated:
L5F, L18F, R21I, P26S, H49Y, L54F, H69Δ/V70Δ, H69Q, D80Y, T95I, S98F, D138Y, Y144Δ, H146Y, W152L, L176F, D215H, D253G, S255F, W258L, A262S, P272L, T307I, F338L, R346I, R346K, N354K, R357K, V367F, V382L, E406Q, Q414R, K417E, K417N, K417T, D420N, N439K, N440K, K444E, K444Q, K444R, V445A, G446S, G446V, G447R, N450D, N450K, L452F, L452Q, L452R, Y453F, L455F, N460K, N460S, N460T, A475V, G476S, S477N, S477R, T478I, T478K, V483A, E484A, E484D, E484K, E484Q, F486L, F486S, F486V, F490S, Q493K, Q493R, S494L, S494P, P499R, N501T, N501Y, V635G, H655Y, Q675H, Q677H, P681H, R682L, R682W, S686G, A892V, D936Y, S982A, E990A, T1009I, and V1176F

Table 11 shows neutralization activity of tixagevimab and cilgavimab (alone or in combination) against major variants derived from the strains assigned letters from the Greek alphabet by the WHO.

Table 11. Neutralization activity of tixagevimab and cilgavimab against major variants

Lineage	Major amino acid substitutions tested	Fold change in neutralization activity[a] (EC_{50}, ng/mL)					
		Pseudotyped virus-like particles[b]			SARS-CoV-2[c]		
		Tixagevimab	Cilgavimab	Tixagevimab and cilgavimab	Tixagevimab	Cilgavimab	Tixagevimab and cilgavimab
B.1.1.7 (Alpha)[d]	N501Y	0.9 - 18	0.6 - 3.4	1.0 - 5.2 (1.1 - 9.0)	0.1 - 4.3	0.3 - 1.0	0.4 - 1.4 (4.0 - 40)
B.1.351 (Beta)	K417N, E484K, N501Y	3.5 - 15	1.0 - 2.0	2.5 - 5.5 (5.6 - 11)	1.8 - 8.9	0.3 - 3.9	0.9 - 3.8 (6.5 - 256)
P.1 (Gamma)	K417T, E484K, N501Y	0.9 -3.5	0.4 - 1.0	0.8 - 1.7 (1.8 - 2.7)	8.0 - 12	0.3 - 0.8	0.4 - 2.0 (3.2 - 8.0)
B.1.617.2 (Delta)	L452R, T478K	1.0	6.8	1.2 (2.2)	0.5 - 2.4	1.5 - 3.9	0.6 - 1.0 (3.0 - 7.5)
AY.1/AY.2 (Delta)	K417N, L452R, T478K	0.6	2.5	1.0 (1.9)	-	-	-
B.1.1.529/BA.1 (Omicron)	G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q489R, N501Y, Y505H	> 600	> 700	132 - 183 (171 - 277)	152 - 230	12 - 268	12 - 30 (147 - 273)
B.1.1.529/BA.1.1 (Omicron)	G339D, R346K, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q489R, N501Y, Y505H	460	500	424 (466)	128	> 1000	176 (1147)
B.1.1.529/BA.2 (Omicron)	G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, H655Y, N679K, P681H, N764K	> 1000	1.9	3.2 (9.8)	68	0.9	5.4 (35)
B.1.1.529/BA.2.12.1 (Omicron)	T19I, L24Δ, P25Δ, P26Δ, A27S, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452Q, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, S704L, N764K, D796Y, Q954H, N969K	> 500	2	5 (11)	-	-	-
B.1.1.529/BA.3 (Omicron)	A67V, H69Δ, V70Δ, T95I, G142D, V143Δ, Y144Δ, Y145Δ, N211I, L212V, V213R, R214Δ, G339D, S371F, S373P, S375F, D405N, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K	> 5000	4	16 (35)	-	-	-

Lineage	Major amino acid substitutions tested	Fold change in neutralization activity[a] (EC_{50}, ng/mL)					
		Pseudotyped virus-like particles[b]			SARS-CoV-2[c]		
		Tixagevimab	Cilgavimab	Tixagevimab and cilgavimab	Tixagevimab	Cilgavimab	Tixagevimab and cilgavimab
B.1.1.529/BA.4 and BA.5 (Omicron)	T19I, L24Δ, P25Δ, P26Δ, A27S, H69Δ, V70Δ, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K	> 10000	7.5 - 9	33 - 65 (65 - 69)	-	-	-
B.1.525 (Eta)	E484K	4.2 - 4.8	0.9 - 1.4	1.8 - 3.1 (5.1 - 9.5)	-	-	-
B.1.526 (Iota)	E484K	0.6 - 8.6	0.6 - 1.4	0.8 - 3.4 (1.9 - 5.2)	0.3 - 2.5	0.3 - 0.5	0.3 - 1.8 (1.0 - 7.0)
B.1.617.1 (Kappa)	L452R, E484Q	0.7 - 1.2	1.9 - 5.1	0.9 - 3.4 (2.5 - 5.1)	0.5 - 1.3	0.5 - 2.4	0.5 - 1.3 (2.0 - 5.0)
C.37 (Lambda)	L452Q, F490S	0.6	8.3	0.7 (1.1)	-	-	-
B.1.621 (Mu)	R346K, E484K, N501Y	5.3	21	7.5 (17)	-	-	-
B.1.427/B.1.429 (Epsilon)	L452R	0.3 - 5.8	1.4 - 4.3	0.8 - 2.9 (1.0 - 4.5)	1.3 - 2.8	2.2 - 2.7	1.3 - 3.5 (5.0 - 14)
R.1	E484K	6.1	1.1	3.5 (4.6)	-	-	-
B.1.1.519	T478K	0.3 - 4.8	0.6 - 1.3	1.0 - 1.4 (2.0 - 2.3)	-	-	-
C.36.3	R346S, L452R	0.5	-	2.3 (3.9)	-	-	-
B.1.214.2	Q414K, N450K	0.5	6.8	0.8 (1.6)	-	-	-
B.1.619.1	N440K, E484K	5.6	3.0	3.3 (7.6)	-	-	-
P.2 (Zeta)	E484K	7.3	1.1	2.9 (10)	-	-	-
B.1.616	V483A	0.5 - 0.7	0.5 - 0.7	0.4 - 0.5 (1.1 - 1.2)	-	-	-
A.23.1	V367F	0.5	0.9	0.4 (0.5)	-	-	-
A.27	L452R, N501Y	0.6	2.6	0.8 (1.8)	-	-	-
AV.1	N439K, E484K	6.8	2.6	5.9 (13)	-	-	-

-: No results are available.
a) EC_{50} against the variant/EC_{50} against reference strain
b) Pseudotyped virus-like particles expressing full-length S-protein or major amino acid substitutions (except for L452Q) of each variant were used. The reference strain has base sequence derived from Wuhan-Hu-1/2019 isolate modified with additional substitution D614G.
c) AUS/VIC01/2020 isolate or USA-WA1/2020 isolate was used as the reference strain.
d) Including results with sequences with additional amino acid substitutions not detected or detected at a negligible frequency in the B.1.1.7 lineage (Alpha) (L455F, E484K, F490S, Q493R or S494P for pseudotyped virus-like particles; E484K or S494P for SARS-CoV-2)

Pseudotyped virus-like particles expressing S-protein with amino acid substitutions identified in variants escaping from other monoclonal antibodies targetingSARS-CoV-2 S-protein were treated with tixagevimab and cilgavimab (alone and in combination), followed by 48-hour incubation with Ad293-hACE2 cells, and their neutralization activity was determined by luciferase reporter assay that detected cells infected with the virus. Table 12 shows the results.

Table 12. Neutralization activity against pseudotyped virus-like particles with substitutions identified in variants escaping from other monoclonal antibodies targeting SARS-CoV-2 S-protein

Monoclonal antibody	Amino acid substitutions identified in escape variants	Frequency [a] (%)	Fold change in neutralization activity [b]		
			Tixagevimab	Cilgavimab	Tixagevimab and cilgavimab
Bamlanivimab[c]	E484D	<0.01	7.1	0.8	2.2
	E484K	6.70	6.2 - 11.9	0.9 - 1.2	2.1 - 5.4
	E484Q	0.31	2.7 - 3.0	1.1 - 1.2	1.5 - 2.0
	F490S	0.35	1.1	1.2	1.0 - 1.2
	Q493R	0.01	7.9	0.8	3.4
	S494P	0.39	0.8 - 0.9	1.0 - 1.1	0.9 - 1.4
Etesevimab[c]	K417N	1.30	0.4 - 0.7	0.5 - 0.8	0.5 - 0.7
	D420N	<0.01	1.4	0.6	1.2
	N460K	<0.01	0.9	0.6	1.0
	N460S	<0.01	0.6	0.8	0.9
	N460T	<0.01	0.6	0.8	0.6
Casirivimab	K417E	<0.01	0.3 - 0.7	0.8 - 0.9	0.5 - 0.8
	Y453F	<0.01	0.7 - 0.8	0.8 - 0.9	0.8 - 0.9
	L455F	0.04	2.5 - 4.7	0.5 - 1.0	1.4 - 2.0
	F486V	<0.01	120.9 - 148.5	0.7 - 0.9	2.6 - 3.9
	Q493K	<0.01	2.4 - 3.2	0.9	1.3 - 1.6
Imdevimab	K444Q	<0.01	0.5 - 0.9	> 200	1.5 - 1.6
	V445A	0.01	0.7 - 1.5	21.3 - 51.5	1.1 - 2.0
Sotrovimab	P337H	<0.01	-	-	-
	P337L	<0.01	-	-	-
	P337R	<0.01	-	-	-
	P337T	<0.01	-	-	-
	E340A	<0.01	-	-	-
	E340G	<0.01	-	-	-
	E340K	<0.01	-	-	-

-: No results available.
a) Percentage frequency with respect to SARS-CoV-2 genome sequences collected across the world (2,620,237 sequences as of September 2, 2021)
b) EC_{50} against the variant/EC_{50} against reference strain (expressing S-protein with D614Gsubstitution derived from SARS-CoV-2 [Wuhan-Hu-1/2019 isolate])
c) Not approved in Japan

3.1.3.4 Fc-mediated effector function (CTD P 4.2.1.1.6)

For evaluation of antibody-dependent cellular phagocytosis (ADCP) mediated by each antibody, complexes of fluorescence-labeled beads coated with S-protein and each antibody (at concentrations of 2.3-5,000 ng/mL for human monocyte THP-1 cells or of 30.6-67,000 ng/mL for human primary neutrophils) were incubated with cells to determine phagocytosis scores.[11] While tixagevimab-WT and cilgavimab-WT (alone and in combination) mediated ADCP in both cells, tixagevimab and cilgavimab (alone and in combination) only slightly mediated ADCP in THP-1 cells and did not in primary neutrophils.

For evaluation of antibody-dependent cellular cytotoxicity (ADCC) mediated by each antibody, a mixture of S-protein-expressing target cells and each antibody (1.526-25,000 ng/mL) were co-cultured with human primary natural killer (NK) cells to determine the percentage of cells undergoing cytolysis. While tixagevimab-WT and cilgavimab-WT (alone and in combination) mediated ADCC, tixagevimab and cilgavimab (alone and in combination) did not.

[11] Percentage of cells that phagocytosed fluorescence-labeled beads coated with S-protein and the degree of phagocytosis

For evaluation of antibody-dependent complement deposition (ADCD), complexes of beads coated with S-protein and each antibody (at concentrations of 45.72-100,000 ng/mL) were incubated with guinea pig complement to determine an amount of complement deposited. While tixagevimab-WT and cilgavimab-WT (alone and in combination) mediated ADCD, tixagevimab and cilgavimab (alone and in combination) did not.

For evaluation of antibody-dependent natural killer cell activation (ADNKA), each antibody was added to a plate coated with S-protein followed by co-incubation with human primary NK cells to determine the percentage of cells positive for CD107a, interferon (IFN)-γ, or macrophage inflammatory protein 1β (MIP-1β). While tixagevimab-WT and cilgavimab-WT (alone and in combination) mediated ADNKA, tixagevimab and cilgavimab (alone and in combination) did not.

For evaluation of antibody-dependent enhancement (ADE) of infection (ADEI), complexes of pseudotyped virus-like particles expressing S-protein and each antibody (at concentrations of 0.125-1 μg/mL) were incubated with Raji cells[12)] to determine the percentage of intracellularly infected cells by luciferase reporter assay. No intracellular infection occurred with tixagevimab-WT, cilgavimab-WT, or their combination, or with tixagevimab, cilgavimab, or their combination; no ADEI was observed.

3.1.4 Emergence of *in vitro* escape variants (CTD P 4.2.1.1.7, reference CTD P 4.3: *Nat Microbiol.* 2021;10:1233-44)

Vero E6 cells were infected with SARS-CoV-2 (USA-WA1/2020 isolate) and subjected to 10 passages in the presence of tixagevimab or cilgavimab (alone or in combination).[13)] The susceptibility of the virus in the used medium to each antibody (at a concentration of 10-fold the EC_{50}) was determined by plaque assay. Plaques were formed only with the virus collected from infected cells passaged in the presence of cilgavimab alone, and S-protein amino acid substitutions N74K (in the amino-terminal domain), R346I (in the RBD), and S686G (in the S1/S2 furin cleavage site) were identified.

In the presence of COV2-2196 or COV2-2130 (alone or in combination, 5 μg/mL), Vero E6 cells were infected with vesicular stomatitis virus (recombinant virus) carrying S-protein gene derived from SARS-CoV-2 (USA-WA1/2020 isolate) to determine cell viability. Decreased viability was observed in cells cultured in the presence of COV2-2130 alone, and S-protein amino acid substitutions K444E and K444R (in the RBD) were identified.

Pseudotyped virus-like particles expressing S-protein or S-protein with amino acid substitutions identified in the above studies for detection of escape variants were used to determine the neutralization activity or binding affinity of tixagevimab and cilgavimab (alone or in combination). Table 13 and Table 14 show the results. Based on amino acid sequences of SARS-CoV-2 S-protein obtained from the GISAID database (8,556,065 sequences collected between December 15, 2015 and April 18, 2022), amino acid substitutions R346I, K444E, and K444R involved in decreased neutralization activity or binding affinity of cilgavimab occurred at frequencies of 0.014%, 0.00035%, and 0.015%.

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12) Human B cell line that expresses FcγRIIa but does not express ACE2

13) The concentration of each antibody was started at EC_{50} (7-17 ng/mL) of neutralization activity against SARS-CoV-2 (USA-WA1/2020 isolate) and up-titrated to EC_{90} (12-36 ng/mL).

Table 13. Neutralization activity[a)] against pseudotyped virus-like particles carrying amino acid substitutions identified in escape variants

	Fold change in neutralization activity[b)]		
Amino acid substitution	Tixagevimab	Cilgavimab	Combination of tixagevimab and cilgavimab
N74K[c)]	-	-	-
R346I	0.89	>200	0.93
S686G	1.26	0.72	1.18
K444E	0.45	>200	0.78
K444R	0.99	>200	2.18

-: No results available.
a) Determined by luciferase reporter assay that detected viral infection in Ad293-hACE2 cells after 48 hours of incubation
b) EC_{50} against the variant/EC_{50} against reference strain (expressing S-protein substitution D614G from SARS-CoV-2 [Wuhan-Hu-1 isolate])
c) Assay was not available because of a limited amount of pseudotyped virus-like particles generated.

Table 14. Binding affinity[a)] to S-protein carrying amino acid substitutions identified in escape variants

	Tixagevimab		Cilgavimab	
Amino acid substitution	Equilibrium dissociation constant (K_D) (pmol/L)	Fold change[b)]	Equilibrium dissociation constant (K_D) (pmol/L)	Fold change[b)]
N74K	298	1.18	<1.00	1.00
R346I	166	0.66	7890	7890
S686G	180	0.71	<1.00	1
K444E	177	0.70	-	-
K444R	231	0.91	17000 [c)]	17000 [c)]

-: No binding
a) Determined by biolayer interferometry.
b) K_D for S-protein with amino acid substitutions/K_D for reference S-protein (Hexapro spike protein with D614G substitution, *Science.* 2020;369:1501-5)
c) Inaccurate value because weak binding of cilgavimab to S-protein with K444R substitution was suggested by the shape of the non-linear regression curve used in calculation of K_D

3.1.5 *In vivo* antiviral activity (CTD P 4.2.1.1.8-11)

Antiviral activity of each individual antibody administered to rhesus monkeys, cynomolgus monkeys, and syrian hamsters before and after viral challenge was investigated. Table 15 and Table 16 show the results.

Table 15. *In vivo* antiviral activity (administration before virus challenge)

Animal species (n/group)	Regimen[a] and virus challenge method	Outline of main results	Submitted data CTD
Rhesus monkeys (3-4 males and females in total/group)	The combination of tixagevimab and cilgavimab (4, 40 mg/kg), the combination of tixagevimab-YTE and cilgavimab-YTE (4 mg/kg), or control antibody (human IgG1κ, 40 mg/kg) was administered intravenously 3 days prior to the intratracheal and intranasal challenge with SARS-CoV-2 (USA-WA1/2020 isolate, 100,000 PFU/animal).	Viral RNA load (test specimens: nasal swabs and bronchoalveolar lavage fluid[b]): No viral RNA was detected in the bronchoalveolar lavage fluid at either dose in the tixagevimab + cilgavimab group. Viral RNA was detected only in the nasal swab from 1 of 4 animals in the tixagevimab + cilgavimab group (4 mg/kg) 2 days after viral challenge, but its load was lower than that in the control antibody group. Viral RNA load did not clearly differ between the tixagevimab-YTE + cilgavimab-YTE group and the tixagevimab + cilgavimab group.	4.2.1.1.8
Cynomolgus monkeys (3 males and females in total/group)	The combination of tixagevimab and cilgavimab (0.04, 0.4, 4 mg/kg) or control antibody (human IgG1κ, 40 mg/kg) was administered intravenously 3 days prior to the intratracheal and intranasal challenge with SARS-CoV-2 (USA-WA1/2020 isolate, 100,000 PFU/animal).	Viral RNA load (test specimens: nasal swabs and bronchoalveolar lavage fluid[c]): Viral RNA load was lower at any dose in the tixagevimab + cilgavimab group than in the control antibody group and tended to decrease in a dose-dependent manner. No viral RNA was detected in the tixagevimab + cilgavimab group (4 mg/kg). Histopathological examination of the lung[d] (necropsy performed 5 days after viral challenge): Inflammation was generally milder in the tixagevimab + cilgavimab group than in the control antibody group. Histological changes in the lung parenchyma and bronchial epithelium were milder in the tixagevimab + cilgavimab group (4 mg/kg) than in any of the other groups.	4.2.1.1.11
Syrian hamsters (10-11 females in total/group)	The combination of tixagevimab-TM and cilgavimab-TM[e] (0.002, 0.02, 0.2, 2 mg) or control antibody (human IgG1κ, 2 mg) was administered intraperitoneally 1 day prior to the intranasal challenge with SARS-CoV-2 (USA-WA1/2020 isolate, 100,000 PFU/animal).	Body weight (up to 7 days after viral challenge): Reduced weight loss in the tixagevimab-TM + cilgavimab-TM group was observed in a dose-dependent manner compared with that in the control antibody group. Viral RNA load and virus titer (test specimens: pulmonary tissue[f]): In the tixagevimab-TM + cilgavimab-TM group (2 mg), viral RNA load decreased 3 days after viral challenge compared with that in the control antibody group, and the virus titer was found below the detection limit. Histopathological examination of the lung[g] (necropsy performed 3 and 7 days after viral challenge): Pathological lesion scores in the tixagevimab-TM + cilgavimab-TM group decreased in a dose-dependent manner compared with that in the control antibody group.	4.2.1.1.9

a) Total dose for administration of combination of antibodies
b) Specimens collected before and 1, 2, 4, 7, 10, and 14 days after virus challenge
c) Specimens collected before and 1, 2, 4, and 5 days after virus challenge
d) Specimens were scored according to inflammatory and pathological changes associated with SARS-CoV-2 infection.
e) Because IgG antibodies with YTE substitutions are rapidly eliminated in rodents (*J Immunol.* 2002;169:5171-80, *J Biol Chem.* 2006;281:23514-24), such antibodies were not used in the study.
f) Specimens collected 3 and 7 days after virus challenge
g) Specimens were assessed based on the total of scores given on a scale of 0 to 5 for each of pathological changes associated with SARS-CoV-2 infection (inflammation, type 2 pneumocyte hyperplasia, epithelial necrosis, fibrin deposition and hemorrhage, and septal fibrous change).

Table 16. *In vivo* antiviral activity (administration after virus challenge)

Animal species (n/group)	Regimen[a] and viral challenge method	Outline of main results	Submitted data CTD
Rhesus monkeys (3-4 males and females in total/group)	The combination of tixagevimab and cilgavimab (40 mg/kg) or control antibody (human IgG1κ, 40 mg/kg) was administered intravenously 1 day after the intratracheal and intranasal challenge with SARS-CoV-2 (USA-WA1/2020 isolate, 100,000 PFU/animal).	Viral RNA load (test specimens: nasal swabs and bronchoalveolar lavage fluid[b]): Viral RNA load in the tixagevimab + cilgavimab group did not decrease 2 days after virus challenge but tended to decrease earlier than that in the control antibody group.	4.2.1.1.8
Cynomolgus monkeys (3-4 males and females in total/group)	The combination of tixagevimab and cilgavimab (40 mg/kg), the combination of tixagevimab-YTE and cilgavimab-YTE (40 mg/kg), or control antibody (human IgG1κ, 40 mg/kg) was administered intravenous 1 day after the intratracheal and intranasal challenge with SARS-CoV-2 (USA-WA1/2020 isolate, 100,000 TCID50/animal).	Viral RNA load (test specimens: nasal swabs and bronchoalveolar lavage fluid[c]): Viral RNA load in the tixagevimab + cilgavimab group tended to decrease earlier than that in the control antibody group. Viral RNA load did not clearly differ between the tixagevimab-YTE + cilgavimab-YTE group and the tixagevimab + cilgavimab group. Histopathological examination of the lung[d] (necropsy performed 5 days after virus challenge): Inflammation was generally milder in the tixagevimab + cilgavimab group than in the control antibody group. Pathological changes did not clearly differ between the tixagevimab-YTE + cilgavimab-YTE group and the tixagevimab + cilgavimab group.	4.2.1.1.11
Syrian hamsters (10-11 females in total/group)	The combination of tixagevimab-TM and cilgavimab-TM[e] (0.5, 1.5, 5 mg) or control antibody (human IgG1κ, 5 mg) was intraperitoneally administered 1 day after the intranasal challenge with SARS-CoV-2 (USA-WA1/2020 isolate, 100,000 PFU/animal), or the combination of tixagevimab-TM and cilgavimab-TM[e] (5 mg) was intraperitoneally administered 2 days after the intranasal challenge.	Body weight (up to 7 days after virus challenge): Reduced weight loss in the tixagevimab-TM + cilgavimab-TM group was observed at any dose or any dosing point compared with that in the control antibody group. Viral RNA load and virus titer (test specimens: pulmonary tissue[f]): When monoclonal antibodies were administered 1 day after virus challenge, viral RNA load 3 days after virus challenge were lower in the tixagevimab-TM + cilgavimab-TM group (5 mg) than in the control antibody group. When monoclonal antibodies were administered 2 days after virus challenge, viral RNA load was not decreased at any dose in the tixagevimab-TM + cilgavimab-TM group compared with the control antibody group. Virus titers in the tixagevimab-TM + cilgavimab-TM group were found below the detection limit at any dose 3 days after virus challenge. Histopathological examination of the lung[g] (necropsy performed 3 days after virus challenge): When monoclonal antibodies were administered 1 day after virus challenge, pathological lesion scores tended to be lower in the tixagevimab-TM + cilgavimab-TM group (1.5 and 5 mg) than in the control antibody group. Pathological lesion scores 7 days after virus challenge tended to be lower at any dose in the tixagevimab-TM + cilgavimab-TM group than in the control antibody group. When monoclonal antibodies were administered 2 days after virus challenge, pathological lesion scores 7 days after virus challenge tended to be lower at any dose in the tixagevimab-TM + cilgavimab-TM group than in the control antibody group.	4.2.1.1.10

a) Total dose for administration of combination of antibodies
b) Specimens collected before and 1, 2, 4, 7, 10, and 14 days after virus challenge
c) Specimens collected before and 1, 2, 4, and 5 days after virus challenge
d) Specimens were scored according to inflammatory and pathological changes associated with SARS-CoV-2 infection.
e) Because IgG antibodies with YTE substitutions are rapidly eliminated in rodents (*J Immunol.* 2002;169:5171-80, *J Biol Chem.* 2006;281:23514-24), such antibodies were not used in the study.
f) Specimens collected 3 and 7 days after virus challenge
g) Specimens were assessed based on the total of scores given on a scale of 0 to 5 for each of pathological changes associated with SARS-CoV-2 infection (inflammation, type 2 pneumocyte hyperplasia, epithelial necrosis, fibrin deposition and hemorrhage, and septal fibrous change)

3.2 Secondary pharmacodynamics

3.2.1 Effects on immune response after vaccination (CTD P 4.2.1.2.1, 4.2.1.2.2)

The combination of tixagevimab-TM and cilgavimab-TM [14)] (5-400 μg), the combination of tixagevimab-WT and cilgavimab-WT (400 μg), or control antibody (human IgG1κ, 400 μg) was administered intraperitoneally to mice (6 females per group) 1 day before the first intramuscular immunization with the adenovirus-vectored SARS-CoV-2 vaccine (1.0×10^8 IU/dose). The animals were immunized with the second vaccine dose 4 weeks later. The titer of serum mouse antibodies that bound to S-protein or RBD was measured 4 weeks after the first vaccine dose and 2 weeks after the second vaccine dose by ELISA, and *ex vivo* CD8-positive T cell response to S-protein antigen (expression of IFNγ, IL-2, or TNFα) was measured 2 weeks each after the first and second vaccine doses by flow cytometry. No clear differences were observed between the tixagevimab-TM + cilgavimab-TM group or the tixagevimab-WT + cilgavimab-WT group and the control antibody group, irrespective of the number of vaccine doses or the level of antibody dose.

The combination of tixagevimab and cilgavimab (0.2-12 mg/kg) or control antibody (human IgG1κ, 12 mg/kg) was administered intravenously to cynomolgus monkeys (4-5 males and females in total per group) 3 days before the first intramuscular immunization with the adenovirus vectored SARS-CoV-2 vaccine (5.0×10^{10}/dose). The animals were immunized with the second vaccine dose 4 weeks later. The titer of serum cynomolgus monkey antibodies that bound to S-protein or RBD was measured 4 weeks each after the first and second vaccine doses by ELISA, and *ex vivo* CD8-positive or CD4-positive T cell response to S-protein antigen (expression of IFNγ, IL-2, or TNFα) was measured 4 weeks after the second vaccine dose by flow cytometry. The titer of antibodies binding to RBD after the second vaccine dose was slightly lower in the tixagevimab + cilgavimab group (4 or 12 mg/kg) than in the control antibody group, but that of antibodies binding to S-protein did not clearly differ between these groups. In addition, CD8-positive or CD4-positive T cell response to S-protein antigen did not clearly differ between the tixagevimab-TM + cilgavimab-TM group or the tixagevimab-WT + cilgavimab-WT group and the control antibody group at either dose.

3.3 Safety pharmacology

Safety pharmacology was evaluated based on clinical signs after a single dose in a systemic toxicity study in cynomolgus [see Section 5.1]. The applicant explained that the combination of tixagevimab and cilgavimab did not have any effect on the cardiovascular, respiratory, or central nervous system.

3.R Outline of the review conducted by PMDA

3.R.1 Inhibitory activity against SARS-CoV-2

The applicant's explanation about the inhibitory activity of tixagevimab and cilgavimab against SARS-CoV-2:

Tixagevimab and cilgavimab non-competitively bind to epitopes on the RBD of SARS-CoV-2 S-protein (that also serve as the ACE binding site) to inhibit SARS-CoV-2 from binding to human ACE2 [see Section 3.1.1], thereby neutralizing SARS-CoV-2 [see Section 3.1.3].

14) Because IgG antibodies with YTE substitutions are rapidly eliminated in rodents (*J Immunol*. 2002;169:5171-80, *J Biol Chem.* 2006;281:23514-24), such antibodies were not used in the study.

Because tixagevimab and cilgavimab have the Fc region with TM substitutions, *in vitro* studies showed that the monoclonal antibodies had limited or no binding affinity to FcγR or complement C1q [see Section 3.1.2] and scarcely mediated ADCP, ADCD, and ADNKA [see Section 3.1.3.4]. In addition, *in vivo* studies showed that antiviral activity of the combination of tixagevimab and cilgavimab was similar to that of the combination of ixagevimab-YTE and cilgavimab-YTE in which TM substitutions were not introduced [see Section 3.1.5]. The antiviral activity of tixagevimab and cilgavimab against SARS-CoV-2 is considered independent of the Fc-mediated effector function.

PMDA's view:
Tixagevimab and cilgavimab are demonstrated to neutralize SARS-CoV-2. From the pharmacological point of view, tixagevimab and cilgavimab can be expected to be effective in the prevention and treatment of COVID-19.

3.R.2 Neutralization activity against variants

The applicant's explanation about the neutralization activity of tixagevimab and cilgavimab against variants:
Based on the results of *in vitro* studies [see Section 3.1.3.3], the combination of tixagevimab and cilgavimab is considered to maintain neutralization activity against the variants tested including ones assigned letters from the Greek alphabets by the WHO. The neutralization activity of the combination of tixagevimab and cilgavimab against some Omicron subvariants was lower than that against the reference strain [see Section 3.1.3.3], but the EC_{50} values were calculated. The combination is therefore considered to maintain neutralization activity against all of the Omicron subvariants tested *in vitro*.

PMDA's view:
Tixagevimab, cilgavimab, and their combination are demonstrated to have certain neutralization activity against the variants tested including the Omicron variant, but the neutralization activity against some Omicron subvariants was found lower than that against the reference strain.

Because whether tixagevimab or cilgavimab neutralizes novel variants is critical for the efficacy of the treatment, the applicant should continue collecting post-marketing information on it and promptly provide any new information to healthcare professionals when it becomes available.

3.R.3 Antibody-dependent enhancement of disease (ADE)

The applicant's explanation about ADE mediated by tixagevimab and cilgavimab:
When antibodies bound to the virus interacts with FcγR through their Fc region, virus entry into the FcγR-expressing cells would be activated, potentially enhancing the inflammatory reaction (ADE). *In vitro*, tixagevimab and cilgavimab was shown to have limited or no binding affinity to FcγR [see Section 3.1.2], and the study using Raji cells presented no findings suggestive of ADE [see Section 3.1.3.4]. In studies of the pre-virus challenge dose in cynomolgus monkeys or of the post-virus challenge dose in syrian hamsters, infection or disease was not enhanced in the tixagevimab + cilgavimab group or tixagevimab-TM + cilgavimab-TM group at doses lower than ones leading to complete neutralization, compared with that in the control antibody group [see Section 3.1.5]. Based on the above findings, the applicant considers that tixagevimab and cilgavimab are unlikely to exert ADE.

PMDA's view:

There are no clear findings suggestive of ADE mediated by tixagevimab and cilgavimab from non-clinical pharmacological point of view, although the results should be carefully interpreted because of the unestablished extrapolation of the results to humans.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Studies were conducted to investigate the pharmacokinetics (PK) of tixagevimab, cilgavimab, and their combination in monkeys. Tixagevimab and cilgavimab concentrations in monkey serum were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (lower limit of quantitation (LLOQ), 9.0 μg/mL).

4.1 Absorption

4.1.1 Single dose study (CTD P 4.2.3.1.1)

Table 17 shows PK parameters in monkeys which received the combination of tixagevimab and cilgavimab as a single intravenous (IV) or intramuscular (IM) dose.

Table 17. PK parameters after single dose of combination of tixagevimab and cilgavimab in monkeys

Dose [b] (mg/kg)	Route of administration	Analyte	Sex	N	C_{max} (μg/mL)	t_{max} (days)	$t_{1/2}$ (days)	$AUC_{0\text{-}56day}$ (μg•day/mL)	V_d [a] (mL/kg)	BA (%)
300/300	IV[c]	Tixagevimab	Male	5	7700±2300	0.04 [0.04, 0.06]	15.2, 21.2	78900, 92200	75.9, 83.6	-
			Female	5	7770±1890	0.04 [0.04, 0.06]	5.88, 18.1	67000, 87400	37.7, 77.7	-
		Cilgavimab	Male	5	8300±827	0.04 [0.04, 0.04]	19.0, 23.3	87800, 100000	80.6, 83.1	-
			Female	5	7090±621	0.06 [0.04, 0.06]	22.2, 22.3	95500, 105000	74.1, 81.6	-
75/75	IM[d]	Tixagevimab	Male	2	883, 983	3, 3	-	28500, 29000	-	134
			Female	2	925, 1000	2, 2	-	17800, 24400	-	109
		Cilgavimab	Male	2	908, 1080	2, 3	-	31500, 31500	-	134
			Female	2	1000, 1040	2, 2	5.72, 20.3	20900, 25300	29.3, 73.2	92

Mean ± standard deviation (SD) (individual values for n = 2); t_{max}, median [range]; BA, mean; and -, "Not applicable" or "Not calculated"
a) Apparent volume of distribution (Vd/F) for intramuscular administration
b) Dose of tixagevimab/dose of cilgavimab
c) Tixagevimab and cilgavimab were administered as two separate sequential intravenous infusions over 15 minutes each.
d) Tixagevimab and cilgavimab were administered as two separate intramuscular injections into different femor sites.

4.2 Distribution

No studies on distribution have been conducted. The applicant provided the following explanation:

The volume of distribution of tixagevimab and cilgavimab administered by intravenous infusion as a single dose [see Section 6.2.1.2] was larger than the volume of plasma in humans (approximately 3.5 L) and smaller than that of extracellular fluid including plasma (approximately 14 L). Thus, tixagevimab and cilgavimab are considered to be distributed mainly in blood vessels and interstitial fluid and scarcely in tissues. Human IgG1 is known to cross the blood placental barrier (*Clin Dev Immunol.* 2012;2012:985646), suggesting that tixagevimab and cilgavimab, IgG drug products, may also cross the placenta.[15]

[15] Although tixagevimab and cilgavimab have the Fc region modified with YTE substitutions and TM substitutions, effects of these substitutions on distribution in the placenta and excretion into milk remain unknown.

4.3 Metabolism and excretion

No studies on metabolism or excretion have been conducted. The applicant provided the following explanation:

Because tixagevimab and cilgavimab, both monoclonal antibody drug products, are considered to be degraded into small peptides and amino acids, no studies on metabolism or excretion have been conducted according to the guidelines titled "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" (PFSB/ELD Notification No. 0323-1 dated March 23, 2012). Since human IgG is known to be excreted in milk (*Obstet Gynecol.* 2022;139:181-91), tixagevimab and cilgavimab, IgG drug products, may be excreted in milk.[15)]

4.R Outline of the review conducted by PMDA

PMDA concluded that no particular problems for the clinical use of Evusheld were identified in the results of the nonclinical pharmacokinetic studies submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant conducted a single-dose toxicity study and tissue cross-reactivity studies to evaluate the toxicity of tixagevimab and cilgavimab. Both tixagevimab and cilgavimab specifically bind to the RBD of SARS-CoV-2 S protein, an adventitious agent, and are therefore unlikely to cross-react with components in animals. Nevertheless, the single-dose toxicity study used cynomolgus monkeys to simultaneously evaluate (a) toxicity attributable to non-specific binding, (b) effects on the cardiovascular and respiratory systems, and (c) estimated blood exposure after an intramuscular administration.

5.1 Systemic toxicity

In the systemic toxicity study, tixagevimab and cilgavimab were administered intravenously (IV) and intramuscularly (IM) as a single dose. Tixagevimab and cilgavimab were administered at 300/300 mg/kg[16)] IV and 75/75 mg/kg IM, and both regimens caused no systemic toxicity including acute symptoms or deaths. The approximate lethal dose and no-observed-adverse-effect level (NOAEL) were determined to be >300/300 mg/kg and 300/300 mg/kg for the IV administration and >75/75 mg/kg and 75/75 mg/kg for the IM administration. Although increases in blood globulin and total protein and a decrease in albumin/globulin ratio were observed after the IV administration, these findings were not considered to be suggestive of toxicity because of no histopathological changes. Blood exposure ($AUC_{0\text{-}28day}$) to tixagevimab at NOAEL for IM administration was 18,700 μg·day/mL in males and 17,000 μg·day/mL in females; and blood exposure ($AUC_{0\text{-}28day}$) to cilgavimab was 20,700 μg·day/mL in males and 18,800 μg·day/mL in females. These exposure levels had safety margin, being approximately 33 and 37 times the blood exposure ($AUC_{0\text{-}30day}$)[17)] to tixagevimab and cilgavimab, respectively, in healthy Japanese men who received tixagevimab and cilgavimab at 150/150 mg as a single IM dose.

16) Doses of tixagevimab/ cilgavimab are expressed in this way.
17) Arithmetic mean in the Japanese phase I study (Study D8850C00005) (tixagevimab, 564.7 μg·day/mL; cilgavimab, 557.8 μg·day/mL)

Table 18. Summary of systemic toxicity study

Test system	Route of administration	Treatment period	Dose (mg/kg)	Main findings	NOAEL (mg/kg)	Submitted data CTD
Females and males Cynomolgus monkeys	IV IM	Single dose	[IV] 0[a)], 300/300[b)] [IM] 0[a)], 75/75[b)]	[IV] 300/300: Increases in blood globulin and total protein, decrease in albumin/globulin ratio (males and females) [IM] 75/75: None	[IV] 300/300[b)] [IM] 75/75[b)]	P 4.2.3.1.1

a) Aqueous solution containing 20 mmol/L histidine/histidine monohydrochloride monohydrate, 240 mmol/L sucrose, and 0.04% polysorbate 80 (pH 6.0)
b) Doses of tixagevimab/cilgavimab

5.2 Genotoxicity

Tixagevimab and cilgavimab are both high-molecular weight proteins that do not pass through the nuclear or mitochondrial membrane and are thus unable to directly interact with DNA or other chromosomal substances in the nucleus. Since they are unlikely to raise any genotoxicity concern, no genotoxicity studies have been conducted.

5.3 Carcinogenicity

Tixagevimab and cilgavimab both target an adventitious agent and do not cross-react with human tissues [see Section 5.6.1]. Since they are unlikely to be carcinogenic, no carcinogenicity studies have been conducted.

5.4 Reproductive and developmental toxicity

Tixagevimab and cilgavimab both target an adventitious agent and do not cross-react with human tissues [see Section 5.6.1]. For these reasons, no reproductive and developmental toxicity studies have been conducted.

5.5 Local tolerance

Local tolerance to the combination of tixagevimab and cilgavimab administered intramuscularly was evaluated in the single-dose systemic toxicity study [see Section 5.1]. No local irritation was observed.

5.6 Other studies

5.6.1 Tissue cross-reactivity

Tissue cross-reactivity was investigated for tixagevimab alone, cilgavimab alone, and their combination, using frozen sections of normal human and cynomolgus monkey tissues as well as human fetal tissues. No cross-reactivity was observed in any of the tissues evaluated (Table 19).

Table 19. Summary of results of tissue cross reactivity studies

Test system	Method	Main findings	Submitted data CTD
Normal human and cynomolgus monkey tissues	Tissue binding capacity of tixagevimab alone, cilgavimab alone, and their combination (0.5 and 2 μg/mL)[a)] was evaluated using immunohistologically stained frozen tissue sections.	None	P 4.2.3.7.7.1
Human fetal tissues	Tissue binding capacity of tixagevimab alone, cilgavimab alone, and their combination (0.5 and 2 μg/mL)[a)] was evaluated using immunohistologically stained frozen tissue sections.	None	P 4.2.3.7.7.2

a) Total concentration of tixagevimab and cilgavimab in combination

5.R Outline of the review conducted by PMDA

PMDA's view:

No particular safety concerns have been suggested for an IM dose of tixagevimab and cilgavimab from the toxicological point of view.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

During the development process of Evusheld, changes were made to the formulation, manufacturing site, manufacturing scale, and other elements of the drug substances and drug products. After each change, the comparability was demonstrated between the pre- and post-change drug substances and between the pre- and post-change drug products [see Sections 2.1.4 and 2.2.3].

Tixagevimab and cilgavimab concentrations in human serum and nasal lining fluid were measured by LC-MS/MS[18)] (LLOQ, 0.300 μg/mL in serum and 5 ng/mL in nasal lining fluid). Anti-drug antibody (ADA) was measured by electrochemiluminescence.

6.2 Clinical pharmacology

The applicant submitted clinical pharmacology data in the form of results from the following studies: a foreign phase I study in healthy non-Japanese subjects and a Japanese phase I study in healthy Japanese subjects (Study D8850C00001 and Study D8850C00005, respectively); foreign phase III study in subjects who were at increased risk for inadequate response to SARS-CoV-2 vaccination or intolerant of vaccine or who were at increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 (PROVENT study); foreign phase III study in subjects who had potential exposure to a specific identified individual with laboratory-conformed SARS-CoV-2 infection and were therefore at appreciable risk of developing COVID-19 (STORM CHASER study); and global phase III study in patients with COVID-19 (TACKLE study). The results of population pharmacokinetic (PPK) analysis were also submitted.

Pharmacokinetic (PK) parameters are expressed as means unless specified otherwise.

18) Tixagevimab and cilgavimab are macromolecules and thus cannot be quantified by LC-MS/MS. Samples were subjected to protein digestion, and then peptides characteristic of tixagevimab and cilgavimab were measured by LC-MS/MS as indicators alternative to human serum tixagevimab and cilgavimab concentrations.

6.2.1 Phase I studies

6.2.1.1 Japanese phase I study (CTD P 5.3.4.1.1, Study D8850C00005, ongoing since March 2021[19] [data cut-off in [redacted] 20[redacted]])

Healthy Japanese subjects (30 evaluable for PK) received a single dose of tixagevimab and cilgavimab 150/150 mg or 300/300 mg as two separate sequential IM injections in the hips or a single dose of tixagevimab and cilgavimab 150/150 mg or 500/500 mg co-administered as an IV infusion. Table 20 shows serum PK parameters based on PK data up to 31 days post-dose. The absolute bioavailability (BA) after a single dose of tixagevimab and cilgavimab 150/150 mg or 300/300 mg as two separate sequential IM injections in the hips was 63.2% and 57.8%, respectively, for tixagevimab and 62.1% and 54.0%, respectively, for cilgavimab.

Of 30 subjects who received tixagevimab and cilgavimab, 2 (6.7%, 1 who received the 300/300 mg IM dose and 1 who received the 150/150 mg IV dose) tested positive for anti-tixagevimab antibodies until Day 31, while none tested positive for anti-cilgavimab antibodies.

Table 20. Serum PK parameters based on PK data in healthy Japanese subjects up to 31 days after single dose of tixagevimab and cilgavimab in combination

Route of administration	Dose[a] (mg)	Sex	N	Analyte	C_{max} (μg/mL)	t_{max} (days)	$AUC_{0\text{-}30day}$ (μg·day/mL)
IM	150/150	Male	6	Tixagevimab	21.1 (18.9)	14.0 [5.04, 14.0]	558 (17.6)
				Cilgavimab	21.3 (14.9)	14.0 [7.07, 14.1]	554 (13.9)
	300/300	Male	6	Tixagevimab	39.3 (36.4)	10.5 [5.04, 14.0]	1021 (34.7)
				Cilgavimab	37.9 (42.8)	14.0 [3.09, 30.1]	964 (43.0)
IV	150/150[b]	Male	6	Tixagevimab	53.6 (12.4)	0.33 [0.01, 0.33]	883 (9.71)
				Cilgavimab	52.8 (12.2)	0.33 [0.33, 0.33]	892 (8.28)
	150/150[b]	Female	6	Tixagevimab	60.5 (8.65)	0.01 [0.01, 0.33]	931 (4.20)
				Cilgavimab	59.9 (7.51)	0.01 [0.01, 0.33]	950 (10.3)
	500/500[c]	Male	6	Tixagevimab	172 (10.4)	0.02 [0.02, 0.33]	2842 (14.1)
				Cilgavimab	166 (8.63)	0.02 [0.02, 0.33]	2681 (12.4)

Geometric mean (geometric CV%); and t_{max}, median [range]
a) Dose of tixagevimab/dose of cilgavimab
b) Tixagevimab and cilgavimab were co-administered as an intravenous infusion at 20 mg/min for the total amount.
c) Tixagevimab and cilgavimab were co-administered as an intravenous infusion at 40 mg/min for the total amount.

6.2.1.2 Foreign phase I study (CTD T 5.3.4.1.1, Study D8850C00001, August 2020 to October 2021)

Healthy non-Japanese subjects (50 evaluable for PK) received a single dose of tixagevimab and cilgavimab 150/150 mg as two separate sequential IM injections in the hips, a single dose of tixagevimab and cilgavimab 150/150 mg, 500/500 mg, or 1,500/1,500 mg as two separate sequential IV infusions, or a single dose of tixagevimab and cilgavimab 1,500/1,500 mg co-administered as an IV infusion. Table 21 shows serum PK parameters. The absolute BA after a single dose of tixagevimab and cilgavimab 150/150 mg as separate sequential IM injections in the hips was 68.7% for tixagevimab and 65.0% for cilgavimab, and the median nasal lining fluid/serum concentration ratio[20] of tixagevimab and cilgavimab (total concentration) was 1.81%.

[19] Follow-up until Day 361 is ongoing.
[20] Calculated from individual nasal lining fluid/serum concentration ratios of tixagevimab and cilgavimab 8 and 31 days after administration of the study drug (Days 8 and 31).

Of 50 subjects who received tixagevimab and cilgavimab, 1 (2.0%, 1 who received the 150/150 mg IM dose) and 7 (14.0%, 4 who received the 150/150 mg IM dose and 3 who received the 150/150 mg IV dose) tested positive for anti-tixagevimab and anti-cilgavimab antibodies, respectively, until Day 361.

Table 21. Serum PK parameters in healthy non-Japanese subjects after single dose of tixagevimab and cilgavimab in combination

Route of administration	Dose[a)] (mg)	N	Analyte	C_{max} (μg/mL)	t_{max} (days)	$t_{1/2}$ (days)	AUC_{inf} (μg·day/mL)	V_{ss} (L)
IM	150/150	10	Tixagevimab	16.5 (35.6)	14.0 [3.05, 30.0]	87.8 (14.6)	2526 (29.8)	-
			Cilgavimab	15.3 (38.5)	14.0 [3.05, 60.2]	79.8 (9.65)	2130 (31.3)	-
IV	150/150[b)]	9	Tixagevimab	53.7 (10.2)	0.04 [0.02, 0.33]	87.0 (5.20)	3677 (13.8)	5.07±0.48
			Cilgavimab	51.7 (12.3)	0.02 [0.02, 0.96]	91.1 (9.15)	3276 (14.2)	5.69±0.47
	500/500[b)]	9	Tixagevimab	162 (11.3)	0.04 [0.02, 0.05]	92.4 (17.2)	9893 (12.6)	6.52±0.97
			Cilgavimab	154 (14.7)	0.02 [0.02, 0.34]	83.1 (16.2)	9712 (11.7)	6.02±0.88
	1500/1500[b)]	10	Tixagevimab	506 (10.5)	0.10 [0.06, 0.13]	91.3 (7.83)	31850 (10.9)	6.12±0.60
			Cilgavimab	466 (11.1)	0.06 [0.06, 0.33]	88.5 (9.09)	29860 (11.7)	6.31±0.67
	1500/1500[c)]	10	Tixagevimab	448 (8.98)	0.05 [0.05, 0.05]	95.3 (11.1)	31850 (11.9)	6.37±0.69
			Cilgavimab	419 (11.6)	0.05 [0.05, 0.33]	87.2 (10.8)	30030 (11.8)	6.29±0.75

Geometric mean (geometric CV%); t_{max}, median [range]; V_{ss}, mean ± SD; and -, Not applicable
a) Dose of tixagevimab/dose of cilgavimab
b) Tixagevimab and cilgavimab were administered sequentially by intravenous infusion at a maximum of 20 mg/min.
c) Tixagevimab and cilgavimab were co-administered as an intravenous infusion at a maximum of 50 mg/min for the total amount.

Based on the serum concentrations of tixagevimab and cilgavimab (total concentration) and regression analysis on 80% neutralization antibody titer against the SARS-CoV-2 wild-type strain (Bav/Pat1/2020 isolate), *ex vivo* EC_{80} values[21)] on Days 8, 31, 61, 91, 151, 211, 271, and 361 were estimated to be 30.6, 35.3, 27.7, 34.6, 36.5, 26.0, 37.2, and 33.2 ng/mL, suggesting that neutralization activity per molecule of tixagevimab and cilgavimab would not decrease with time.

6.2.2 Phase III studies

6.2.2.1 Foreign phase III study (CTD P 5.3.5.1.1, Study D8850C00002 [PROVENT study], ongoing since November 202 [data cut-off in June 2021]; CTD P 5.3.5.1.2, Study D8850C00003 [STORM CHASER study], ongoing since December 2020 [data cut-off in April 2021])

Non-Japanese subjects aged ≥18 years (without COVID-19) (1,853 in the PROVENT study and 198 in the STORM CHASER study; evaluable for PK) received a single dose of tixagevimab 150 mg and cilgavimab 150 mg as two separate sequential IM injections in the hips. Table 22 shows the serum concentrations of tixagevimab and cilgavimab.

21) Antibody titer determined in SARS-CoV-2 neutralization assay is a reciprocal of the maximum dilution at which the antibody inhibits viral entry by 80%. A reciprocal of the slope of the regression line between the serum concentration of tixagevimab and cilgavimab (total concentration) and 80% neutralization antibody titer against SARS-CoV-2, therefore, reflects the EC_{80} of tixagevimab and cilgavimab (total concentration).

Table 22. Serum concentrations of tixagevimab and cilgavimab after a single dose of tixagevimab 150 mg and cilgavimab 150 mg as separate sequential IM injections in the hips in non-Japanese subjects (without COVID-19)

Study	Sampling point	Serum concentration (μg/mL)			
		N	Tixagevimab	N	Cilgavimab
PROVENT study	Day 8	1544	9.41 (93.3)	1544	9.03 (101)
	Day 29	1222	11.9 (65.4)	1222	11.3 (83.7)
	Day 58	1052	9.33 (71.9)	1049	8.92 (86.4)
	Day 92	647	7.32 (69.7)	646	7.00 (90.8)
	Day 183	35	4.03 (46.5)	35	3.65 (49.7)
STORM CHASER study	Day 8	104	9.02 (90.6)	104	9.21 (85.7)
	Day 29	126	11.3 (53.9)	126	11.1 (57.3)
	Day 58	12	13.1 (39.1)	12	11.7 (44.1)

Geometric mean (geometric CV%)

ADA data from 46 subjects who received tixagevimab and cilgavimab were available in the PROVENT study. Of note, 0.0% (0 of 36) of subjects and 2.8% (1 of 36) of subjects tested positive for anti-tixagevimab and anti-cilgavimab antibodies, respectively, until Day 58. No ADA data from the STORM CHASER study have been submitted.

6.2.2.2 Global phase III study (CTD T 5.3.5.1.1, Study D8851C00001 [TACKLE study], ongoing since January 2021 [data cut-off in August 2021])

Patients aged ≥18 years with COVID-19 (426 evaluable for PK) received a single dose of tixagevimab 300 mg and cilgavimab 300 mg as two separate sequential IM injections in the hips. Table 23 shows serum PK parameters.

Table 23. Serum PK parameters of tixagevimab and cilgavimab after a single dose of tixagevimab 300 mg and cilgavimabas 300 mg as two separate sequential IM injections in the hips in patients with COVID-19

N	Analyte	C_{max} (μg/mL)	t_{max} (days)	$AUC_{0\text{-}28day}$ (μg·day/mL)
144	Tixagevimab	21.9 (61.7)	14.9 [1.10, 86.0]	472 (70.0) [a)]
142	Cilgavimab	20.3 (63.6)	15.0 [1.10, 85.1]	434 (72.1) [b)]

Geometric mean (geometric C V%); t_{max}, median [range]; a) n = 133; b) n = 132

ADA data from 134 patients who received tixagevimab and cilgavimab were available. Of note, 1.8% (2 of 112) of subjects and 8.3% (10 of 121) of subjects tested positive for anti-tixagevimab and anti-cilgavimab antibodies, respectively, until Day 85.

6.2.3 PPK analysis (CTD P 5.3.3.5)

PK data (2,527 subjects, 7,375 sampling points) were obtained from healthy subjects, subjects without COVID-19, and patients with COVID-19 who received a single dose of the combination of tixagevimab and cilgavimab intramuscularly or by intravenous infusion in the foreign phase I study (Study D8850C00001), foreign phase III study (PROVENT and STORM CHASER studies), and global phase III study (TACKLE study). A PPK analysis (NONMEM version 7.4.4) was performed using these PK data.

The final model was described by a 2-compartment model with the first-order absorption by intramuscular injection or intravenous infusion and linear elimination process. Covariates selected were body weight and underlying diabetes mellitus for the total body clearance (CL) of tixagevimab and

cilgavimab (total concentration); body weight, underlying diabetes mellitus, and sex for the central volume of distribution (Vc); body weight for the peripheral volume of distribution (Vp) and intercompartmental clearance (Q); and sex and age for the first-order absorption rate constant (Ka) after an IM dose.[22)]

An impact of each covariate on the PK of tixagevimab and cilgavimab (total concentration) after a single IM dose was investigated based on the final model, but none of the covariates showed any clinically meaningful change in PK.

The median and 90th percentile range[23)] of $AUC_{0\text{-}3month}$ and $AUC_{0\text{-}9month}$ ratios (pediatrics weighing 40-95 kg[24)]/adults weighing 36-177 kg[25)]) estimated using the final model were 1.09 [1.04, 1.15] and 1.08 [1.04, 1.16], respectively.

6.R Outline of the review conducted by PMDA

6.R.1 Ethnic differences in PK of tixagevimab and cilgavimab

The applicant's explanation about differences in the PK of tixagevimab and cilgavimab between the Japanese and non-Japanese populations:

Healthy Japanese subjects (Study D8850C00005) [see Section 6.2.1.1] and healthy non-Japanese subjects (Study D8850C00001) [see Section 6.2.1.2] received a single dose of tixagevimab and cilgavimab at 150/150 mg as two separate sequential IM injections in the hips or a single dose of tixagevimab and cilgavimab at 150/150 mg or 500/500 mg as IV infusions. Table 24 shows serum PK parameters based on PK data up to Day 31. Geometric mean C_{max} and $AUC_{0\text{-}30day}$ were 1.3 to 1.4 times higher in the Japanese population than in the non-Japanese population after the intramuscular administration and 1.1 to 1.2 times higher after the intravenous infusion. The differences were considered partly attributable to a difference in body weight between the Japanese and non-Japanese populations.[26)]

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22) Potential covariates tested were chronic liver disease, chronic kidney disease, chronic obstructive pulmonary disease, immunodeficiency or use of immunosuppressive agents, COVID-19 status, and cardiovascular disease, clinical study, age (continuous variable), age (≥65 or <65 years), race, ethnic group, sex, AST, ALT, bilirubin, baseline serum albumin, eGFR, diabetes mellitus, cardiovascular disease (including hypertension), drug substances used (Process 2 or Process 3 [see Section 2.1.4]), and previous SARS-CoV-2 vaccination for CL; age (continuous variable), age (≥65 or <65 years), race, ethnic group, sex, diabetes mellitus, cardiovascular disease (including hypertension) for Vc; age (continuous variable), age (≥65 or <65 years), race, ethnic group, and sex for Vp; and BMI (<30 kg/m^2 or ≥30 kg/m^2), age (continuous variable), age (≥65 or <65 years), race, ethnic group, and sex for Ka. For the CL, Vc, Vp, and Q, body weight was incorporated in the base model as a covariate.

23) The datasets of the adult population (n = 2,527) and pediatric population (n = 1,900) provided in Footnotes 24 and 25 were used for analysis. The median and 90th percentile range of $AUC_{0\text{-}3month}$ and $AUC_{0\text{-}9month}$ ratios (pediatrics/ adults) were determined from the estimated serum concentration of tixagevimab and cilgavimab (total concentration) obtained from a total of 10 runs of the simulation of a single IM dose of tixagevimab and cilgavimab at 150/150 mg for individual populations.

24) Of all the subjects (n = 2,527) included in the PPK modeling, 1,900 who fell within a range between the median at 12 years (40 kg) and the 95th percentile at 18 years (95 kg) according to the body weight growth curves of boys published by the Centers for Disease Control and Prevention (CDC) in the US (https://www.cdc.gov/growthcharts/data/set1clinical/cj41c021.pdf [last accessed on July 5, 2022]) were used for the body weight distribution in the pediatric population.

25) Body weight distribution in all the subjects (n = 2,527) included in the PPK modeling was handled as that in the adult population.

26) The mean body weights in the tixagevimab and cilgavimab 150/150 mg IM group, 150/150 mg IV group, and 500/500 mg IV group were 66.3, 60.3, and 65.5 kg in the Japanese phase I study in healthy Japanese subjects (Study D8850C00005) and 75.5, 72.2, and 74.3 kg in the foreign phase I study in healthy non-Japanese subjects (Study D8850C00001).

Table 24. PK parameters in healthy Japanese and non-Japanese subjects after a single IM or IV dose of combination of tixagevimab and cilgavimab

Route of administration	Dose[a)] (mg)	Race	N	C_{max} (μg/mL)		$AUC_{0\text{-}30day}$ (μg·day/mL)	
				Tixagevimab	Cilgavimab	Tixagevimab	Cilgavimab
IM	150/150	Japanese	6	21.1 (18.9)	21.3 (14.9)	558 (17.6)	554 (13.9)
		Non-Japanese	10	16.5 (35.6)	15.3 (38.5)	421 (42.2)	390 (42.0)
IV	150/150[b)]	Japanese	12	57.0 (12.0)	56.2 (11.7)	907 (7.66)	920 (9.49)
		Non-Japanese	10	52.7 (11.5)	50.1 (15.3)	812 (12.2)	775 (15.1)
	500/500[b)]	Japanese	6	172 (10.4)	166 (8.63)	2842 (14.1)	2681 (12.4)
		Non-Japanese	10	162 (11.3)	154 (14.7)	2361 (13.3)	2339 (13.3)

Geometric mean (geometric CV%)
a) Doses of tixagevimab/cilgavimab
b) Tixagevimab and cilgavimab were co-administered as an intravenous infusion at 20 mg/min for the total amount.

PMDA accepts the explanation of the applicant.

6.R.2 Rationale for dosage regimen in adults

6.R.2.1 Rationale for the dosage regimen in the foreign phase III study intended to evaluate the efficacy in prevention of COVID-19

The dosage regimen in the foreign phase III studies intended to evaluate the efficacy of Evusheld in the prevention of COVID-19 (PROVENT and STORM CHASER studies) was a single IM dose of tixagevimab 150 mg and cilgavimab 150 mg.

The applicant's explanation about rationale for the above dosage regimen:

- Tixagevimab and cilgavimab do not compete each other for binding to the RBD of SARS-CoV-2 S-protein and show comparable neutralization activity *in vitro* [see Section 3.1.3.1]. These findings support the administration of the two monoclonal antibodies at a ratio of 1:1.
- In the foreign phase III studies (PROVENT and STORM CHASER studies) a single IM dose of tixagevimab 150 mg and cilgavimab 150 mg was selected to ensure that concentrations of tixagevimab and cilgavimab (total concentration) in the lung endothelial lining fluid (ELF) remain above the *in vitro* EC_{80} (40 or 104 ng/mL)[27)] against SARS-CoV-2 wild-type strain (USA-WA1/2020 isolate) for an adequate period on the assumption that 1% of the antibodies administered were distributed in the lung ELF.
- The dosage regimen selected in the foreign phase III studies (PROVENT and STORM CHASER studies) was justified by the following investigations:
  - After the dosage regimen had been selected in the foreign phase III studies (PROVENT and STORM CHASER studies), the minimum protective serum concentration was determined using the upper respiratory tract as the site of interest to inhibit SARS-CoV-2 viral load increase and prevent the onset of related symptoms. In view of the additionally obtained nasal lining fluid/serum concentration ratio of tixagevimab and cilgavimab (total concentration) (1.81%) [see Section 6.2.1.2] and *in vitro* EC_{80} (40 ng/mL), the minimum protective serum concentration of tixagevimab and cilgavimab (total concentration) against the wild-type strain to inhibit viral entry into the upper respiratory tract by 80% was estimated to be 2.2 μg/mL.
  - Using the final model in the PPK analysis [see Section 6.2.3], serum concentrations of tixagevimab and cilgavimab after a single IM dose of tixagevimab 150 mg and cilgavimab

[27)] Calculated from *in vitro* EC_{50} (10 ng/mL determined by microneutralization assay [see Section 3.1.3.1] and 26 ng/mL determined by focus reduction neutralization test) using a formula where the Hill coefficient was 1 ($EC_{80} = EC_{50} \times 4$).

150 mg were predicted.[28)] The predicted concentrations were inferred to be remain above the minimum protective serum concentration (2.2 μg/mL) against the wild-type strain for at least 6 months post-dose in the overall population. In addition, time to achieve the minimum protective serum concentration (2.2 μg/mL) in at least 90% of the population was estimated to be ≤36 hours post-dose.

6.R.2.2 Rationale for the dosage regimen in global phase III study to evaluate the efficacy in treatment of COVID-19

The dosage regimen in the global phase III study (TACKLE study) intended to evaluate the efficacy of Evusheld in the treatment of COVID-19 was a single IM dose of tixagevimab 300 mg and cilgavimab 300 mg.

The applicant's explanation about rationale for the selected dosage regimen:

- In the treatment of COVID-19, Evusheld should be administered at the earliest possible time upon the onset of the symptoms to ensure that the concentrations of tixagevimab and cilgavimab (total concentration) in the lung ELF promptly reach the *in vitro* EC_{80} (40 ng/mL) against the SARS-CoV-2 wild-type strain (USA-WA1/2020 isolate) and then remain above the concentration throughout the treatment period. The dosage regimen in the global phase III study (TACKLE study) therefore employed a single IM dose of tixagevimab 300 mg and cilgavimab 300 mg, which was higher than that in the foreign phase III studies (PROVENT and STORM CHASER studies) which were intended to evaluate the efficacy of Evusheld in the prevention of COVID-19.
- The dosage regimen selected in the global phase III study (TACKLE study) was justified by the following investigations:
  - After the dosage regimen had been selected in the global phase III study (TACKLE study), the minimum protective serum concentration was determined using the lower respiratory tract as the target site for the treatment of COVID-19. In view of the lower respiratory tract/serum concentration ratios of other monoclonal antibodies (6.5%, *Clin Pharmacol Ther.* 2022;111:595-604; 12%, *Antimicrob Agents Chemother.* 2019;63:e00350-19) and *in vitro* EC_{80} (40 ng/mL), the minimum protective serum concentration of tixagevimab and cilgavimab (total concentration) against the wild-type strain to inhibit viral entry into the lower respiratory tract by 80% was estimated to be 0.615 μg/mL (on the assumption that 6.5% of the antibodies administered was distributed in the lower respiratory tract) and 0.333 μg/mL (on the assumption of 12%).
  - Using the final model in the PPK analysis [see Section 6.2.3], serum concentrations of tixagevimab and cilgavimab after a single IM dose of tixagevimab and cilgavimab 150/150 mg or 300/300 mg were predicted,[29)] and time to reach the minimum protective serum concentrations (0.615 and 0.333 μg/mL) were estimated. Table 25 shows the results. In addition, at either dose, the serum concentrations in all the subjects were predicted to remain above the minimum protective serum concentrations (0.615 and 0.333 μg/mL) against the wild-type strain for ≥28 days post-dose.

[28)] The datasets of all the subjects (n = 2,527) included in the PPK modeling [see Section 6.2.3] were used to obtain individual serum concentration estimates of tixagevimab and cilgavimab (total concentration) from a total of 10 runs of the simulation of a single IM dose of tixagevimab 150 mg and cilgavimab 150 mg.

[29)] The datasets of all the subjects (n = 2,527) included in the PPK modeling [see Section 6.2.3] were used to obtain individual serum concentration estimates of tixagevimab and cilgavimab (total concentration) from a total of 10 runs of the simulation of a single IM dose of tixagevimab and cilgavimab 150/150 mg or 300/300 mg.

Table 25. Time to reach the minimum protective serum concentration against SARS-CoV-2 wild-type strain in ≥50% and ≥90% of the population after administration of single IM dose of tixagevimab and cilgavimab 150/150 mg or 300/300 mg

Dose	Minimum protective serum concentration: 0.615 μg/mL (6.5% of the dose distributed in the lower respiratory tract)		Minimum protective serum concentration: 0.333 μg/mL (12% of the dose distributed in the lower respiratory tract)	
	Time to reach in 50% of the population (h)	Time to reach in 90% of the population (h)	Time to reach in 50% of the population (h)	Time to reach in 90% of the population (h)
150/150 mg	1.92	6.72	1.44	3.36
300/300 mg	0.96	3.36	0.48	1.92

PMDA's view:

In light of the applicant's explanation in Sections 6.R.2.1 and 6.R.2.2, rationales for the dosage regimens of Evusheld for planning the phase III studies (PROVENT, STORM CHASER, and TACKLE studies) are understandable to a certain extent from the clinical pharmacological point of view. The appropriateness of the dosage and administration of Evusheld for the treatment and prevention of COVID-19 is further discussed based on the efficacy and safety data of Evusheld from phase III studies (PROVENT, STORM CHASER, and TACKLE studies) in Section 7.R.5.

6.R.3 Rationale for dosage and administration in pediatrics

The proposed dosage and administration in pediatrics aged ≥12 years and weighing ≥40 kg are the same as those in adults.

The applicant's explanation about the rationale:

Although the PK data of tixagevimab and cilgavimab in pediatrics are not available, the use of Evusheld in pediatrics is not considered to raise any safety or efficacy concern that is not found in adults, because (a) the results of an analysis using the PPK model predicted that exposure in pediatrics aged ≥12 years and weighing ≥40 kg would be comparable to that in adults [see Section 6.2.3]; and (b) both tixagevimab and cilgavimab specifically bind to the RBD of SARS-CoV-2 S-protein, an adventitious agent, and do not cross-react with human tissues [see Section 5.6.1]. In addition, subjects who received a single IM dose of tixagevimab 150 mg and cilgavimab 150 mg in the foreign phase III studies (PROVENT and STORM CHASER studies) weighed (median [minimum to maximum], hereinafter the same) 82.3 [36.0, 216.0] kg in the PROVENT study and 81.0 [41.7, 194.1] kg in the STORM CHASER study. Subjects who received a single IM dose of tixagevimab 300 mg and cilgavimab 300 mg in the global phase III study (TACKLE study) weighed 78.4 [45.0, 160.0] kg. These findings support the safety of Evusheld used at the proposed dosage and administration in subjects weighing approximately 40 kg [see Section 7.2.3]. In the Japanese phase I study (Study D8850C00005) and foreign phase I study (Study D8850C00001), the combination of tixagevimab and cilgavimab administered as a single IV dose higher than the proposed dosage and administration was demonstrated to be safe and tolerable [see Sections 7.1.1 and 7.1.2]. In view of the above results, the applicant considers that the same dosage and administration as those in adults can be selected in pediatrics aged ≥12 years and weighing ≥40 kg.

The currently ongoing clinical studies are as follows: a foreign phase I study (Study D8850C00006)[30] in fetuses aged ≥29 weeks of gestation and pediatrics aged <18 years and a foreign phase II study (Study D8850C00010)[31] in adults and pediatrics aged ≥12 years and weighing ≥40 kg who have moderate to severe immunodeficiency or have inadequate immune response to SARS-CoV-2 vaccines owing to the use of immunosuppressive agents.

PMDA's view:
Although pediatric clinical study data are not currently available, the applicant explains that Evusheld would be unlikely to raise particular safety and efficacy concerns if Evusheld at the dosage and administration for adults is used in pediatrics aged ≥12 years and weighing ≥40 kg. The applicant's explanation is understandable to a certain extent. Under the current situation of the COVID-19 pandemic, it is acceptable to select the same dosage and administration for pediatric patients. Evusheld has been authorized or approved for the indication of pre-exposure prophylaxis of COVID-19 in the US and EU, and the dosage and administration in pediatrics aged ≥12 years and weighing ≥40 kg are the same as those in adults.

The applicant, however, should continue collecting the safety information about the use of Evusheld in pediatrics in the post-marketing setting, including the results of currently ongoing Studies D8850C00006 and D8850C00010. The applicant should promptly provide any new information to healthcare professionals when it becomes available.

6.R.4 ADA

The applicant's explanation about ADA formation and the effects of ADA on the PK, efficacy, and safety of tixagevimab and cilgavimab:
In the Japanese phase I study (Study D8850C00005), 2 subjects tested positive for anti-tixagevimab antibodies [see Section 6.2.1.1]; 1 tested positive at baseline and 1 on Day 7. the ADA titer was negative in both subjects (below the lower limit of detection [80]).

In the foreign phase I study (Study D8850C00001), 1 and 7 subjects tested positive for anti-tixagevimab and anti-cilgavimab antibodies, respectively [see Section 6.2.1.2]; all of them were shown to be ADA-positive at the last sampling point (Day 361). ADA titers in 1 subject positive for anti-tixagevimab and anti-cilgavimab antibodies and the other one positive for anti-cilgavimab antibodies were close to the lower limit of detection (80 for anti-tixagevimab antibodies and 40 for anti-cilgavimab antibodies). ADA

[30] Study D8850C00006 is an open-label study intended to evaluate the PK and safety of tixagevimab and cilgavimab in combination and is planned to include a total of 100 subjects in the following cohorts:
- Cohort 1: Subjects without COVID-19 receive a single IM dose of the combination of tixagevimab and cilgavimab 30 to 300 mg each or a single IV dose of the combination of tixagevimab and cilgavimab 25 to 220 mg each according to the body weight.
- Cohort 2: Patients with mild to moderate COVID-19 receive a single IM dose of the combination of tixagevimab and cilgavimab 30 to 300 mg each or a single IV dose of the combination of tixagevimab and cilgavimab 25 to 220 mg according to the body weight.
- Cohort 3: Patients with severe COVID-19 receive a single IV dose of the combination of tixagevimab and cilgavimab 30 to 300 mg each according to the body weight.

[31] Study D8850C00010 is an open-label study intended to evaluate the safety and immunogenicity of tixagevimab and cilgavimab in combination and consists of the following groups:
- Group A (n = 100): Subjects receive the combination of tixagevimab 300 mg and cilgavimab 300 mg IM followed by the combination of tixagevimab 150 mg and cilgavimab 150 mg IM every 3 months over 12 months.
- Group B (n = 100): Subjects receive the combination of tixagevimab 600 mg and cilgavimab 600 mg IV followed by the combination of tixagevimab 300 mg and cilgavimab 300 mg IM every 6 months over 12 months.

titers in 5 subjects positive for anti-cilgavimab antibodies were negative (below the lower limit of detection [40]).

In the foreign phase III study (PROVENT study), 1 subject tested positive for anti-cilgavimab antibodies at baseline with the ADA titer of 640 [see Section 6.2.2.1].

In the global phase III study (TACKLE study), 2 and 10 subjects tested positive for anti-tixagevimab and anti-cilgavimab antibodies, respectively [see Section 6.2.2.2]; the positive result was obtained in 2 subjects on Day 85 for anti-tixagevimab antibodies as well as in 1 subject at baseline, 3 subjects on Day 29, and 9 subjects on Day 85 for anti-cilgavimab antibodies. ADA titers were 160.0 and 160.0 (individual values) for anti-tixagevimab antibodies and 80.0 (40.0, 320) (median [range]) for anti-cilgavimab antibodies. The following findings were obtained as the effects of ADA on the PK, efficacy, and safety of tixagevimab and cilgavimab:

- Serum tixagevimab or cilgavimab concentrations in subjects positive for ADA over time fell within a range of serum concentrations over time in subjects negative for ADA.
- Of 18 subjects in the Evusheld group who experienced the primary endpoint Event,[32)] 2 were tested for ADA and 1 was found positive for anti-cilgavimab antibodies. The positive result, however, was obtained at baseline, and the ADA titer was at the lower limit of detection (40).
- Of 5 subjects who experienced serious adverse events of cardiac and non-cardiac thrombosis, 1 was tested for ADA and found negative for anti-tixagevimab and anti-cilgavimab antibodies. Of 14 subjects who experienced injection site reaction, 3 were tested for ADA and found negative for anti-tixagevimab and anti-cilgavimab antibodies. Of note, neither anaphylaxis nor other serious hypersensitivity reactions occurred.

As described above, ADA is not shown to have any clear effects on the PK, efficacy, or safety of tixagevimab and cilgavimab, albeit ADA detected in clinical studies.

PMDA's view:
The applicant's explanation is acceptable. Nevertheless, the applicant should still continue collecting post-marketing information about ADA, including the data from currently ongoing clinical studies, and should promptly provide any new information to healthcare professionals when it becomes available.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted the main efficacy and safety data, in the form of results from clinical studies listed in Table 26.

[32)] Severe COVID-19 or all-cause death until Day 29

Table 26. Summary of clinical studies

Data category	Region	Study identifier	Phase	Population	No. of subjects enrolled	Dosage regimen	Main endpoints
Evaluation	Japan	Study D8850C00005	I	Healthy adults	Cohort 1 (a) n = 6 (b) n = 2 Cohort 2 (a) n = 6 (b) n = 2 Cohort 3[a)] (a) n = 12 (b) n = 4 Cohort 4 (a) n = 6 (b) n = 2	Cohort 1 (a) 150/150 mg IM: A single dose of tixagevimab 150 mg and cilgavimab 150 mg as separate sequential IM injections in the hips (b) Placebo: A single dose of placebo as IM injections in the hips Cohort 2 (a) 300/300 mg IM: A single dose of tixagevimab 300 mg and cilgavimab 300 mg as separate sequential IM injections in the hips (b) Placebo: A single dose of placebo as IM injections in the hips Cohort 3[a)] (a) 150/150 mg IV: A single dose of tixagevimab 150 mg and cilgavimab 150 mg co-administered as an IV infusion (b) Placebo: A single dose of placebo as an IV infusion Cohort 4 (a) 500/500 mg IV: A single dose of tixagevimab 500 mg and cilgavimab 500 mg co-administered as an IV infusion (b) Placebo: A single dose of placebo as an IV infusion	Safety PK
Evaluation	Foreign	Study D8850C00001	I	Healthy adults	Cohort 1a (a) n = 10 (b) n = 2 Cohort 1b (a) n = 10 (b) n = 2 Cohort 2 (c) n = 10 (d) n = 2 Cohort 3 (a) n = 10 (b) n = 2 Cohort 4 (a) n = 10 (b) n = 2	Cohort 1a (a) 150/150 mg IM: A single dose of tixagevimab 150 mg and cilgavimab 150 mg as separate sequential IM injections in the hips (b) Placebo: A single dose of placebo as IM injections in the hips Cohort 1b (a) 150/150 mg IV: A single dose of tixagevimab 150 mg and cilgavimab 150 mg as separate sequential IV infusions (b) Placebo: A single dose of placebo as IV infusions Cohort 2 (a) 500/500 mg IV: A single dose of tixagevimab 500 mg and cilgavimab 500 mg as separate sequential IV infusions (b) Placebo: A single dose of placebo as IV infusions Cohort 3 (a) 1,500/1,500 mg IV (sequential): A single dose of tixagevimab 1,500 mg and cilgavimab 1,500 mg as sequential IV infusions (b) Placebo: A single dose of placebo as IV infusions Cohort 4 (a) 1,500/1,500 mg IV (co-administration): A single dose of tixagevimab 1,500 mg and cilgavimab 1,500 mg co-administered as an IV infusion (b) Placebo: A single dose of placebo as an IV infusion	Safety PK

Data category	Region	Study identifier	Phase	Population	No. of subjects enrolled	Dosage regimen	Main endpoints
Evaluation	Foreign	Study D8850C00002 (PROVENT)	III	Individuals who are at increased risk for inadequate response to active immunization (predicted poor responder to SARS-CoV-2 vaccines) or intolerant of vaccine or who are at increased risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 (pre-exposure dose)	(a) n = 3,500 (b) n = 1,754	(a) Evusheld: A single dose of tixagevimab 150 mg and cilgavimab 150 mg as separate sequential IM injections in the hips (b) Placebo: A single dose of placebo as IM injections in the hips	Efficacy Safety PK
Evaluation	Foreign	Study D8850C00003 (STORM CHASER)	III	Individuals who have potential exposure to a specific identified person with laboratory-confirmed SARS-CoV-2 infection and are at appreciable risk of developing COVID-19 (post-exposure dose)	(a) n = 756 (b) n = 375	(a) Evusheld: A single dose of tixagevimab 150 mg and cilgavimab 150 mg as separate sequential IM injections in the hips (b) Placebo: A single dose of placebo as IM injections in the hips	Efficacy Safety PK
Evaluation	Global	Study D8851C00001 (TACKLE)	III	Patients with COVID-19	(a) n = 456 (b) n = 454	(a) Evusheld: A single dose of tixagevimab 300 mg and cilgavimab 300 mg as separate sequential IM injections to the hips (b) Placebo: A single dose of placebo as IM injections in the hips	Efficacy Safety PK

a) Consisted of 2 sub-cohorts each including either 8 men or 8 women (6 in the 150/150 mg IV group and 2 in the placebo group)

7.1 Phase I studies

7.1.1 Japanese phase I study (CTD P 5.3.4.1.1, Study D8850C00005, ongoing since March 2021[33)] [data cut-off in [redacted] 20[redacted]])

A randomized, double-blind, placebo-controlled study was conducted at 1 study site in Japan to investigate the safety of the combination of tixagevimab and cilgavimab in healthy Japanese subjects aged ≥18 years.

Table 27 shows the dosage regimen.

33) Follow-up until Day 361 is ongoing.

Table 27. Dosage regimens in Japanese phase I study

Cohort	Group	Dosage regimen
Cohort 1	150/150 mg IM	A single dose of tixagevimab 150 mg/1.5 mL (100 mg/mL) and cilgavimab 150 mg/1.5 mL (100 mg/mL) as separate sequential IM injections in the right and left hips)
	Placebo	A single dose of placebo as IM injections in the hips
Cohort 2	300/300 mg IM	A single dose of tixagevimab 300 mg/3.0 mL (100 mg/mL) and cilgavimab 300 mg/3.0 mL (100 mg/mL) as separate sequential IM injections in the right and left hips)
	Placebo	A single dose of placebo as IM injections in the hips
Cohort 3	150/150 mg IV	A single dose of tixagevimab 150 mg and cilgavimab 150 mg co-administered as an IV infusion at 20 mg/min
	Placebo	A single dose of placebo as an IV infusion
Cohort 4	500/500 mg IV	A single dose of tixagevimab 500 mg and cilgavimab 500 mg co-administered as an IV infusion at 40 mg/min
	Placebo	A single dose of placebo as an IV infusion

A total of 40 subjects were randomized and received the study drug (Cohorts 1, 2 and 4 each consisted of 6 subjects in the Evusheld group and 2 in the placebo group; and Cohort 3 consisted of 12 subjects in the Evusheld group and 4 in the placebo group). All of the subjects were included in the safety analysis set.

Safety data were analyzed. Adverse events occurred in 1 subject in the 150/150 mg IM group (headache), 1 in the 150/150 mg IV group (headache), and 1 in the placebo group (all cohorts pooled) (blood creatine phosphokinase increased) up to Day 31. A causal relationship between the study drug and the event in 1 subject in the 150/150 mg IM group (headache) could not be ruled out. The outcome of the event was “resolved.”

No deaths, serious adverse events, or adverse events leading to discontinuation occurred.

7.1.2 Foreign phase I study (CTD T 5.3.4.1.1, Study D8850C00001, August 2020 to October 2021)

A randomized, double-blind, placebo-controlled study was conducted at 1 study site in the UK to investigate the safety and other aspects of the combination of tixagevimab and cilgavimab in healthy non-Japanese subjects aged ≥18 years.

Table 28 shows the dosage regimen.

Table 28. Dosage regimens in foreign phase I study

Cohort	Group	Dosage regimen
Cohort 1a	150/150 mg IM	A single dose of tixagevimab 150 mg/1.5 mL (100 mg/mL) and cilgavimab 150 mg/1.5 mL (100 mg/mL) as separate sequential IM injections in the right and left hips)
	Placebo	A single dose of placebo as IM injections in the hips
Cohort 1b	150/150 mg IV	A single dose of tixagevimab 150 mg and cilgavimab 150 mg as separate sequential IV infusions at a maximum of 20 mg/min
	Placebo	A single dose of placebo as IV infusions
Cohort 2	500/500 mg IV	A single dose of tixagevimab 500 mg and cilgavimab 500 mg as separate sequential IV infusions at a maximum of 20 mg/min
	Placebo	A single dose of placebo as IV infusions
Cohort 3	1,500/1,500 mg IV (sequential)	A single dose of tixagevimab 1,500 mg and cilgavimab 1,500 mg as separate sequential IV infusions at a maximum of 20 mg/min
	Placebo	A single dose of placebo as IV infusions
Cohort 4	1,500/1,500 mg IV (co-administration)	A single dose of tixagevimab 1,500 mg and cilgavimab 1,500 mg co-administered as an IV infusion at a maximum of 50 mg/min
	Placebo	A single dose of placebo as an IV infusion

A total of 60 subjects were randomized and received the study drug (Cohorts 1a-4, 10 subjects per group for Evusheld and 2 per group for placebo). All the subjects were included in the safety analysis set. Of note, 1 subject in the 500/500 mg IV group and 1 subject in the placebo group discontinued the study due to consent withdrawal after receiving the study drug.

Safety data were analyzed. Adverse events occurred until Day 361 in 2 subjects in the 150/150 mg IM group (nasopharyngitis, coronavirus infection and memory impairment in 1 subject each [some subjects had more than 1 event]), 5 subjects in the 150/150 mg IV group (headache, abdominal distension, and abdominal pain in 2 subjects each; and diarrhoea, energy increased, lymphadenitis, malaise, nail infection, nausea, pain in extremity, tremor, and urinary tract infection in 1 subject each [some subjects had more than 1 event]), 6 subjects in the 500/500 mg IV group (headache and toothache in 2 subjects each; and back pain, diarrhoea, fatigue, myalgia, nasopharyngitis, abdominal discomfort, application site irritation, ligament sprain, and tooth repair in 1 subject each [some subjects had more than 1 event]), 7 subjects in the 1,500/1,500 mg IV (sequential) group (headache in 3 subjects; and back pain, myalgia, arthralgia, constipation, heavy menstrual bleeding, nasal congestion, oral herpes, rhinorrhoea, rotator cuff syndrome, seasonal allergy, and tooth infection in 1 subject each [some subjects had more than 1 event]), 6 subjects in the 1,500/1,500 mg IV (co-administration) group (fatigue in 2 subjects; and back pain, diarrhoea, COVID-19, dizziness, hypoaesthesia, muscle strain, musculoskeletal discomfort, and myxoid cyst in 1 subject each [some subjects had more than 1 event]), and 8 subjects in the placebo group (all cohorts pooled) (headache and oropharyngeal pain in 2 subjects each; and back pain, nasal congestion, urinary tract infection, dysmenorrhoea, injury, palpitations, paraesthesia, vessel puncture site pain, vitreous floaters, and vulval vaginal candidiasis in 1 subject each [some subjects had more than 1 event]). A causal relationship to the study drug could not be ruled out for several events, i.e., the events in 1 subject in the 150/150 mg IM group (memory impairment), 2 subjects in the 150/150 mg IV group (tremor, headache, and lymphadenitis in 1 subject each [a subject had more than 1 event]), 2 subjects in the 500/500 mg IV group (fatigue and myalgia in 1 subject each), 2 subjects in the 1,500/1,500 mg IV (sequential) group (headache in 2 subjects and arthralgia in 1 subject [a subject had more than 1 event]), 1 subject in the 1,500/1,500 mg IV (co-administration) group (fatigue), and 2 subjects in the placebo group (all cohorts pooled) (headache and paraesthesia in 1 subject each). The outcomes of these events were all “resolved.”

No deaths, serious adverse events, or adverse events leading to discontinuation occurred.

7.2 Phase III studies

7.2.1 Foreign phase III study (CTD P 5.3.5.1.1: Study D8850C00002 [PROVENT], ongoing since November 2020 [data cut-off in May, June, and August 2021])

A randomized, double-blind, placebo-controlled, parallel group study was conducted at 87 study sites in 5 countries (the US, the UK, Belgium, France, and Spain) to evaluate the efficacy and safety of the combination of tixagevimab and cilgavimab (in a pre-exposure prophylaxis setting) in subjects aged ≥18 years who were at increased risk for inadequate response to active immunization (predicted poor responder to SARS-CoV-2 vaccines) or intolerant of vaccine, or who are at risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 or COVID-19 (target sample size, 5,150 subjects; 3,433 in the Evusheld group and 1,717 in the placebo group).[34)]

Table 29 shows the key inclusion and exclusion criteria of this study.

[34)] The target sample size was calculated as the number of subjects required to provide the statistical power of approximately 90% at a 2-sided significance level of 5% on the assumption that the expected relative risk reduction ({1 – (incidence of Events in the Evusheld group/incidence of Events in the placebo group)} × 100) would be 80% for subjects with SARS-CoV-2 RT-PCR-positive symptomatic illness occurring through Day 183 (Event).

Table 29. Main inclusion and exclusion criteria

Inclusion criteria	1. Any of the following is met: (a) Individuals who are at risk for inadequate response to active immunization (predicted poor responder to SARS-CoV-2 vaccines) or intolerant of vaccine, defined as: • ≥60 years of age • Obese (≥BMI 30 kg/m^2) • Congestive cardiac failure • Chronic obstructive pulmonary disease • Chronic kidney disease (GFR <30 mL/min/1.73 m^2) • Chronic liver disease • Immunocompromised state (solid organ transplant, blood or bone marrow transplant, immunodeficiency, HIV, or use of corticosteroids or other immunosuppressive agents) • Previous history of severe adverse events or serious adverse events after receiving any approved vaccine. (b) Individuals who are at increased risk for of SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 or COVID-19. Examples are: • Healthcare workers and other staff members for long-term care facilities (e.g., skilled nursing facilities, assisted living facilities, or independent facilities for senior citizens) • Workers in industrial settings shown to have been at an increased risk of SARS-CoV-2 infection (e.g., meat-packing plants) • Military personnel living or working in high-density settings (e.g., barracks, military ships, or close-quarters working environments.) • Students living in dormitory settings • Others living or working in settings of similar close or high-density proximity. 2. Serologically negative for SARS-CoV-2 at screening. 3. Medically stable, defined as not requiring significant change in therapy or hospitalization for worsening of underlying disease during the 1 month before enrollment, with no acute change in condition at the time of enrollment, judged by a (sub-)investigator.
Exclusion criteria	1. Has significant infection or other acute illness, including fever (>37.8°C), on the day prior to or day of randomization. 2. Has a history of SARS-CoV-2 infection or a positive result for SARS-CoV-2 antibody at screening. 3. Previously received vaccine, monoclonal antibodies, or biological preparations for prevention of SARS-CoV-2 infection (irrespective of approval status) or is scheduled to receive any of them during the follow-up period.

In this study, subjects received a single dose of the combination of tixagevimab 150 mg and cilgavimab 150 mg or placebo intramuscularly. More specifically, tixagevimab 150 mg/1.5 mL (100 mg/mL) and cilgavimab 150 mg/1.5 mL (100 mg/mL) were administered as separate sequential IM injections in 1 site each of the right and left hips.

Of the randomized 5,254 subjects (3,500 in the Evusheld group and 1,754 in the placebo group), 5,197 received the study drug and were included in the full analysis set (FAS) (3,460 in the Evusheld group and 1,737 in the placebo group) on the basis of the assigned group and in the safety analysis set (3,461 in the Evusheld group and 1,736 in the placebo group) on the basis of the study drug actually administered. Of the FAS, 5,172 subjects (3,441 in the Evusheld group and 1,731 in the placebo group) were included in the full pre-exposure analysis set (FPAS), and the remaining 25 subjects were excluded from the analysis because they were found positive for SARS-CoV-2 at baseline (19 in the Evusheld group and 6 in the placebo group). The FPAS was also used as the efficacy analysis population.

The primary endpoint was the relative risk reduction [{1 − (the incidence of Events in the Evusheld group/the incidence of Events in the placebo group)} × 100], expressed as the percentage of subjects

who experienced COVID-19 symptoms[35)] and had a SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR)-positive[36)] result after administration of the study drug through Day 183 ("Event"). The primary analysis was planned to be performed at the time when approximately 24 Events for the primary endpoint had been confirmed or 30% of the subjects had become unblinded, whichever occurred earlier. The analysis was eventually performed when 30% of the subjects became unblinded.[37)] As of the data cut-off for the primary analysis (May 5, 2021), in the FPAS, the percentage of unblinded subjects[38)] was 29.9% (1,548 of 5,172 subjects) (29.3% [1,008 of 3,441 subjects] in the Evusheld group and 31.2% [540 of 1,731 subjects] in the placebo group), and the percentage of subjects who received SARS-CoV-2 vaccine was 18.6% (961 of 5,172 subjects) (12.3% [424 of 3,441 subjects] in the Evusheld group and 31.0% [537 of 1,731 subjects] in the placebo group). The median duration (range) of follow-up from administration of the study drug to the data cut-off for the primary analysis was 83 (4, 166) days in the Evusheld group and 83 (3, 166) days in the placebo group.

Of the 5,254 subjects randomized up until the data cut-off for the primary analysis (May 5, 2021), 145 (2.8%) discontinued the study after receiving the study drug. More specifically, 2.6% (91 of 3,500) of the subjects in the Evusheld group discontinued the study owing to subject's withdrawal (56 subjects), lost to follow-up (11 subjects), death (4 subjects), protocol deviation (1 subject) and decision of the physician (1 subject), and other reasons (18 subjects); and 3.1% (54 of 1,754) of subjects in the placebo group discontinued the study owing to subject's withdrawal (32 subjects), lost to follow-up (8 subjects), death (4 subjects), and other reasons (10 subjects).

Efficacy data were analyzed. Table 30 shows the primary endpoint results, the relative risk reduction[39)] expressed as the percentage of subjects with SARS-CoV-2 RT-PCR-positive[36)] symptomatic illness[35)] occurring through Day 183 (incidence of Events) in each group, showing a statistically significant difference between the Evusheld group and the placebo group. Figure 1 shows the Kaplan-Meier curves of the cumulative incidence of the primary endpoint Events.

35) Any of the symptoms, irrespective of time of onset, such as fever, shortness of breath, dyspnoea, new onset of confusion (subjects aged ≥60 years only), inappetence or decreased dietary intake (subjects aged ≥60 years only), and increased oxygen dose (subjects aged ≥60 years requiring supplemental oxygen at baseline only) or any of the ≥2-day persistent symptoms such as chilliness, cough, fatigue, myalgia, body pain, headache, new onset of ageusia, new onset of smell loss, pharyngodynia, nasal congestion, nasal discharge, nausea, vomiting, and diarrhoea.

36) RT-PCR testing within 3 days was recommended for a subject reporting any of the specified symptoms. Of note, an analysis on the primary endpoint employed the results of RT-PCR tests performed for 5 days before and 10 days after the onset of the symptom.

37) The analysis was initially planned to be performed when 24 primary analysis Events were confirmed, but the protocol was changed in accordance with Protocol Amendment 6 ([redacted], 20[redacted]) because an increasing number of subjects became unblinded for assessment of eligibility for vaccination in this study. The analysis was to be performed when approximately 24 Events had been confirmed or 30% of the subjects had become unblinded, whichever occurred earlier.

38) Based on the exclusion criteria specified before the start of the study, all the initially enrolled subjects were not vaccinated with any SARS-CoV-2 vaccine. After the start of the study, however, vaccines became available. In accordance with Protocol Amendment 4 (December 21, 2021), the protocol allowed post-enrollment vaccination if requested by the subject. In light of a possibility that tixagevimab and cilgavimab administered in combination before vaccination might interfere with immune response to the vaccine, unblinding of the subject was recommended to determine the necessity and timing of the vaccination.

39) {1 – (the incidence of Events in the Evusheld group/the incidence of Events in the placebo group)} × 100

Table 30. Percentage of subjects with SARS-Cov-2 RT-PCR-positive symptomatic illness occurring through Day 183 (FPAS, data cut-off on May 5, 2021)

	Evusheld	Placebo
Incidence of Events	0.2% (8/3,441)	1.0% (17/1,731)
Relative risk reduction [95% confidence interval][a)]	76.7% [46.1%, 90.0%]	
P value [b)]	< 0.001	

Subjects who had become unblinded, had been vaccinated with SARS-CoV-2 vaccine, or had received other COVID-19 preventive drugs (drugs for preventing the onset of COVID-19) before the onset of the Events were censored at unblinding, SARS-CoV-2 vaccination, or receipt of COVID-19 preventive drugs, whichever occurred earlier.

a) Estimated based on a Poisson regression model with robust variance. The model included treatment group and age at informed consent (≥60 years or <60 years) as covariates with the log of the follow-up period as an offset variable.

b) A 2-sided significance level of 5%

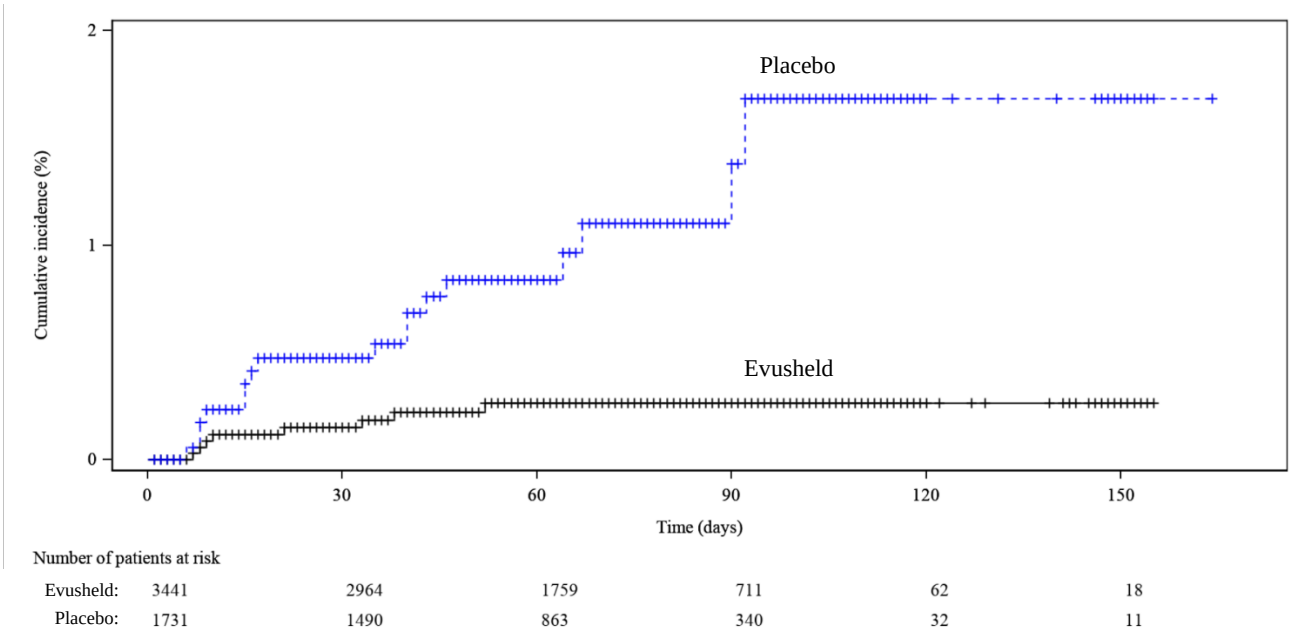

Figure 1. Cumulative incidence of primary endpoint Events (FPAS, data cut-off on May 5, 2021)

Severe COVID-19 or death[40)] did not occur in the Evusheld group but occurred in 1 subject in the placebo group.[41)]

Enrollment of new subjects was suspended after the primary analysis on the primary endpoint, but follow-up of the subjects was continued. An additional analysis was performed with a median duration of follow-up (from administration of the study drug to data cut-off) of 6 months where 5 months had passed since administration of the study drug in all the subjects (data cut-off on August 29, 2021). The median duration (range) of follow-up from administration of the study drug to data cut-off was 196 (4, 282) days in the Evusheld group and 196 (3, 282) days in the placebo group. Table 31 shows the relative risk reduction expressed as the percentage of subjects with SARS-CoV-2 RT-PCR-positive[36)] symptomatic illness[35)] occurring through Day 183 (incidence of Events) in each group. Figure 2 shows the Kaplan-Meier curves of the cumulative incidence of the Events.

40) Defined as conditions accompanying pneumonia (fever, cough, tachypnoea or dyspnoea, and lung infiltration) or hypoxaemia (SpO_2 <90% on room air or severe respiratory distress) and a score of ≥5 on the WHO Clinical Progression Scale (hospitalization with supplemental oxygen by mask or nasal cannula [score 5]) (*Lancet Infect Dis.* 2020;20:e192-e197)

41) Other 2 subjects in the placebo group had severe or fatal COVID-19 but the subjects were censored owing to unblinding.

Table 31. Percentage of subjects with SARS-CoV-2 RT-PCR-positive symptomatic illness occurring through Day 183 (FPAS, data cut-off on August 29, 2021)

	Evusheld	Placebo
Incidence of Events	0.3% (11/3,441)	1.8% (31/1,731)
Relative risk reduction [95% confidence interval] a)	82.8% [65.8%, 91.4%]	

Subjects who had become unblinded, had been vaccinated with SARS-CoV-2 vaccine, or had received other COVID-19 preventive drugs (drugs for preventing the onset of COVID-19) before the onset of the Events were censored at unblinding, SARS-CoV-2 vaccination, or receipt of preventive drugs, whichever occurred earlier.

a) Estimated based on a Poisson regression model with robust variance. The model included treatment group and age at informed consent (≥60 years or <60 years) as covariates with the log of the follow-up period as an offset variable.

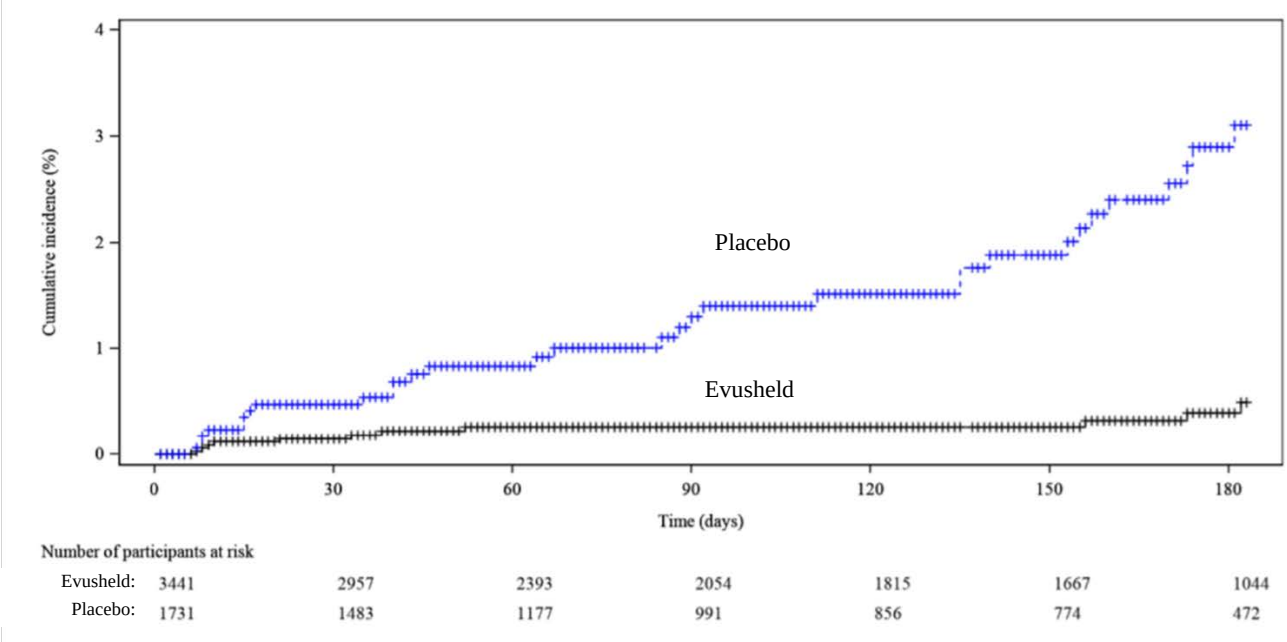

Figure 2. Cumulative incidence of primary endpoint Events (FPAS, data cut-off on August 29, 2021)

Safety data (data cut-off on June 29, 2021[42]) were analyzed. The incidences of adverse events and adverse drug reactions[43] were 40.9% (1,417 of 3,461 subjects) and 8.5% (293 of 3,461 subjects), respectively, in the Evusheld group, and 40.2% (698 of 1,736 subjects) and 6.9% (119 of 1,736 subjects), respectively, in the placebo group. Table 32shows adverse events and/or adverse reactions occurring ≥1% of subjects in either group. The median duration (range) of follow-up from administration of the study drug to data cut-off was 137 (4, 221) days in the Evusheld group and 135 (3, 221) days in the placebo group.

[42] The data cut-off was preliminarily scheduled prior to unblinding as a time point when 3 months have passed since administration of the study drug in all the subjects

[43] Adverse events considered causally related to the study drug by the (sub-)investigator

Table 32. Adverse events and/or adverse drug reactions occurring in ≥1% of subjects in either group (safety analysis set, data cut-off on June 29, 2021)

Event	Adverse events		Adverse drug reactions	
	Evusheld (N = 3,461)	Placebo (N = 1,736)	Evusheld (N = 3,461)	Placebo (N = 1,736)
Any event	1,417 (40.9)	698 (40.2)	293 (8.5)	119 (6.9)
Headache	227 (6.6)	112 (6.5)	59 (1.7)	24 (1.4)
Fatigue	163 (4.7)	76 (4.4)	43 (1.2)	18 (1.0)
Cough	120 (3.5)	63 (3.6)	0	1 (0.1)
Oropharyngeal pain	109 (3.1)	42 (2.4)	2 (0.1)	1 (0.1)
Rhinorrhoea	106 (3.1)	41 (2.4)	3 (0.1)	1 (0.1)
Diarrhoea	105 (3.0)	42 (2.4)	14 (0.4)	6 (0.3)
Nausea	87 (2.5)	37 (2.1)	17 (0.5)	4 (0.2)
Nasal congestion	86 (2.5)	28 (1.6)	5 (0.1)	1 (0.1)
Myalgia	83 (2.4)	35 (2.0)	10 (0.3)	5 (0.3)
Urinary tract infection	70 (2.0)	33 (1.9)	1 (< 0.1)	2 (0.1)
Arthralgia	66 (1.9)	26 (1.5)	4 (0.1)	1 (0.1)
Pain	64 (1.8)	23 (1.3)	5 (0.1)	2 (0.1)
Chills	54 (1.6)	30 (1.7)	11 (0.3)	2 (0.1)
Dyspnoea	54 (1.6)	24 (1.4)	0	0
Hypertension	53 (1.5)	26 (1.5)	0	0
Back pain	50 (1.4)	34 (2.0)	4 (0.1)	1 (0.1)
Vaccination complication	43 (1.2)	32 (1.8)	0	0
Pyrexia	37 (1.1)	31 (1.8)	5 (0.1)	4 (0.2)
Vomiting	35 (1.0)	20 (1.2)	3 (0.1)	1 (0.1)
Pain in extremity	20 (0.6)	19 (1.1)	1 (< 0.1)	1 (0.1)
COVID-19	15 (0.4)	27 (1.6)	0	0

n (%), MedDRA ver.24.0

Adverse events leading to death occurred in 7 subjects in the Evusheld group (overdose[44)] in 2 subjects; and arrhythmia, myocardial infarction, septic shock, end stage renal disease, and renal failure in 1 subject each) and in 5 subjects in the placebo group (COVID-19, overdose,[44)] toxicity to various agents, dementia Alzheimer's type, and acute respiratory distress syndrome in 1 subject each). A causal relationship to the study drug was ruled out for all of the events.

Serious adverse events (including adverse events leading to death) occurred in 92 subjects in the Evusheld group and 42 in the placebo group (Table 33). A causal relationship between the study drug and the event in 1 subject in the Evusheld group (mesenteric artery thrombosis) could not be ruled out. The outcome of the event was "resolved."

44) Overdose of illicit drugs

Table 33. Breakdown of serious adverse events

Evusheld (N = 92)	Cellulitis and hypertension in 4 subjects each; acute myocardial infarction, osteomyelitis, sepsis and overdose in 3 each; leukocytosis, cardiac failure congestive, myocardial infarction, cholelithiasis, cholecystitis, abscess limb, septic shock, musculoskeletal chest pain, cerebrovascular accident, syncope, transient ischaemic attack, nephrolithiasis, acute kidney injury, and pulmonary embolism in 2 each; and atrial fibrillation, angina pectoris, arrhythmia, cardiac failure, cardiomyopathy, coronary artery disease, paroxysmal atrioventricular block, abdominal pain, gastrointestinal haemorrhage, abdominal hernia, diarrhoea, faeces discoloured, gastrointestinal ulcer haemorrhage, haemorrhoids, irritable bowel syndrome, mesenteric artery thrombosis, pancreatitis chronic, peritoneal cyst, asthenia, cholecystitis acute, hepatic cirrhosis, pneumonia, appendicitis perforated, cystitis, device related infection, diverticulitis, gastroenteritis, gastroenteritis viral, localised infection, lower respiratory tract infection, peritonitis, soft tissue infection, ankle fracture, concussion, multiple injuries, peritoneal dialysis complication, heart rate irregular, troponin increased, dehydration, diabetes mellitus, diabetes mellitus inadequate control, diabetes with hyperosmolarity, hyperglycaemia, hyponatraemia, arthralgia, osteoarthritis, lung neoplasm malignant, rectal adenocarcinoma, bell's palsy, carotid artery stenosis, complex regional pain syndrome, epilepsy, hepatic encephalopathy, metabolic encephalopathy, migraine, partial seizures, presyncope, seizure, abortion spontaneous, alcohol abuse, suicidal ideation, end stage renal disease, hydronephrosis, renal failure, intermenstrual bleeding, vaginal bleeding, chronic obstructive pulmonary disease, and diabetic foot in 1 subject each (some subjects had more than 1 event)
Placebo (N = 42)	Non-cardiac chest pain and COVID-19 in 2 subjects each; and acute myocardial infarction, atrial fibrillation, acute left ventricular failure, retinal detachment, gastrointestinal haemorrhage, pancreatitis, pancreatitis acute, cholelithiasis, gallbladder obstruction, COVID-19 pneumonia, postoperative wound infection, staphylococcal infection, urinary tract infection, overdose, fall, femur fracture, fibula fracture, gun shot wound, incisional hernia obstructive, joint injury, procedural pain, road traffic accident, subdural haemorrhage, tendon rupture, tibia fracture, toxicity to various agents, wound, hepatic enzyme increased, costochondritis, brain neoplasm benign, Hodgkin's disease, lung adenocarcinoma recurrent, malignant neoplasm of unknown primary site, meningioma benign, rectal cancer, renal cell carcinoma, cerebrovascular accident, syncope, dementia Alzheimer's type, dizziness, loss of consciousness, depression, pelvi-ureteric obstruction, acute respiratory distress syndrome, pulmonary oedema, aortic aneurysm, arteriosclerosis, and hypotension in 1 subject each (some subjects had more than 1 event)

Adverse events leading to treatment discontinuation occurred in 1 subject in the Evusheld group (cerebrovascular accident) and in 1 subject in the placebo group (alcoholism). A causal relationship to the study drug was ruled out for both events. The outcome of cerebrovascular accident was "resolved," and that of alcoholism was "did not resolve."

As of the data cut-off on August 29, 2021,[45)] the median duration (range) of follow-up from administration of the study drug to data cut-off was 196 (4, 282) days in the Evusheld group and 196 (3, 282) days in the placebo group. Adverse events occurred in 45.6% (1,579 of 3,461) of subjects in the Evusheld group and 45.5% (790 of 1,736) of subjects in the placebo group.

After the data cut-off on June 29, 2021, adverse events leading to death were newly reported in 2 subjects in the Evusheld group (cardiac failure congestive and cardio-respiratory arrest in 1 subject each) and 2 subjects in the placebo group (malignant neoplasm of unknown primary site and hepatic cirrhosis in 1 subject each). A causal relationship to the study drug was ruled out for all of the events. The deaths were adjudicated to be unrelated to COVID-19 by an independent committee.

After the data cut-off on June 29, 2021, serious adverse events were newly reported in 43 subjects in the Evusheld group and 21 in the placebo group (Table 34). A causal relationship to the study drug was ruled out for all of the events.

45) The cut-off date was scheduled after unblinding as a time point when the median duration of follow-up from administration of the study drug to data cut-off has reached 6 months, and 5 months have passed since administration of the study drug in all the subjects

Table 34. Breakdown of serious adverse events

Evusheld (N = 43)	Myocardial infarction and cardiac failure congestive in 3 subjects each; cholecystitis and pneumonia in 2 subjects each; and acute myocardial infarction, cerebral infarction, fall, osteoarthritis, appendicitis, urosepsis, blood creatine phosphokinase increased, ruptured cerebral aneurysm, lung neoplasm malignant, suicidal ideation, chronic obstructive pulmonary disease, uncoded, hepatic cyst, fatigue, oesophageal haemorrhage, abdominal abscess, lung abscess, gun shot wound, colon cancer stage IV, colon cancer, lower limb fracture, fluid overload, cholecystitis acute, skin laceration, influenza, enterococcal bacteraemia, bipolar disorder, squamous cell carcinoma of lung, cardiomegaly, pneumonia aspiration, sialoadenitis, acute kidney injury, sepsis, gastric ulcer, and depression in 1 subject each (some subjects had more than 1 event)
Placebo (N = 21)	COVID-19 pneumonia in 5 subjects; COVID-19 in 2 subjects; and inner ear disorder, vomiting, confusional state, pulmonary oedema, lacunar infarction, subdural haemorrhage, acute myocardial infarction, cholecystitis, pancreatitis acute, arteriovenous graft site infection, osteomyelitis, cholecystitis acute, septic shock, concussion, acute respiratory failure, atrial fibrillation, hydronephrosis, acute kidney injury, asthenia, small intestinal obstruction, depression, and gastritis in 1 subject each (some subjects had more than 1 event)

After the data cut-off on June 29, 2021, no adverse events leading to discontinuation newly reported.

7.2.2 Foreign phase III study (CTD P 5.3.5.1.2: Study D8850C00003 (STORM CHASER), ongoing since December 2020 [data cut-off in April, June, and August 2021])

A randomized, double-blind, placebo-controlled, parallel group study was conducted at 60 study sites in 2 countries (the US and UK) to evaluate the efficacy and safety of the combination of tixagevimab and cilgavimab (in a post-exposure setting) in subjects aged ≥18 years with potential exposure to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection, and who were therefore at appreciable risk of imminently developing COVID-19 (target sample size, 1,125 subjects; 750 in the Evusheld group and 375 in the placebo group).[46)]

Table 35 shows the key inclusion and exclusion criteria of this study.

Table 35. Key inclusion and exclusion criteria

Inclusion criteria	1. Persons with potential exposure, within 8 days, to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection (symptomatic or asymptomatic) who are therefore at appreciable risk of imminently developing COVID-19 at the time of enrollment (as defined below) • Residents living in long-term care facilities, including skilled nursing facilities, assisted living facilities, residences for senior citizens, and healthcare workers and other staff members for such facilities • Workers in industrial settings shown to have been at an increased risk of SARS-CoV-2 infection (e.g., meat-packing factories) • Military and civilian personnel living or working in military-related facilities (e.g., barracks, military ships, or close-quarters working environments) • Healthcare workers and other staff members at medical facilities • Students living in dormitories • Household contacts including any person living in the same household as an index case • Others living or working in similar close or high-density proximity 2. Absence of COVID-19 symptoms within 10 days prior to administration of the study drug 3. Serologically negative for SARS-CoV-2 at screening
Exclusion criteria	1. Has a history of SARS-CoV-2 infection or a positive result for SARS-CoV-2 antibody at screening 2. Previously received vaccine, monoclonal antibodies, or biological preparations for prevention of SARS-CoV-2 infection (irrespective of approval status) or is scheduled to receive any of them during the follow-up period.

46) The target sample size was calculated as the number of subjects required to provide the statistical power of approximately 90% at a 2-sided significance level of 5% on the assumption that the expected relative risk reduction [{1 – (incidence of Events in the Evusheld group/incidence of Events in the placebo group)} × 100) would be 75% for subjects with SARS-CoV-2 RT-PCR-positive symptomatic illness occurring through Day 183 (Event) and that the incidence of Events in the placebo group would be 4.5%.

In this study, subjects received a single dose of the combination of tixagevimab 150 mg and cilgavimab 150 mg or placebo intramuscularly. More specifically, tixagevimab 150 mg/1.5 mL (100 mg/mL) and cilgavimab 150 mg/1.5 mL (100 mg/mL) were administered as separate sequential IM injections in 1 site each of the right and left hips.

Of the randomized 1,131 subjects (756 in the Evusheld group and 375 in the placebo group), 1,121 (749 in the Evusheld group and 372 in the placebo group) received the study drug and were included in the FAS, which was also used as the safety analysis set and efficacy analysis population.

The primary endpoint was the relative risk reduction [{1 − (the incidence of Events in the Evusheld group/the incidence of Events in the placebo group)} × 100], expressed as the percentage of subjects who experienced COVID-19 symptoms[47)] and had a SARS-CoV-2 RT-PCR-positive[48)] result after administration of the study drug through Day 183 ("Event"). The primary analysis was performed 30 days after the onset of the 25th Event.[49)] As of the data cut-off for the primary analysis (April 7, 2021), in the randomized subjects, the percentage of unblinded subjects[50)] was 10.2% (115 of 1,131 subjects) (8.2% [62 of 756 subjects] in the Evusheld group and 14.1% [53 of 375 subjects] in the placebo group), and the percentage of subjects who received SARS-CoV-2 vaccine was 6.5% (73 of 1,131 subjects) (3.4% [26 of 756 subjects] in the Evusheld group and 12.5% [47 of 375 subjects] in the placebo group). The median duration (range) of follow-up from administration of the study drug to the data cut-off for the primary analysis was 49 (5, 115) days in the Evusheld group and 48 (20, 113) days in the placebo group.

Of the subjects randomized up until the data cut-off for the primary analysis (April 7, 2021), 1.9% (21 of 1,131) discontinued the study after receiving the study drug; more specifically, 2.0% (15 of 756) of the subjects in the Evusheld group discontinued the study owing to subject's withdrawal (7 subjects), lost to follow-up (2 subjects), and decision of the physician (1 subjects), and other reasons (5 subjects); and 1.6% (6 of 375) in the placebo group discontinued the study owing to subject's withdrawal (3 subjects), protocol deviation (1 subjects), and other reasons (2 subjects).

Efficacy data were analyzed. Table 36 shows the primary endpoint results, the relative risk reduction[51)] expressed as the percentage of subjects with SARS-CoV-2 RT-PCR-positive[48)] symptomatic illness[47)] occurring through Day 183 (incidence of Events) in each group, showing no statistically significant

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47) Any of the symptoms, irrespective of time of onset, such as fever, shortness of breath, dyspnoea, new onset of confusion (subjects aged ≥60 years only), inappetence or decreased dietary intake (subjects aged ≥60 years only), and increased oxygen dose (subjects aged ≥60 years requiring supplemental oxygen at baseline only) or any of the ≥2-day persistent symptoms such as chilliness, cough, fatigue, myalgia, body pain, headache, new onset of ageusia, new onset of smell loss, pharyngodynia, nasal congestion, nasal discharge, nausea, vomiting, and diarrhoea.

48) RT-PCR testing within 3 days was recommended for a subject reporting any of the specified symptoms. Of note, an analysis on the primary endpoint employed the results of RT-PCR tests performed for 5 days before and 10 days after the onset of the symptom.

49) The analysis was initially planned to be performed when 90 Events were reported, but the protocol was changed in accordance with Protocol Amendment 4 ([redacted], 20[redacted]) to review the incidence of the Events based on information obtained outside this study. The analysis was to be performed when approximately 50 Events had been confirmed. Then, another change was made to the protocol in accordance with Protocol Amendment 6 (March 12, 2021) because the number of Events in this study would decrease with the increasing number of vaccinated individuals. The primary analysis was to be performed 30 days after the 25th Event reported.

50) Based on the exclusion criteria specified before the start of the study, all the initially enrolled subjects were not vaccinated with any SARS-CoV-2 vaccine. After the start of the study, however, vaccines became available. In accordance with Protocol Amendment 4 ([redacted], 20[redacted]), the protocol was changed to allow post-enrollment vaccination if requested by the subject. In light of a possibility that tixagevimab and cilgavimab administered in combination before vaccination might interfere with immune response to the vaccine, unblinding of the subject was recommended to determine the necessity and timing of the vaccination.

51) {1 – (the incidence of Events in the Evusheld group/the incidence of Events in the placebo group)} × 100

difference between the Evusheld group and the placebo group. Figure 3 shows the Kaplan-Meier curves of the cumulative incidence of the primary endpoint Events.

Table 36. Percentage of subjects SARS-CoV-2 RT-PCR-positive symptomatic illness occurring through Day 183 (FAS, data cut-off on April 7, 2021)

	Evusheld	Placebo
Incidence of Events	3.1% (23/749)	4.6% (17/372)
Relative risk reduction [95% confidence interval][a)]	33.3% [-25.9%, 64.7%]	
P value[b)]	0.212	

The analysis was performed on Events occurring through Day 183 regardless of unblinding for assessment of eligibility for SARS-CoV-2 vaccination before the onset of an Event, SARS-CoV-2 vaccination, or receipt of other COVID-19 preventive drugs against (drugs for preventing the onset of COVID-19).

a) Estimated based on a Poisson regression model with robust variance. The model included treatment group as a covariate with the log of the follow-up period as an offset variable.

b) A 2-sided significance level of 5%

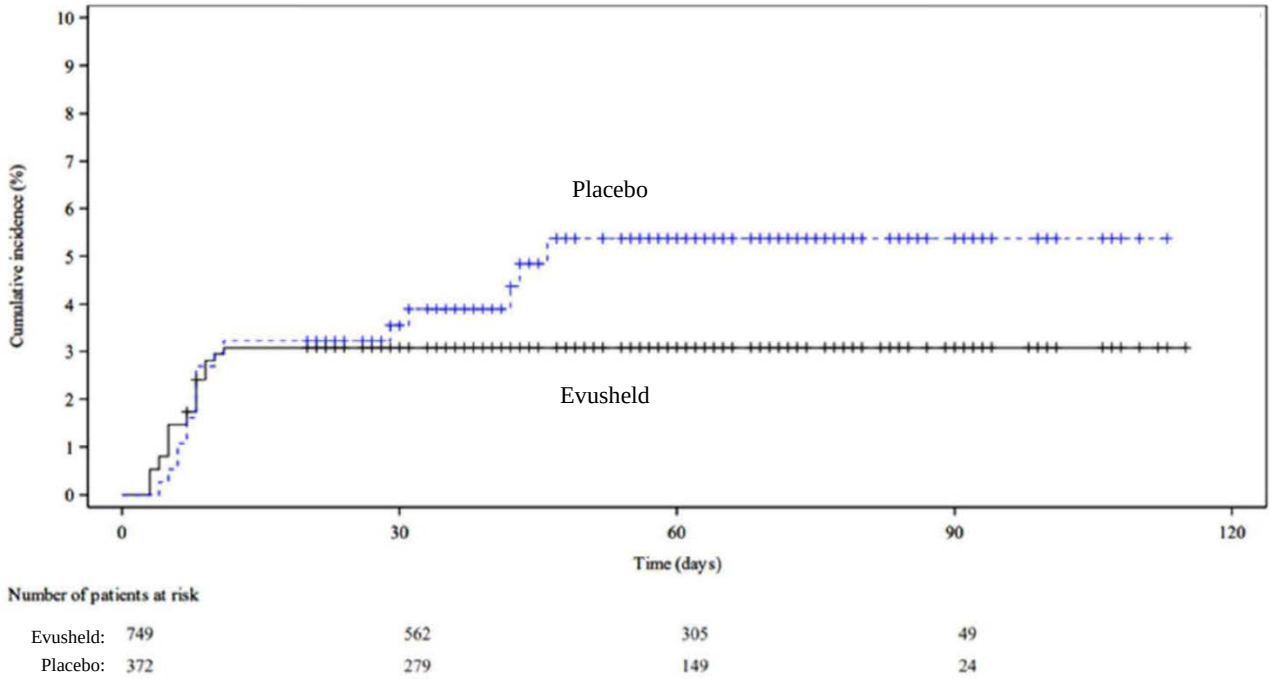

Figure 3. Cumulative incidence of primary endpoint Events (FAS, data cut-off on April 7, 2021)

Severe COVID-19 or death[52)] did not occur in the Evusheld group but occurred in 1 subject in the placebo group.

Enrollment of new subjects was suspended after the primary analysis on the primary endpoint, but follow-up of the subjects was continued. An analysis was performed on the data with a median duration of follow-up (from administration of the study drug to data cut-off) of 6 months where 5 months had passed since administration of the study drug in all the subjects (data cut-off on August 19, 2021). The median duration (range) of follow-up from administration of the study drug to data cut-off was 182 (5, 249) days in the Evusheld group and 178 (11, 247) days in the placebo group. Table 37 shows the relative risk reduction expressed as the percentage of subjects with SARS-CoV-2 RT-PCR-positive[48)]

[52)] Defined as a condition accompanying pneumonia (pyrexia, cough, tachypnoea or dyspnoea, and lung infiltration) or hypoxaemia (SpO_2 <90% on room air or severe respiratory distress) and scored ≥5 on the WHO Clinical Progression Scale (hospitalization with supplemental oxygen by mask or nasal cannula [score 5]) (*Lancet Infect Dis.* 2020;20:e192-e197).

symptomatic illness[47)] occurring through Day 183 (incidence of Events) in each group. Figure 4 shows the Kaplan-Meier curves of the cumulative incidence of the Events.

Table 37. Percentage of subjects with SARS-CoV-2 RT-PCR-positive symptomatic illness occurring through Day 183 (FAS, data cut-off on August 19, 2021)

	Evusheld	Placebo
Incidence of Events	3.6% (27/749)	6.2% (23/372)
Relative risk reduction [95% confidence interval] [a)]	43.2% [0.1%, 67.7%]	

The analysis was performed on the Events occurring through Day 183 regardless of unblinding for assessment of eligibility for SARS-CoV-2 vaccination before the onset of an Event, SARS-CoV-2vaccination, or receipt of COVID-19 preventive drugs (drugs for preventing the onset of COVID-19).

a) Estimated based on a Poisson regression model with robust variance. The model included treatment group as a covariate with the log of the follow-up period as an offset variable.

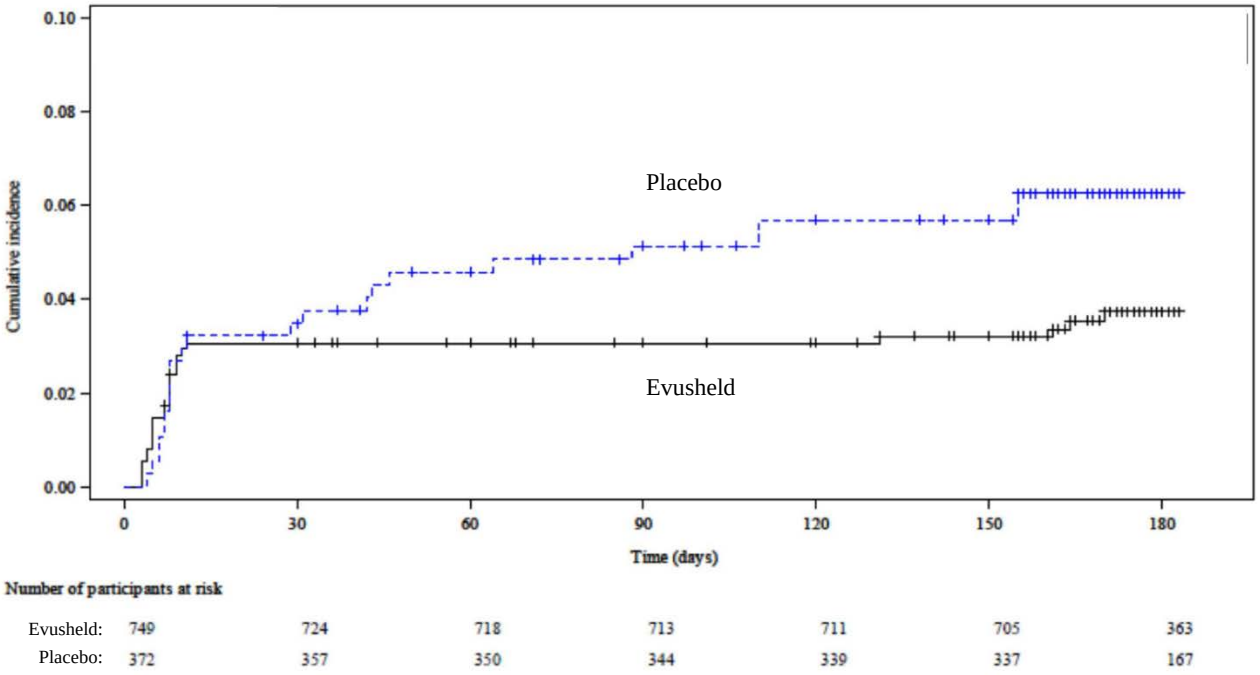

Figure 4. Cumulative incidence of primary endpoint Events (FAS, data cut-off on August 19, 2021)

For the safety (data cut-off on June 19, 2021[53)]), adverse events and adverse drug reactions[54)] occurred in 30.6% (229 of 749) and 4.5% (34 of 749) of subjects in the Evusheld group and 40.3% (150 of 372) and 5.9% (22 of 372) of subjects in the placebo group. Table 38shows adverse events and adverse reactions with an incidence of ≥1% in either group. The median duration (range) of follow-up from administration of the study drug to data cut-off was 121 (5, 188) days in the Evusheld group and 118 (11, 186) days in the placebo group.

53) The data cut-off was preliminarily scheduled prior to unblinding as a time point when 3 months have passed since administration of the study drug in all the subjects.

54) Adverse events considered causally related to the study drug by the (sub-)investigator.

Table 38. Adverse events and/or adverse drug reactions occurring in ≥1% of subjects in either group (safety analysis set, data cut-off on June 19, 2021)

Event	Adverse events		Adverse drug reactions	
	Evusheld (N = 749)	Placebo (N = 372)	Evusheld (N = 749)	Placebo (N = 372)
Any event	229 (30.6)	150 (40.3)	34 (4.5)	22 (5.9)
Headache	50 (6.7)	36 (9.7)	9 (1.2)	8 (2.2)
Rhinorrhoea	32 (4.3)	12 (3.2)	0	0
Cough	31 (4.1)	19 (5.1)	3 (0.4)	0
Fatigue	29 (3.9)	22 (5.9)	3 (0.4)	3 (0.8)
Oropharyngeal pain	29 (3.9)	16 (4.3)	1 (0.1)	0
Nasal congestion	25 (3.3)	18 (4.8)	2 (0.3)	0
Pyrexia	22 (2.9)	16 (4.3)	3 (0.4)	0
COVID-19	18 (2.4)	20 (5.4)	0	0
Pain	16 (2.1)	18 (4.8)	0	0
Chills	14 (1.9)	15 (4.0)	2 (0.3)	0
Nausea	14 (1.9)	12 (3.2)	2 (0.3)	0
Urinary tract infection	12 (1.6)	11 (3.0)	0	0
Myalgia	11 (1.5)	14 (3.8)	1 (0.1)	2 (0.5)
Diarrhoea	11 (1.5)	14 (3.8)	0	0
Dyspnoea	10 (1.3)	7 (1.9)	0	0
Vomiting	8 (1.1)	4 (1.1)	1 (0.1)	1 (0.3)
Back pain	3 (0.4)	4 (1.1)	2 (0.3)	1 (0.3)
Pain in extremity	2 (0.3)	4 (1.1)	1 (0.1)	0

n (%), MedDRA ver.24.0

Serious adverse events occurred in 9 subjects in the Evusheld group (abdominal pain, COVID-19, pneumonia, overdose, lumbar vertebral fracture, subdural haematoma, adrenal adenoma, basal ganglia haemorrhage, cerebral ischaemia, bipolar I disorder, and suicide attempt in 1 subject each [some subjects had more than 1 event]) and in 7 subjects in the placebo group (unevaluable event, pneumonia, COVID-19 pneumonia, burns second degree, diabetic ketoacidosis, nephrolithiasis, renal infarct, chronic obstructive pulmonary disease, and acute respiratory failure in 1 subject each [some subjects had more than 1 event]). A causal relationship to the study drug was ruled out for all of the events.

No adverse events led to death or treatment discontinuation.

As of data cut-off on August 19, 2021,[55)] the median duration (range) of follow-up from administration of the study drug to data cut-off was 182 (5, 249) days in the Evusheld group and 178 (11, 247) days in the placebo group. Adverse events occurred in 33.4% (250 of 749) of subjects in the Evusheld group and 42.7% (159 of 372) of subjects in the placebo group.

After the data cut-off on June 19, 2021, adverse events leading to death were newly reported in 2 subjects in the Evusheld group (cerebral ischaemia and lung cancer metastatic in 1 subject each) and 1 subject in the placebo group (death). A causal relationship to the study drug was ruled out for all of the events. The deaths due to cerebral ischaemia and lung cancer metastatic were adjudicated to be unrelated to COVID-19 by an independent committee.

After the data cut-off on June 19, 2021, serious adverse events (including adverse events leading to death) were newly reported in 4 subjects in the Evusheld group (cholecystitis, lung cancer metastatic,

55) The cut-off date was scheduled after unblinding as a timepoint when the median duration of follow-up from administration of the study drug to data cut-off has reached 6 months, and 5 months have passed since administration of the study drug in all the subjects.

pyelonephritis acute, dehydration) and 2 subjects in the placebo group (cholecystitis acute, death). A causal relationship to the study drug was ruled out for all of the events.

After the data cut-off on June 19, 2021, no adverse events leading to discontinuation were newly reported.

7.2.3 Global phase III study (CTD T 5.3.5.1.1, Study D8851C00001 [TACKLE study], ongoing since January 2021 [data cut-off in August 2021])

A randomized, double-blind, placebo-controlled, parallel group study was conducted at 95 study sites in 14 countries (the US, the UK, Argentina, Brazil, Czech Republic, Germany, Hungary, Italy, Mexico, Poland, Russia, Spain, Ukraine, and Japan) to evaluate the efficacy and safety of tixagevimab and cilgavimab in combination in patients with COVID-19 aged ≥18 years (target sample size, up to 1,700 subjects; 850 in the Evusheld group and 850 in the placebo group).[56)] Of the subjects, ≥60% were patients with a risk factor for severe COVID-19.[57)]

Table 39 shows the key inclusion and exclusion criteria of this study.

Table 39. Key inclusion and exclusion criteria

Inclusion criteria	1. SARS-CoV-2 positive (confirmed by antigen or nucleic acid test using oropharyngeal, nasopharyngeal, or nasal swab, or saliva collected within 3 days prior to enrollment). 2. WHO Clinical Progression Scale score > 1 and < 4.[a)] 3. Mild to moderate COVID-19 symptoms[b)] occurring within 7 days before administration of the study drug and at least one COVID-19 symptom[c)] presented within 24 hours before administration of the study drug. 4. Oxygen saturation of ≥ 92% (on room air)[d)] within 24 hours before administration of the study drug.
Exclusion criteria	1. History or current hospitalization for COVID-19 (excluding hospitalization for observation or isolation). 2. Current need for hospitalization or immediate medical attention in a clinic or emergency room indicated by the (sub-)investigator. 3. Previous receipt of vaccine, monoclonal antibodies or biological preparations to prevent or treat COVID-19 (irrespective of approval status) or scheduled receipt of any of them after enrollment.

a) Patients with a score of >1 and <4 are ambulatory and symptomatic (*Lancet Infect Dis.* 2020;20:e192-e197).
b) Subjective fever or feeling feverish, cough, shortness of breath or dyspnoea at rest or on exercise, sore throat, body pain or myalgia, fatigue, headache, chills, nasal obstruction or nasal congestion, nasal discharge, new onset of ageusia or smell loss, nausea or vomiting, diarrhoea, body temperature >37.8°C/100°F, new onset of confusion (patients aged ≥60 years only), inappetence or decreased dietary intake (patients aged ≥60 years only), and increased oxygen dose (those requiring supplemental oxygen at baseline only)
c) Cough, sore throat, shortness of breath or dyspnoea at rest or on exercise, body pain or myalgia, fatigue, headache, chills, nasal obstruction or nasal congestion, nasal discharge, nausea or vomiting, diarrhoea, and new onset of ageusia or smell loss
d) Excluding patients on chronic supplemental oxygen for an underlying lung condition

In this study, subjects received a single dose of the combination of tixagevimab 300 mg and cilgavimab 300 mg or placebo intramuscularly. More specifically, tixagevimab 300 mg/3.0 mL (100 mg/mL) and cilgavimab 300 mg/3.0 mL (100 mg/mL) were administered as separate sequential IM injections in 1 site each of the right and left hips.

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56) The target sample size was calculated as the number of subjects required to provide the statistical power of 90% at a 2-sided significance level of 5% on the assumption that the expected relative risk reduction [{1 – (incidence of Events in the Evusheld group/incidence of Events in the placebo group)} × 100) would be 65% for subjects who had severe COVID-19 or died from any cause through Day 29 (Event) and that the incidence of Events in the placebo group would be 4.6%.

57) Defined as any of the following conditions:
Age ≥65 years, cancer, chronic lung disease, moderate to severe asthma, obesity (BMI >30 kg/m^2), hypertension, cardiovascular disease (including past history of stroke), diabetes mellitus, chronic kidney disease, chronic liver disease, immunocompromised state (solid organ transplant, blood or bone marrow transplant, immunodeficiency, HIV infection, use of corticosteroids, or use of other immunosuppressive agents), sickle cell disease, and current or past smokers.

Of the randomized 910 subjects (456 in the Evusheld group and 454 in the placebo group), 903 (452 in the Evusheld group and 451 in the placebo group) received the study drug and were included in the FAS, which was also used as the safety analysis set. Of the FAS, 834 subjects (413 in the Evusheld group and 421 in the placebo group) were not hospitalized for SARS-CoV-2 infection at baseline and received the study drug within 7 days after the onset of the symptoms. They were included in the mFAS, which was then used as the efficacy analysis population.

The primary endpoint was the relative risk reduction [{1 − (incidence of Events in the Evusheld group/incidence of Events in the placebo group)} × 100] expressed as the percentage of subjects who had severe COVID-19[58)] or died from any cause through Day 29 (incidence of Event). The primary analysis was performed 30 days after the 43rd Event.[59)]

Of the subjects randomized up until the data cut-off for the primary analysis (August 21, 2021), 3.8% (35 of 910) discontinued the study after receiving the study drug; more specifically, 3.5% (16 of 456) of the subjects in the Evusheld group discontinued the study owing to death (6 subjects), lost to follow-up (2 subjects), decision of the physician (1 subjects), and subject's withdrawal (7 subjects); and 4.2% (19 of 454) in the placebo group discontinued the study owing to death (5 subjects), adverse events (2 subjects), lost to follow-up (2 subjects), subject's withdrawal (7 subjects), and other reasons (3 subjects).

Efficacy data were analyzed. Table 40 shows the primary endpoint results, the relative risk reduction[60)] expressed as the percentage of subjects who had severe COVID-19[58)] or died from any cause until Day 29 (incidence of Event) in each group, showing a statistically significant difference between the Evusheld group and the placebo group. No Events occurred in either group in the Japanese subgroup (mFAS, 6 subjects in the Evusheld group and 3 subjects in the placebo group). Figure 5 shows the Kaplan-Meier curves of the cumulative incidence of the primary endpoint Events. Of the subjects with Events, 16 subjects in the Evusheld group and 37 subjects in the placebo group had severe COVID-19 (death occurred in 1 and 4 subjects, respectively). Death unrelated to COVID-19 occurred in 2 subjects in the Evusheld group and 0 subjects in the placebo group.

Table 40. Percentage of subjects who had severe COVID-19 or died from any cause through Day 29 (mFAS, data cut-off on August 21, 2021)

	Evusheld	Placebo
Incidence of Events	4.4% (18/407)	8.9% (37/415)
Relative risk reduction [95% confidence interval][a)]	50.5% [14.6%, 71.3%]	
P value[b)]	0.010	

The analysis did not include subjects who discontinued/dropped out or were lost to follow-up before the onset of any Event.

a) Estimated by a Mantel-Haenszel method using time from symptom onset (≤5 days or >5 days) and risk for severe COVID-19 (high risk or low risk) as stratification factors

b) Cochran-Mantel-Haenszel test at a 2-sided significance level of 5% using time from symptom onset (≤5 days or >5 days) and risk for severe COVID-19 (high risk or low risk) as stratification factors

58) Defined as a condition accompanying pneumonia (fever, cough, tachypnoea or dyspnoea, and lung infiltration) or hypoxaemia (oxygen saturation <90% on room air or severe respiratory distress) and a score of ≥5 on the WHO Clinical Progression Scale.

59) The analysis was initially planned to be performed when 90 Events were reported, but the protocol was changed in accordance with Protocol Amendment 5 ([redacted], 20[redacted]) on the assumption that the number of individuals eligible for enrollment in this study would decrease with the increasing number of vaccinated individuals. The analysis was to be performed 30 days after the 52nd Event. Then, another change was made to the protocol in accordance with Protocol Amendment 7 ([redacted], 20[redacted]) because of a change of the required statistical power from 95% to 90%. The analysis was to be performed 30 days after the 43rd Event.

60) {1 – (incidence of Events in the Evusheld group/incidence of Events in the placebo group)} × 100

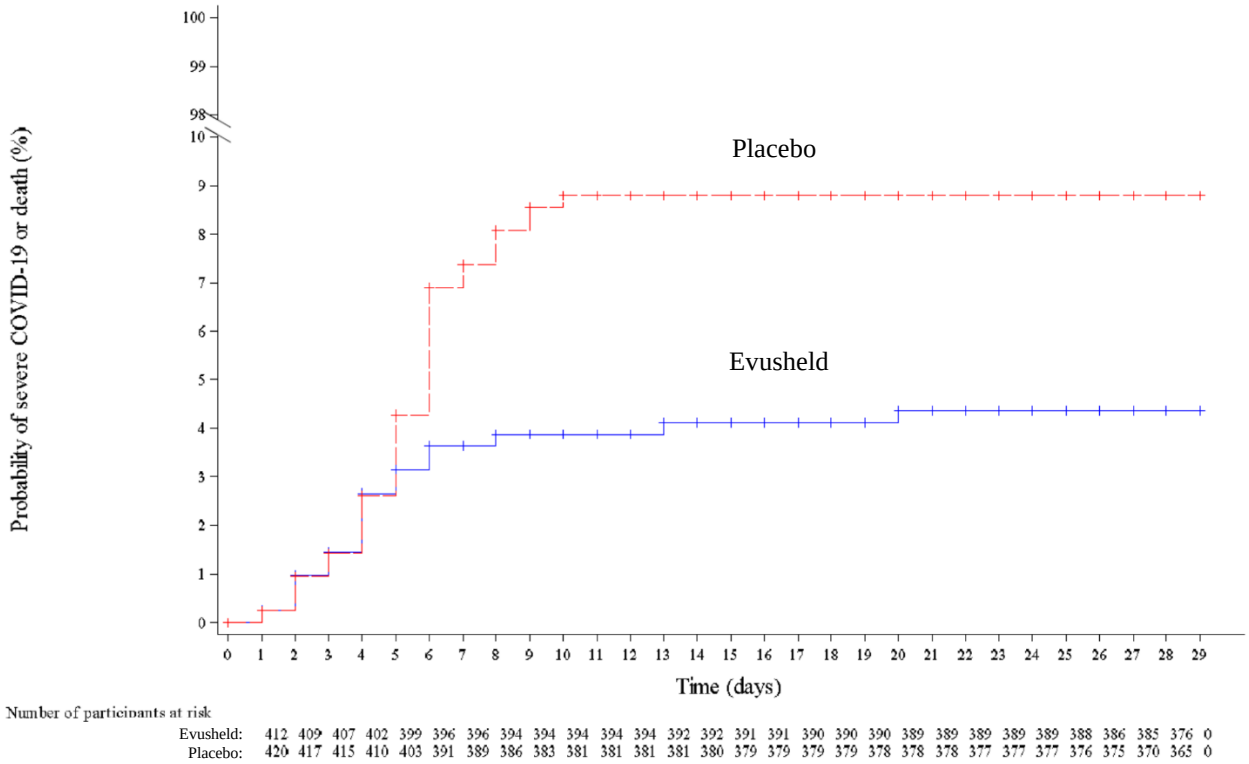

Figure 5. Cumulative incidence of primary endpoint Events (mFAS, data cut-off on August 21, 2021)

Table 41 shows changes in time-weighted mean viral load (nasopharyngeal swab) from baseline to Day 6.

Table 41. Changes in time-weighted mean viral load (nasopharyngeal swab) from baseline to Day 6 (mFAS)

	Evusheld	Placebo
Baseline viral load (mean ± SD)	5.79 ± 1.539 (n = 383)	5.79 ± 1.648 (n = 377)
Changes in time-weighted mean viral load from baseline to Day 6 (least squares mean [95% confidence interval])	-0.86 [-0.95, -0.76]	-0.65 [-0.74, -0.55]
Difference between groups (least squares mean [95% confidence interval])	-0.21 [-0.31, -0.11]	

Viral load: Log_{10} copies/mL
ANCOVA model using the baseline viral load, treatment group, time from symptom onset (≤5 days or >5 days), risk for severe COVID-19 (high risk or low risk), and interaction between the baseline viral load and treatment group as covariates for the log of time-weighted mean change.

Safety data were analyzed. The incidences of adverse events and adverse drug reactions[61)] were 29.2% (132 of 452 subjects) and 5.1% (23 of 452 subjects), respectively, in the Evusheld group, and 36.1% (163 of 451 subjects) and 4.7% (21 of 451 subjects), respectively, in the placebo group. Table 42 shows adverse events and/or adverse reactions occurring in ≥1% of subjects in either group. The median duration (range) of follow-up from administration of the study drug to data cut-off was 84 (3, 177) days in the Evusheld group and 84 (1, 183) days in the placebo group.

61) Adverse events considered causally related to the study drug by the (sub-)investigator

Table 42. Adverse events and/or adverse drug reactions occurring in ≥1% of subjects in either group (safety analysis set, data cut-off on August 21, 2021)

Event	Adverse events		Adverse drug reactions	
	Evusheld (N = 452)	Placebo (N = 451)	Evusheld (N = 452)	Placebo (N = 451)
Any event	132 (29.2)	163 (36.1)	23 (5.1)	21 (4.7)
COVID-19 pneumonia	26 (5.8)	49 (10.9)	0	0
Injection site pain	8 (1.8)	10 (2.2)	8 (1.8)	10 (2.2)
Insomnia	6 (1.3)	1 (0.2)	0	0
Type 2 diabetes mellitus	6 (1.3)	2 (0.4)	0	0
Diabetes mellitus inadequate control	5 (1.1)	2 (0.4)	0	0
Diarrhoea	5 (1.1)	3 (0.7)	0	0
Dizziness	5 (1.1)	0	2 (0.4)	0
Headache	5 (1.1)	2 (0.4)	0	1 (0.2)
Hypertension	3 (0.7)	7 (1.6)	0	1 (0.2)
COVID-19	1 (0.2)	9 (2.0)	0	0

n (%), MedDRA ver.24.0

Adverse events leading to death occurred in 6 subjects in the Evusheld group (COVID-19 pneumonia in 2 subjects, and acute left ventricular failure, sudden cardiac death, COVID-19, and malignant neoplasm progression in 1 subject each) and 6 subjects in the placebo group (COVID-19 pneumonia in 4, and COVID-19 and septic shock in 1 subject each). A causal relationship to the study drug was ruled out for all of the events.

Serious adverse events (including adverse events leading to death) occurred in 33 subjects in the Evusheld group and 54 subjects in the placebo group (Table 43). A causal relationship to the study drug was ruled out for all of the events.

Table 43. Breakdown of serious adverse events

Evusheld (n = 33)	COVID-19 pneumonia in 23 subjects, acute myocardial infarction in 2 subjects, and anaemia of malignant disease, acute left ventricular failure, sudden cardiac death, COVID-19, appendicitis, immobilisation syndrome, malignant neoplasm progression, syncope, chronic kidney disease, nephrolithiasis, pulmonary embolism, circulatory collapse, hypertensive crisis, and peripheral artery thrombosis in 1 subject each (some subjects had more than 1 event)
Placebo (n = 54)	COVID-19 pneumonia in 37 subjects, COVID-19 in 9 subjects, and arrhythmia, gastrointestinal haemorrhage, oesophageal varices haemorrhage, biliary colic, portal vein thrombosis, disseminated tuberculosis, post-acute COVID-19 syndrome, septic shock, superinfection bacterial, forearm fracture, jaw fracture, loss of consciousness, optic neuritis, superior sagittal sinus thrombosis, ureteric obstruction, and pneumothorax in 1 subject each (some subjects had more than 1 event)

Adverse events leading to discontinuation occurred in 2 subjects in the placebo group (COVID-19 pneumonia and asthenia). A causal relationship to the study drug was ruled out for both events. The outcome of COVID-19 pneumonia was “resolved,” and that of asthenia was “not resolved.”

Safety data was analyzed for the Japanese subgroup. The incidences of adverse events and adverse drug reactions[61)] were 61.5% (16 of 26 subjects) and 7.7% (2 of 26 subjects), respectively, in the Evusheld group, and 50.0% (7 of 14 subjects) and 0%, respectively, in the placebo group. Adverse events reported in ≥2 subjects in the Evusheld group were COVID-19 pneumonia in 6 subjects, and constipation, pyrexia, and vaccination site pain in 2 subjects each. Adverse drug reactions reported in the Evusheld group were injection site hypoaesthesia and pyrexia in 1 subject each. Adverse events coded to “Cardiac disorders” or “Vascular disorders” in the System Organ Class (SOC) occurred in 2 subjects in the Evusheld group (atrioventricular block first degree, nodal rhythm, and deep vein thrombosis in 1 subject each [a subject

had more than 1 event]). A causal relationship to the study drug was ruled out for all of the events. The outcomes of the events were “not resolved.”

An adverse event leading to death occurred in 1 subject in the Evusheld group (COVID-19 pneumonia), and a causal relationship to the study drug was ruled out.

Serious adverse events (including adverse events leading to death) occurred in 7 subjects in the Evusheld group (COVID-19 pneumonia in 6 subjects, and appendicitis and immobilisation syndrome in 1 subject each [a subject had more than 1 event]) and 2 subjects in the placebo group (COVID-19 pneumonia in 2 subjects). A causal relationship to the study drug was ruled out for all of the events. COVID-19 pneumonia in 1 subject resulted in “death,” and the outcomes of other events were “resolved.”

No adverse events leading to discontinuation occurred.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

7.R.1.1 Prevention of COVID-19

The applicant’s explanation about the efficacy of Evusheld for the prevention of COVID-19:
In both foreign phase III studies, the PROVENT study (pre-exposure setting) in subjects who were at increased risk for inadequate response to active immunization (predicted poor responder to SARS-CoV-2 vaccine) or intolerant of vaccine or who were at risk for SARS-CoV-2 infection, defined as those whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and the STORM CHASER study (post-exposure setting) in subjects who had potential exposure to a specific identified individual with laboratory-confirmed SARS-CoV-2 infection and were therefore at appreciable risk of developing COVID-19, the primary endpoint was the relative risk reduction[62)] expressed as the percentage of subjects with SARS-CoV-2 RT-PCR-positive symptomatic illness[63)] occurring after administration of the study drug through Day 183 (incidence of Events). The primary endpoint was defined based on a list of symptoms[64)] issued by the CDC in the US. Collecting samples for RT-PCR within 3 days after symptom onset was recommended in light of a report indicating that time from SARS-CoV-2 infection to symptom onset would be usually in the range of2 to 8 days, and that the viral RNA would be detectable for up to 15 days after symptom onset (*J Infect.* 2020;81:357-371). The efficacy analysis used the results of RT-PCR tests performed during a period from 5 days before to 10 days after the onset of symptoms. The efficacy analysis population was the FPAS (the population of the FAS excluding subjects infected with SARS-CoV-2 at baseline) in the PROVENT study, and the FAS in the STORM CHASER study.

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62) {1 – (incidence of Events in the Evusheld group/incidence of Events in the placebo group)} × 100

63) Any of the following symptoms, irrespective of symptom duration: pyrexia, shortness of breath, dyspnoea, new onset of confusion (subjects aged ≥60 years only), inappetence or decreased food intake (subjects aged ≥60 years only), and increased oxygen dose (subjects aged ≥60 years requiring supplemental oxygen at baseline only) or any of the ≥2-day persistent symptoms such as chilliness, cough, fatigue, myalgia, body pain, headache, new onset of ageusia, new onset of smell loss, pharyngodynia, nasal congestion, nasal discharge, nausea, vomiting, and diarrhoea

64) https://web.archive.org/web/20200701020729/https:/www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html (last accessed on July 5, 2022)

Table 44 shows the primary endpoint results. A comparison between the Evusheld and placebo groups in the efficacy analysis population showed a statistically significant difference in the PROVENT study but did not in the STORM CHASER study.

Table 44. Primary endpoint results (PROVENT study, FPAS, data cut-off on May 5, 2021; STORM CHASER study, FAS, data cut-off on April 7, 2021)

	PROVENT study (pre-exposure setting)		STORM CHASER study (post-exposure setting)	
	Evusheld	Placebo	Evusheld	Placebo
Incidence of Events	0.2% (8/3,441)	1.0% (17/1,731)	3.1% (23/749)	4.6% (17/372)
Relative risk reduction [95% confidence interval][a)]	76.7% [46.1%, 90.0%]		33.3% [-25.9%, 64.7%]	
P value[a),b)]	<0.001		0.212	

Subjects who had been unblinded for assessment of eligibility for vaccination against COVID-19, had been vaccinated with SARS-CoV-2 vaccine, or had received other COVID-19 preventive drugs (drugs for preventing the onset of COVID-19) before the onset of the Events were censored at unblinding, SARS-CoV-2 vaccination, or receipt of COVID-19 preventive drugs in the PROVENT study, whichever occurred earlier. In the STORM CHASER study, the analysis was performed on the Events occurring through Day 183, irrespective of these events.

a) In the PROVENT study, estimates are based on a Poisson regression model with robust variance, including treatment group and age at informed consent (≥60 years or <60 years) as covariates with the log of the follow-up time as an offset variable. In STORM CHASER study, estimates are based on a Poisson regression model with robust variance, including treatment group as a covariate with the log of the follow-up time as an offset variable.

b) A 2-sided significance level of 5%

In the STORM CHASER study, no statistically significant difference was observed for the primary endpoint. A potential cause for this result is that the administration of Evusheld might have been too late to prevent COVID-19 symptoms. The study enrolled individuals who had potential exposure to, within 8 days, a person with laboratory-confirmed SARS-CoV-2 infection, but some subjects were at the late incubation period when receiving the study drug, according to a report that the median duration (95% CI) from exposure to the source of infection to symptom onset was 5.1 (4.5, 5.8) days (*Ann Intern Med.* 2020;172:577-82). The study, on the other hand, demonstrated that the administration of Evusheld in a post-exposure prophylaxis setting could prevent the onset of COVID-19, because (a) severe COVID-19 or death[65)] occurred in 1 subject in the placebo group but did not in the Evusheld group; and (b) most of the enrolled subjects (95.7%) were SARS-CoV-2 RT-PCR status negative or missing, and an analysis on the predetermined primary endpoint in this population produced the relative risk reduction of 73.2% (95% CI; 27.1%, 90.1%). On the basis of the above findings, the applicant considers that the administration of Evusheld in both pre- and post-exposure settings could prevent COVID-19.

In the PROVENT study, the efficacy analysis population (FPAS) excluded subjects who had been SARS-CoV-2 RT-PCR-positive at baseline, but the primary endpoint results in the FAS, which included subjects irrespective of SARS-CoV-2 RT-PCR status, also showed the efficacy of Evusheld to a certain extent (Table 45). The applicant considers that access to Evusheld for the prevention of COVID-19 should be allowed irrespective of SARS-CoV-2 status given that pre-dose SARS-CoV-2 testing may result in an inappropriate delay in the administration of Evusheld and in view of limited testing capacity in laboratories.

65) Defined as a condition accompanying pneumonia (pyrexia, cough, tachypnoea or dyspnoea, and lung infiltration) or hypoxaemia (SpO_2 <90% on room air or severe respiratory distress) and scored ≥5 on the WHO Clinical Progression Scale (hospitalization with supplemental oxygen by mask or nasal cannula [score 5]) (*Lancet Infect Dis.* 2020;20:e192-e197).

Table 45. Primary endpoint results (PROVENT study)

	Data cut-off on May 5, 2021		Data cut-off on August 29, 2021	
	Evusheld	Placebo	Evusheld	Placebo
Overall (FAS)				
Incidence of Events	0.3% (11/3,460)	1.0% (17/1,737)	0.4% (14/3,460)	1.8% (31/1,737)
Relative risk reduction [95% confidence interval][a)]	68.1% [31.9%, 85.1%]		78.2% [59.0%, 88.4%]	
SARS-CoV-2 RT-PCR status negative or missing at baseline (FPAS)				
Incidence of Events	0.2% (8/3,441)	1.0% (17/1,731)	0.3% (11/3,441)	1.8% (31/1,731)
Relative risk reduction [95% confidence interval][a)]	76.7% [46.1%, 90.0%]		82.8% [65.8%, 91.4%]	
SARS-CoV-2 RT-PCR status positive at baseline (FPAS)				
Incidence of Events	15.8% (3/19)	0% (0/6)	15.8% (3/19)	0% (0/6)
Relative risk reduction [95% confidence interval][a)]	-		-	

-: Not calculated

Subjects who had been unblinded for assessment of eligibility for SARS-CoV-2 vaccination, had been vaccinated with SARS-CoV-2 vaccine, or had received other COVID-19 preventive drugs (drugs for preventing the onset of COVID-19) before the onset of the Events were censored at unblinding, SARS-CoV-2 vaccination, or receipt of COVID-19 preventive drugs, whichever occurred earlier.

a) Estimated based on a Poisson regression model with robust variance. The model included treatment group and age at informed consent (≥60 years or <60 years) as covariates with the log of the follow-up period as an offset variable.

The applicant considers that the results of the foreign phase III studies (PROVENT and STORM CHASER studies) support the efficacy of Evusheld (combination of tixagevimab and cilgavimab) in the Japanese population, though the studies did not include Japanese subjects. This is because (a) COVID-19 symptoms are similar between Japanese and non-Japanese patients, (b) tixagevimab and cilgavimab are both antibodies against an adventitious agent, and (c) no clear difference was observed in the PK of tixagevimab or cilgavimab between the Japanese and non-Japanese populations [see Section 6.R.1].

Impacts of SARS-CoV-2 variants are discussed below. During the period of the foreign phase III studies (PROVENT and STORM CHASER studies), predominant SARS-CoV-2 strains detected in participating countries were strains with no letters from the Greek alphabets assigned by the WHO; B.1.1.7 lineage (Alpha) and B.1.427/B.1.429 lineage (Epsilon). Other strains reported included B.1.351 lineage (Beta)[66)]), P.1 lineage (Gamma), B.1.617.2/AY.2 lineage (Delta), B.1.525 lineage (Eta),[66)] B.1.526 lineage (Iota), and B.1.621 lineage (Mu). In the PROVENT and STORM CHASER studies, base sequence data were also obtained from specimens from 21 subjects (6 subjects in the Evusheld group and 15 in the placebo group) and 19 subjects (12 in the Evusheld group and 7 in the placebo group), respectively. The specimens were collected at hospital visit by the subjects due to the onset of symptoms. Strains with spike substitutions detected at an allele fraction ≥25%, assigned letters from the Greek alphabets by the WHO, were B.1.1.7 lineage (Alpha) in 8 subjects (8 subjects in the placebo group), B.1.351 lineage (Beta) in 1 subject (1 in the Evusheld group), B.1.617.2 lineage (Delta) in 3 subjects (3 in the placebo group), and B.1.429 lineage (Epsilon) in 2 subjects (2 in the Evusheld group) in the PROVENT study; and B.1.1.7 lineage (Alpha) in 9 subjects (5 in the Evusheld group and 4 in the placebo group), and B.1.427/B.1.429 lineages (Epsilon) in 3 subjects (2 in the Evusheld group and 1 in the placebo group) in the STORM CHASER study. As of June 2022, on the other hand, the SARS-CoV-2 strain predominantly circulating in Japan is the Omicron variant; for more details, Omicron subvariants circulating in Tokyo are BA.2 (67.1%), BA.5 (25.1%), BA.2.12.2 (6.4%), and BA.4 (1.4%).[67)] The *in*

66) Only reported in countries participating in the PROVENT study.

67) Updates on SARS-CoV-2 infection in Tokyo based on the results of tests performed from June 14 to 20, 2022 (Bureau of Social Welfare and Public Health, Tokyo Metropolitan Government: https://www.bousai.metro.tokyo.lg.jp/_res/projects/default_project/_page_/001/021/799/91/ 20220630_13.pdf [last accessed on July 1, 2022])

vitro neutralization activity of the combination of tixagevimab and cilgavimab against the predominantly circulating BA.2 subvariant is not shown to greatly decrease, although there are no clinical study data that can be directly applied to evaluation of the clinical efficacy of the combination.

PMDA's view:
In the PROVENT and STORM CHASER studies, timing of the primary analysis was changed after the start of the study although such changes had not been predetermined [see Sections 7.2.1 and 7.2.2]. These changes were inevitable in light of changes in the prevalence of COVID-19 and the development and availability of vaccines. It is possible to evaluate the efficacy based on the results of these studies, despite the changes, which were made under a double-blinded condition. Results of the PROVENT study (in a pre-exposure setting), therefore, demonstrated the efficacy of Evusheld in the prevention of COVID-19 in non-close contacts with patients with COVID-19. In contrast, the STORM CHASER study (in a post-exposure setting) showed no statistically significant difference in the primary endpoint between the groups in the efficacy analysis population (FAS). Although time from exposure to the source of infection to the administration of Evusheld (timing of subject enrollment) might have affected the efficacy evaluation, it is difficult to conclude that the study results demonstrated the efficacy of Evusheld in the prevention of COVID-19 in close contacts with patients with COVID-19.

In the PROVENT study, the efficacy analysis population (FPAS) excluded subjects who had been SARS-CoV-2 RT-PCR-positive at baseline, but the primary endpoint results in the FAS, which included subjects irrespective of SARS-CoV-2 RT-PCR status, also showed the efficacy of Evusheld to a certain extent. In view of this result, it is acceptable to allow Evusheld to be used for the prevention of COVID-19 irrespective of SARS-CoV-2 status without SARS-CoV-2 testing prior to the treatment.

PMDA concluded that Evusheld is expected to be effective in the Japanese population to a certain extent for the following reasons: (a) COVID-19 symptoms are similar between Japanese and non-Japanese patients, as explained by the applicant, although the foreign phase III studies (PROVENT and STORM CHASER studies) did not include Japanese subjects; (b) tixagevimab and cilgavimab are both antibodies against an adventitious agent; and (c) no clear difference was observed in the PK of tixagevimab or cilgavimab between the Japanese and non-Japanese populations [see Section 6.R.1].

Of note, the applicant should continue collecting information about the efficacy of Evusheld against variants in the post-marketing setting and promptly provide information to healthcare professionals when new findings become available.

The above conclusions of PMDA will be discussed at the Expert Discussion.

7.R.1.2 Treatment of COVID-19

The applicant's explanation about the efficacy of Evusheld in the treatment of COVID-19:
In the global phase III study in patients with COVID-19 (TACKLE study), the primary endpoint was relative risk reduction[68)] expressed as the percentage of subjects with severe COVID-19 or death from any cause occurring through Day 29 ("Event"). Severe COVID-19 was selected as the primary endpoint,

[68)] {1 – (incidence of Events in the Evusheld group/incidence of Events in the placebo group)} × 100

based on the recommendations by the International Coalition of Medicines Regulatory Authorities (ICMRA),[69] and severe COVID-19[70] was defined according to the guidance for clinical studies (*Lancet Infect Dis.* 2020;20:e192-97) developed by the WHO Working Group.

Table 46 shows results on the primary endpoint. Comparison between the Evusheld and placebo groups indicated a statistically significant difference, showing the efficacy of Evusheld in the treatment of COVID-19.

Table 46. Primary endpoint results (mFAS, data cut-off on August 21, 2021)

	TACKLE study (treatment)	
	Evusheld	Placebo
Incidence of Events	4.4% (18/407)	8.9% (37/415)
Relative risk reduction [95% confidence interval][a]	50.5% [14.6%, 71.3%]	
P value [b]	0.010	

The analysis did not include subjects who discontinued/dropped out from the study or were lost to follow-up before the onset of any Event.

a) Estimated by a Mantel-Haenszel method using time from symptom onset (≤5 days or >5 days) and risk for severe COVID-19 (high risk or low risk) as stratification factors

b) Cochran-Mantel-Haenszel test at a 2-sided significance level of 5% using time from symptom onset (≤5 days or >5 days) and risk for severe COVID-19 (high risk or low risk) as stratification factors

Table 47 shows the results of the main subgroup analysis in the TACKLE study. The relative risk reduction tended to increase with reducing time from symptom onset to administration. The subgroup of patients without risk factors for severe COVID-19 accounted for only 10.4% of the overall population, which precludes drawing a definitive conclusion. However, results in this subgroup had a similar trend to those in the overall population. The applicant therefore considers that patients without risk factors for severe COVID-19 can also benefit from Evusheld.

Table 47. Subgroup analysis on the primary endpoint (mFAS, data cut-off on August 21, 2021)

			Evusheld (N = 407)	Placebo (N = 415)
Time from symptom onset to administration	≤7 days	Incidence of Events	4.4% (18/407)	8.9% (37/415)
		Relative risk reduction [95% CI][b]	50.5% [14.6%, 71.3%]	
	≤5 days	Incidence of Events	3.6% (9/253)	10.8% (27/251)
		Relative risk reduction [95% CI][b]	66.9% [31.1%, 84.1%]	
	≤3 days	Incidence of Events	1.1% (1/90)	9.5% (8/84)
		Relative risk reduction [95% CI][b]	88.0% [9.4%, 98.4%]	
Risk factors for severe COVID-19[a]	Yes	Incidence of Events	4.7% (17/364)	8.9% (33/371)
		Relative risk reduction [95% CI][b]	47.5% [7.5%, 70.2%]	
	No	Incidence of Events	2.3% (1/43)	9.1% (4/44)
		Relative risk reduction [95% CI][b]	75.4% [-115.1%, 97.2%]	

The analysis did not include subjects who discontinued/dropped out from the study or were lost to follow-up before the onset of any Event.

a) Age ≥65 years, cancer, chronic lung disease, moderate to severe asthma, obesity (BMI >30 kg/m^2), hypertension, cardiovascular disease (including past history of stroke), diabetes mellitus, chronic kidney disease, chronic liver disease, immunocompromised state (solid organ transplant, blood or bone marrow transplant, immunodeficiency, HIV infection, use of corticosteroids, or use of other immunosuppressive agents), sickle cell disease, and current or past smokers

b) Estimated by a Mantel-Haenszel method using time from symptom onset (≤5 days or >5 days) and risk for severe COVID-19 (high risk or low risk) as stratification factors

In the TACKLE study, the mFAS included 9 Japanese subjects (6 subjects in the Evusheld group and 3 in the placebo group), and no primary endpoint Events occurred in any of them. Thus, a definitive conclusion cannot be drawn from results in the Japanese population. However, the applicant considers that the overall results of the TACKLE study can demonstrate the efficacy of Evusheld in Japanese

69) http://icmra.info/drupal/news/20july2020/summary (last accessed on July 5, 2022)

70) Defined as conditions accompanying pneumonia (pyrexia, cough, tachypnoea or dyspnoea, and lung infiltration) or hypoxaemia (oxygen saturation <90% on room air or severe respiratory distress) and a score of ≥5 on the WHO Clinical Progression Scale.

patients with COVID-19, for the following reasons: (a) circulating variants, diagnosis criteria, severity classification, and therapeutic options[71] in Japan are not substantially different from those outside Japan; (b) tixagevimab and cilgavimab are both antibodies against an adventitious agent; and (c) the PK of tixagevimab or cilgavimab is unlikely to substantially differ between the Japanese and non-Japanese populations [see Section 6.R.1]. Of note, in the Japanese population in the TACKLE study, adverse events related to COVID-19 occurred more frequently in the Evusheld group than in the placebo group, and this difference is considered partly attributable to a bias in time from symptom onset to the treatment between the Evusheld and placebo groups and thus does not deny the efficacy of Evusheld.

In the TACKLE study, SARS-CoV-2 base sequence data were obtained from specimens collected from 834 subjects at baseline (413 subjects in the Evusheld group and 421 in the placebo group). Table 48 shows variants at allele frequency ≥25% (with letters from the Greek alphabets assigned by the WHO) found in the above sequence data and the primary endpoint results by variant.

Table 48. Primary endpoint results by variant in TACKLE study (data cut-off on August 21, 2021)

Lineage	Proportion of variants	Incidence of Events		Relative risk reduction [95% CI] [a)]
		Evusheld (N = 413)	Placebo (N = 421)	
B.1.1.7 (Alpha)	30.9% (258/834)	5.0% (7/139)	5.9% (7/119)	16.0% [-134.7%, 69.9%]
B.1.351 (Beta)	0.1% (1/834)	- (0/0)	0% (0/1)	-
P.1 (Gamma)	0.1% (1/834)	0% (0/1)	- (0/0)	-
P.1_1 (Gamma)	10.0% (83/834)	8.1% (3/37)	17.4% (8/46)	50.1% [-76.9%, 85.9%]
B.1.617.2 (Delta)	7.9% (66/834)	3.0% (1/33)	12.1% (4/33)	70.6% [-107.4%, 95.8%]
C.37 (Lambda)	2.4% (20/834)	0% (0/11)	11.1% (1/9)	100% [-, -]
B.1.621 (Mu)	0.1% (1/834)	- (0/0)	0% (0/1)	-
B.1.621.1 (Mu)	0.1% (1/834)	- (0/0)	0% (0/1)	-

-: Not calculated
The analysis did not include subjects who discontinued/dropped out from the study or were lost to follow-up before the onset of any Event.
a) Estimated by a Mantel-Haenszel method using time from symptom onset (≤5 days or >5 days) and risk for severe COVID-19 (high risk or low risk) as stratification factors.

As of June 2022, on the other hand, the SARS-CoV-2 strain predominantly circulating in Japan is Omicron variant; more specifically, Omicron subvariants circulating in Tokyo are BA.2 (67.1%), BA.5 (25.1%), BA.2.12.2 (6.4%), and BA.4 (1.4%).[67] *In vitro* neutralization activity of the combination of tixagevimab and cilgavimab against the predominantly circulating the BA.2 subvariant is not shown to greatly decrease, although there are no clinical study data that can be directly applied to evaluation of the clinical efficacy of the combination.

PMDA's view:
In the TACKLE study, timing of the primary analysis was changed after the start of the study although such change had not been predetermined [see Section 7.2.3]. The change was inevitable in light of changes in the prevalence of COVID-19 and the development and availability of vaccines. In addition, it is possible to evaluate the efficacy based on the results of the study, despite the change, which was made under a double-blinded condition. The results of the TACKLE study demonstrated the efficacy of Evusheld in the treatment of COVID-19 requiring no supplemental oxygen.

[71] MHLW *Guidelines for Diagnosis and Treatment of COVID-19*, ver. 7.2. (May 9, 2022), Living guidance for clinical management of COVID-19: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2 (last accessed on July 5, 2022), *Lancet Infect Dis.* 2020;20:e192-97

Although no primary endpoint Events occurred in either group in the Japanese population in the TACKLE study, Evusheld is expected to be effective in Japanese patients with COVID-19 to a certain extent, for the following reasons: (a) circulating variants, diagnostic criteria, severity classification, and therapeutic options in Japan are not substantially different from those outside Japan; (b) tixagevimab and cilgavimab are both antibodies against an adventitious agent and do not cross-react with human tissues; and (c) the PK of tixagevimab or cilgavimab is unlikely to substantially differ between the Japanese and non-Japanese populations [see Section 6.R.1].

Of note, the applicant should continue collecting information about the efficacy of Evusheld against variants in the post-marketing setting and promptly provide any new information to healthcare professionals when it becomes available.

The use of Evusheld in patients without risk factors for severe COVID-19 is discussed in Section 7.R.3 as well.

The above conclusions of PMDA will be discussed at the Expert Discussion.

7.R.1.3 Evusheld treatment-emergent substitutions in SARS-CoV-2 S-protein

The applicant's explanation about SARS-CoV-2 variants harboring substitutions in the S-protein detected after the use of Evusheld:

In the TACKLE study,[72)] the base sequence data of SARS-CoV-2 S-protein at baseline and post-treatment were obtained from 18 subjects in the Evusheld group. After treatment with Evusheld, new substitutions (treatment-emergent substitutions) were identified in 6 of 18 subjects (4 subjects with new substitutions detected at an allele fraction ≥25% [18 amino acid residues in total] and 6 subjects with new substitutions detected at an allele fraction 3%-25% [17 amino acid residues in total]). Of the above treatment-emergent substitutions involving 35 amino acid residues, ones involving 16 residues were evaluated for their effects on the neutralization activity of tixagevimab and cilgavimab using pseudotyped virus. Fold changes in neutralization activity against pseudotyped virus harboring any of the substitutions evaluated with respect to that against the control strain (Wuhan-Hu-1 isolate/D614G) were less than 10. None of the primary endpoint Events, severe COVID-19 and death from any cause, occurred in any of the subjects who gave specimens of SARS-CoV-2 variants harboring treatment-emergent substitutions.

At present, no treatment-emergent substitutions in SARS-CoV-2 S-protein that lead to a decrease in the neutralization activity of the combination of tixagevimab and cilgavimab have been detected, but the applicant should continue collecting information about the emergence of treatment-emergent substitutions in the post-marketing setting and promptly provide any new information to healthcare professionals when it becomes available.

The above conclusions of PMDA will be discussed at the Expert Discussion.

[72)] Data cut-off on August 21, 2021

7.R.2 Safety

7.R.2.1 Safety profile

The applicant's explanation about the safety profile of the combination of tixagevimab and cilgavimab: Table 49 summarizes the safety profile in phase III studies (PROVENT, STORM CHASER, and TACKLE studies). No substantial differences were observed in the incidence of adverse events or adverse drug reactions between the Evusheld and placebo groups.

Table 49. Safety profile in phase III studies (safety analysis set)[a)]

	PROVENT study (pre-exposure prevention)		STORM CHASER study (post-exposure prevention)		TACKLE study (treatment)	
	Evusheld[b)] (N = 3,461)	Placebo (N = 1,736)	Evusheld[b)] (N = 749)	Placebo (N = 372)	Evusheld[b)] (N = 452)	Placebo (N = 451)
Adverse events	1,417 (40.9)	698 (40.2)	229 (30.6)	150 (40.3)	132 (29.2)	163 (36.1)
Adverse drug reactions	293 (8.5)	119 (6.9)	34 (4.5)	22 (5.9)	23 (5.1)	21 (4.7)
Serious adverse events	92 (2.7)	42 (2.4)	9 (1.2)	7 (1.9)	33 (7.3)	54 (12.0)
Adverse events leading to death	7 (0.2)	5 (0.3)	0	0	6 (1.3)	6 (1.3)
Adverse events leading to treatment discontinuation	4 (0.1)[c)]	1 (0.1)	0	0	0	2 (0.4)

n (%)

a) Data cut-off on June 29, 2021 in the PROVENT study; data cut-off on June 19, 2021 in the STORM CHASER study, and data cut-off on August 21, 2021 in the TACKLE study

b) Dose: Tixagevimab 150 mg and cilgavimab 150 mg in the PROVENT and STORM CHASER studies and tixagevimab 300 mg and cilgavimab 300 mg in the TACKLE study

c) Of the events, 3 were wrongly reported after death as ones with adverse events leading to treatment discontinuation.

Table 50 summarizes the safety profile in the Japanese population in the TACKLE study. Adverse events tended to be more common in the Japanese population than in the overall population, but none of adverse events tended to occur more frequently in the Japanese population than in the overall population. In the Japanese population, the incidence of adverse events was slightly higher in the Evusheld group than in the placebo group, but all of the adverse events except for COVID-19 pneumonia were assessed as "mild" or "moderate" according to the severity classification. In the Japanese population, serious adverse events tended to occur more frequently in the Evusheld group than in the placebo group, but serious adverse events reported in more than 1 subject in the Evusheld group were only COVID-19 pneumonia. These events were considered unrelated to Evusheld, raising no particular safety concerns.

In addition, in the Japanese phase I study in healthy Japanese subjects (Study D8850C00005), the reported adverse events were all mild, raising no particular safety concerns.

Table 50. Safety profile in Japanese population
(TACKLE study, safety analysis set, data cut-off on August 21, 2021)

	Evusheld (N = 26)	Placebo (N = 14)
Adverse events	16 (61.5)	7 (50.0)
Adverse drug reactions	2 (7.7)	0
Serious adverse events	7 (26.9)	2 (14.3)
Adverse events leading to death	1 (3.8)	0
Adverse events leading to treatment discontinuation	0	0

n (%)

In the phase III studies (PROVENT, STORM CHASER, and TACKLE studies) and foreign and Japanese phase I studies (Studies D8850C00001 and D8850C00005), anaphylaxis and other serious hypersensitivity reaction (including immunocomplex mediated diseases) as well as injection site

reaction were analyzed as adverse events of interest. Adverse events of interest occurred in 2.7% (92 of 3,461) of subjects in the Evusheld group and 2.1% (37 of 1,736) in the placebo group in the PROVENT study, 0.7% (5 of 749) in the Evusheld group and 1.3% (5 of 372) in the placebo group in the STORM CHASER study, and 3.3% (15 of 452) in the Evusheld group and 3.3% (15 of 451) in the placebo group in the TACKLE study. There were no substantial differences in the incidence of adverse events of interest between the Evusheld and placebo groups. Most of the events were injection site reaction. Anaphylaxis was reported in 1 subject in the Evusheld group in the PROVENT study as a non-serious adverse event. Its causal relationship to the study drug could not be ruled out, and the outcome of the was "resolved."[73)] No adverse events of interest occurred in the Japanese population in the TACKLE study, or the foreign or Japanese phase I study (Studies D8850C00001 and D8850C00005). Of note, since an Emergency Use Authorization granted to Evesheld in the US, Evusheld was used in individuals who were intolerant of vaccine and had a history of serious hypersensitivity to vaccination. Multiple cases of hypersensitivity reaction were reported in such individuals, although the relationship remains unclear.[74)]

After the approval or authorization of Evusheld outside Japan, 1,079,628 units of Evusheld were distributed until March 31, 2022, and safety information was submitted for 654 events in 222 individuals (of which, 153 events in 67 individuals were serious). The most common adverse events were headache (33 events), fatigue (26 events), COVID-19 (18 events), nausea (16 events), and chills (14 events). A total of 11 adverse events leading to death were reported in 7 individuals (cardiac arrest and death in 2 individuals each; and brain death, subarachnoid haemorrhage, headache, sudden death, haemolytic anaemia, ventricular fibrillation, and acute cardiac event in 1 each [some persons had more than 1 event]). The events in 3 individuals (headache, haemolytic anaemia, ventricular fibrillation, acute cardiac event, cardiac arrest, and death in 1 each [some persons had more than 1 event]) were considered "causally related to Evusheld" by a submitter, but they were not unexpected events because all of the patients had complex underlying diseases, and neither trends nor patterns suggestive of safety concerns were observed. Based on the above, no additional safety concerns have been raised since the approval or authorization of Evusheld outside Japan, nor have been any trends different from the safety profile observed in the clinical studies.

The applicant therefore considers the safety profile of Evusheld acceptable. In light of hypersensitivity (including anaphylaxis) reported in clinical studies, the applicant will include a precautionary statement regarding the risk of the event in the package insert.

PMDA's view:
The safety risk of Evusheld is acceptable in view of its benefit in treatment and prevention of COVID-19. However, healthcare professionals should be appropriately informed of the risk of hypersensitivity including anaphylaxis, based on the information obtained in foreign phase III studies. Although the currently available safety data in the Japanese population are limited, they have raised no particular safety concerns. In addition, because Evusheld consisting of antibodies against an adventitious agent do not cross-react with human tissues, the safety profile in the Japanese population is unlikely to be

73) The event was reported as anaphylaxis based on symptoms of dyspnoea and headache by an (sub-)investigator, but it did not meet the criteria for anaphylaxis defined in the protocol.
74) Emergency Use Authorization (EUA) for EVUSHELD Center for Drug Evaluation and Research Review Memorandum: https://www.fda.gov/media/158520/download (last accessed on July 5, 2022)

substantially different from that in the non-Japanese population. The applicant, however, should continue collecting information about the safety of Evusheld in the Japanese population in the post-marketing setting and appropriately provide the information to healthcare professionals.

The risk of cardiovascular disorders is discussed in Section 7.R.2.2.

The above conclusions of PMDA will be discussed at the Expert Discussion.

7.R.2.2 Cardiovascular risk

The applicant's explanation about the cardiovascular risk of Evusheld:

Table 51 shows serious adverse events reported in the foreign phase III study (PROVENT study), and coded to "Cardiac disorders" in the SOC. The incidence of the events tended to be higher in the Evusheld group (0.7%) than in the placebo group (0.3%). All of the events were considered unrelated to the study drug. Adverse events leading to death occurred in 4 subjects in the Evusheld group (arrhythmia, cardiac failure congestive, cardio-respiratory arrest, and myocardial infarction in 1 subject each).

Table 51. Serious adverse events coded to "Cardiac disorders" in the SOC (PROVENT study, safety analysis set, data cut-off on August 29, 2021)

Event	Evusheld (N = 3,461)	Placebo (N = 1,736)
Cardiac disorders	23 (0.7)	5 (0.3)
Acute myocardial infarction	4 (0.1)	2 (0.1)
Myocardial infarction	5 (0.1)	0
Cardiac failure congestive	4 (0.1)	0
Atrial fibrillation	1 (<0.1)	2 (0.1)
Acute left ventricular failure	0	1 (0.1)
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
Paroxysmal atrioventricular block	1 (<0.1)	0

n (%), MedDRA ver.24.0

In the global phase III study (TACKLE study), serious adverse events coded to "Cardiac disorders" in the SOC occurred in 2 of 452 subjects in the Evusheld group (acute myocardial infarction in 2 subjects and acute left ventricular failure in 1 [a subject had more than 1 event]) and 1 of 451 subjects in the placebo group (arrhythmia), and an adverse event leading to death occurred in 1 of 451 subjects in the Evusheld group (acute left ventricular failure). All of the above events were considered unrelated to the study drug. No serious adverse events coded to "Cardiac disorders" of the SOC occurred in the foreign phase III study (STORM CHASER study) or foreign or Japanese phase I study (Studies D8850C00001 and D8850C00005).

In the phase III studies (PROVENT and TACKLE studies), subjects with serious adverse events related to cardiac disorders all had risk factors for or a prior history of cardiovascular diseases[75] at baseline. In addition, tixagevimab and cilgavimab do not cross-react with human tissues [see Section 5.6.1], and no effects on the cardiovascular system were observed in cynomolgus monkeys [see Section 3.3]. In view of the above findings, cardiovascular events are considered unrelated to Evusheld, i.e., not adverse drug reactions.

PMDA's view:
A risk of cardiac disorders-related adverse events associated with the use of Evusheld in individuals with risk factors for or a prior history of cardiovascular diseases remains unclear at present. In view of the limited number of individuals evaluated, a precautionary statement regarding the risk of cardiac disorder-related events should be included in the package insert and other materials, as done in the EU and the US. The applicant should also continue collecting relevant information in the post-marketing setting and appropriately provide the information to healthcare professionals.

The above conclusions of PMDA will be discussed at the Expert Discussion.

7.R.3 Clinical positioning

The applicant's explanation about the clinical positioning of Evusheld:
Multiple vaccines for the prevention of COVID-19 are approved in Japan, and vaccination should therefore remain the first-line option. However, Evusheld can serve as a treatment option for individuals who are intolerant of vaccination or may have an inadequate immune response to vaccination. Individuals who may have an inadequate immune response to vaccination should include patients with severe combined immunodeficiency, those with hematologic malignancies who are on active therapy, those receiving immunosuppressive agents, according to the inclusion criteria of clinical studies and guideline[76] developed by the National Institute of Health (NIH) in the US.

Remdesivir, casirivimab + imdevimab, sotrovimab, molnupiravir, and nirmatrelvir and ritonavir are approved for the treatment of patients with mild to moderate I COVID-19 in Japan, according to the Guidelines for Diagnosis and Treatment of COVID-19, ver. 7.2. (May 9, 2022). Some drugs such as casirivimab + imdevimab, however, have shown reduced neutralization activity against the Omicron variant, which resulted in the restricted use of them in Japan. The global phase III study (TACKLE study) demonstrated the efficacy and safety of Evusheld in patients with COVID-19 at oxygen saturation ≥92% (on room air) requiring no supplemental oxygen. Thus, Evusheld can be a treatment option for patients with mild to moderate I COVID-19.

PMDA's view:
For the prevention of COVID-19, Evusheld should not be a substitute for vaccine but may serve as an option for individuals who are intolerant of vaccine or may have an adequate immune response to vaccination, for the following reasons: (a) vaccination is the fundamental means for the prevention of

[75] Type 2 diabetes mellitus, arterial hypertension, past history of cardiac diseases, smoking, obesity, hypercholesterolaemia, advanced age, etc.
[76] https://www.covid19treatmentguidelines.nih.gov/overview/prioritization-of-therapeutics/ (last accessed on July 5, 2022)

SARS-CoV-2 infection; and (b) multiple SARS-CoV-2 vaccines are approved in Japan and have shown a relatively high prophylactic effect. In addition, the applicant should appropriately take measures, such as providing healthcare professionals with information about individuals eligible for the use of Evusheld through academic societies' guidelines or other sources to avoid confusion in clinical settings. Furthermore, based on the review in Section 7.R.1.1, healthcare professionals should be warned that the use of Evusheld is limited to non-close contacts with patients with COVID-19 (in a pre-exposure setting).

For the treatment of COVID-19, Evusheld provides a treatment option for patients with mild to moderate I COVID-19. The global phase III study (TACKLE study) included patients irrespective of risk factors for severe COVID-19, and the efficacy of Evusheld was demonstrated in the overall population, although patients without risk factors for severe COVID-19 accounted for only 10.4% of the overall population. In view of the limited proportion of such patients, Evusheld should be indicated for the treatment of COVID-19 in patients with risk factors for severe disease, as with other SARS-CoV-2-neutralizing monoclonal antibody products.

The *in vitro* neutralization assay showed the reduced neutralization activity of the combination of tixagevimab and cilgavimab against some Omicron subvariants [see Section 3.1.3.3]. The applicant should therefore continue collecting information about the efficacy of Evusheld while being updated on circulating variants and should advise healthcare professionals to consider whether the patient is eligible for the use of Evusheld.

The above conclusions of PMDA will be discussed at the Expert Discussion.

7.R.4 Indications

Based on the review in Sections 7.R.1 and 7.R.2, PMDA has concluded that the proposed indications of Evusheld ("treatment and prevention of COVID-19") is acceptable.

The above conclusions of PMDA will be discussed at the Expert Discussion.

7.R.5 Dosage and administration

The applicant's explanation about the dosage and administration of Evusheld:
Based on the results of non-clinical studies and the foreign phase I study (Study D8850C00001), the study designs of the subsequent studies were specified as follows: A single IM dose of the combination of tixagevimab 150 mg and cilgavimab 150 mg was selected as the dosage regimen in the foreign phase III studies (PROVENT and STORM CHASER studies) which were intended to evaluate the efficacy of the combination of the antibodies in the prevention of COVID-19, and a single IM dose of the combination of tixagevimab 300 mg and cilgavimab 300 mg was selected as the dosage regimen in the global phase III study (TACKLE study) which was intended to evaluate the efficacy of the combination of the antibodies in the treatment of COVID-19 [see Section 6.R.2]. These studies demonstrated the efficacy and safety of the treatment [see Sections 7.R.1 and 7.R.2]. The dosage and administration, therefore, should be a single IM dose of the combination oftixagevimab 150 mg and cilgavimab 150 mg for the prevention of COVID-19 and a single IM dose of the combination of tixagevimab 300 mg and cilgavimab 300 mg for the treatment of COVID-19. Data on the efficacy and safety of Evusheld in

pediatric individuals aged <18 years are not available, but in view of the results of clinical pharmacology studies, the applicant considers that pediatrics aged ≥12 years and weighing ≥40 kg may receive Evusheld, with the same dosage and administration as those for adults.

No clinical study data with multiple doses of Evusheld are available, and thus re-administration of Evusheld is not appropriate at present. The safety and tolerability of multiple doses of Evusheld are planned to be evaluated in a substudy of the ongoing PROVENT study (Study D8850C00002)[77)] and ENDURE study (Study D8850C00010).[78)]

PMDA's view:
In view of the review in Sections 6.R.2, 6.R.3, 7.R.1, and 7.R.2, a single IM dose of the combination of tixagevimab 150 mg and cilgavimab 150 mg for the prevention of COVID-19 and a single IM dose of the combination of tixagevimab 300 mg and cilgavimab 300 mg for the treatment of COVID-19 are acceptable as the dosage and administration in adults and pediatric individuals aged ≥12 years and weighing ≥40 kg. However, because no clinical study data in pedicatrics aged ≥12 years and weighing ≥40 kg are available, the applicant should evaluate the dosage and administration in pediatrics aged ≥12 years and weighing ≥40 kg as soon as the results of ongoing or planned clinical studies in the pediatric population are obtained. The applicant should also promptly provide information to healthcare professionals when new findings become available.

Evusheld is expected to serve as an option for the prevention of COVID-19 in individuals who may have inadequate response to SARS-CoV-2 vaccine or are intolerant of vaccine. The efficacy and safety of re-administration of Evusheld should be continuously investigated.

The above conclusions of PMDA will be discussed at the Expert Discussion.

7.R.6 Post-marketing investigations

The applicant has no plan to conduct additional pharmacovigilance activities such as post-marketing use-results survey.

In order to monitor the safety of Evusheld in the Japanese population, the applicant should conduct a post-marketing use-results survey, for the following reasons:

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77) An open-label study that includes subjects previously enrolled in the PROVENT study and is intended to evaluate the safety, immunogenicity, and PK of Evusheld administered as multiple doses according to the following dosage regimens:
- 12-month interval group: Subjects who received an IM dose of tixagevimab 150 mg and cilgavimab 150 mg in combination in the PROVENT study are to be given another IM dose of tixagevimab 150 mg and cilgavimab 150 mg in combination 365 days later.
- 6-month interval group: Subjects who received an IM dose of placebo in the PROVENT study are to be given an IM dose of tixagevimab 150 mg and cilgavimab 150 mg in combination 365 days later, and then another IM dose of tixagevimab 150 mg and cilgavimab 150 mg in combination 182 days later.

78) An open-label study that includes adults and pediatrics aged ≥12 years and weighing ≥40 kg and is intended to evaluate the safety, immunogenicity, PK, and pharmacodynamics profile of Evusheld administered as multiple doses according to the following dosage regimens:
- Group A (n = 100): The first dose of the combination of tixagevimab 300 mg and cilgavimab 300 mg intramuscularly administered and then 4 doses of the combination of tixagevimab 150 mg and cilgavimab 150 mg intramuscularly administered at an interval of 3 months over a period of 12 months (5 doses in total)
- Group B (n = 100): The first dose of the combination of tixagevimab 600 mg and cilgavimab 600 mg intramuscularly administered and then 2 doses of the combination of tixagevimab 300 mg and cilgavimab 300 mg intramuscularly administered at an interval of 6 months over a period of 12 months (3 doses in total)

(a) There is limited experience with the use of tixagevimab and cilgavimab in combination in the Japanese population;
(b) Hypersensitivity (including anaphylaxis) has been reported in individuals receiving tixagevimab and cilgavimab in combination [see Section 7.R.2.1]; and
(c) Serious adverse events related to cardiac disorders occurred more frequently in the Evusheld group than in the placebo group in the phase III studies [see Section 7.R.2.2].

The above conclusions of PMDA will be discussed at the Expert Discussion.

8. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The inspection is currently ongoing. Results and the conclusion of PMDA will be reported in the Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The inspection is currently ongoing. Results and the conclusion of PMDA will be reported in the Review Report (2).

9. Overall Evaluation during Preparation of the Report on Special Approval for Emergency (1)

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment and prevention of disease caused by SARS-CoV-2 infection (COVID-19), and that the product has acceptable safety in view of its benefits. Evusheld is clinically meaningful because it offers a new treatment option for the treatment and prevention of COVID-19.

PMDA has concluded that Evusheld may be approved if Evusheld is not considered to have any particular problems based on comments from the Expert Discussion.

Report on Special Approval for Emergency (2)

August 18, 2022

Product Submitted for Approval

Brand Name	Evusheld Intramuscular Injection Set
Non-proprietary Name	Tixagevimab (Genetical Recombination) and Cilgavimab (Genetical Recombination)
Applicant	AstraZeneca K.K.
Date of Application	June 9, 2022

List of Abbreviations
See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

At the Expert Discussion, the expert advisors supported PMDA's conclusion on issues presented in the Report on Special Approval for Emergency (1) (Sections "7.R.2 Safety," "7.R.3 Clinical positioning," "7.R.4 Indications," "7.R.5 Dosage and administration," and "7.R.6 Post-marketing investigations").

1.1 Dosage and administration

The proposed dosage and administration of Evusheld for the prevention of COVID-19 were tixagevimab 150 mg and cilgavimab 150 mg administered as two separate subsequential intramuscular injections (150 mg IM dose of each antibody). After the Expert Discussion, however, the applicant claimed that tixagevimab 300 mg and cilgavimab 300 mg administered as two separate subsequential intramuscular injections (300 mg IM dose of each antibody) could also be selected as the dosage and administration, for the following reasons (but not limited to):

- As of July 2022, the BA.5 lineage is superseding the BA.2 lineage as the predominantly circulating SARS-CoV-2 strain in Japan. Neutralization activity of the combination of tixagevimab and cilgavimab against pseudotyped virus-like particles expressing S-protein with the same substitutions as those in the BA.4/BA.5 lineages (EC_{50} = 65-69 ng/mL) was 33 to 65 times lower than that against the reference strain [see Section "3.1.3.3 Neutralization activity against variants" of the Report on Special Approval for Emergency (1)].

- Based on *in vitro* neutralization activity, the target serum concentration[79)] of the antibodies against BA.4/BA.5 lineages was specified, and the probability of achieving the target serum concentration at 3 and 6 months post-dose was calculated to be 58% and 1%, respectively, after administration of 150 mg IM dose of each antibody and 97% and 61%, respectively, after administration of 300 mg IM dose of each antibody.
- No clinical study data on the efficacy of Evusheld (300 mg IM dose of each antibody) in the prevention of COVID-19 are available, but the global phase III study in patients with COVID-19 (TACKLE study) presented no particular safety problems.

PMDA's view:

There are no clinical studies evaluating a 300 mg IM dose of each antibody for the prevention of COVID-19, and a relationship between the drug concentration in the upper respiratory tract and clinical efficacy remains unclear. However, depending on the prevalence of circulating SARS-CoV-2 variants, it is acceptable to propose a 300 mg IM dose of each antibody, in addition to a 150 mg IM dose of each antibody, as the dosage and administration of Evusheld, which is a product for which emergency approval is sought for the prevention of COVID-19, for the following reasons: (i) the US FDA granted an Emergency Use Authorization for Evusheld administered as a 300 mg IM dose of each antibody; and (ii) no particular safety problems have been observed with administration of a 300 mg IM of each antibody. Because multiple dosage regimens will be available for the prevention of COVID-19, the applicant should take appropriate measures, for example, by providing information to healthcare professionals to avoid confusion in clinical settings.

1.2 Risk management plan (draft)

In view of the discussions presented in Section "7.R.6 Post-marketing investigations" in the Report on Special Approval for Emergency (1) and comments from the expert advisers at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for Evusheld should include the safety specifications presented in Table 52, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 53 and Table 54.

Table 52. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Serious hypersensitivity such as anaphylaxis	• Cardiovascular events	Not applicable
Efficacy specification		
Not applicable		

Table 53. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • General use-results survey	Not applicable	• Disseminate data gathered during early post-marketing phase vigilance

79) The value calculated based on the *in vitro* neutralization activity (EC_{80} [EC_{50} × 4]) and the partition rate in the upper respiratory tract (nasal lining fluid/serum concentration ratio (1.8%) was 14.4 μg/mL.

Table 54. Outline of use-results survey (draft)

Objective	To collect information about the safety and efficacy of Evusheld in clinical use
Survey method	Central registry system
Population	• Patients with COVID-19 having risk factors for severe COVID-19 and requiring no supplemental oxygen • Individuals who are intolerant of vaccine or may have inadequate immune response to SARS-CoV-2 vaccination owing to the immunocompromised state and have not had recent close contact with someone who are infected with SARS-CoV-2
Observation period	6 months after administration of Evusheld
Planned sample size	700 individuals (enrolled)
Main survey items	Patient characteristics, status of Evusheld therapy, comorbidities, concomitant medication, adverse events, onset of COVID-19 after administration of Evusheld, and pregnancy status

2. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

Data relating to application for marketing approval of Evusheld for prevention of COVID-19

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted, which were organized and prepared in accordance with the data integrity standards overall. The following issue was identified in CTD 5.3.5.1.1 although it would not considerably affect the overall evaluation of the study. This issue was notified to the applicant as a finding requiring corrective action.[80)]

Finding requiring corrective action

Sponsor

- The blinded condition was not completely secured in a part of the subjects owing to inappropriate settings of the Electronic Data Capture system.

Data relating to application for marketing approval of Evusheld for treatment of COVID-19

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

Data relating to application for marketing approval of Evusheld for prevention of COVID-19

The new drug application data (CTD 5.3.5.1.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including

80) Settings of the Electronic Data Capture system were inappropriate in CTD 5.3.4.1.1 and CTD 5.3.5.1.2. In addition, the blinded condition was not completely secured in a part of the subjects in CTD 5.3.5.1.2.

Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

Data relating to application for marketing approval of Evusheld for treatment of COVID-19

The new drug application data (CTD 5.3.5.1.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indications and the dosage and administration as shown below, with the following approval conditions. The re-examination period is 8 years as the product consists of drugs with new active ingredients. The product is classified as a biological product. Neither the drug substances nor the drug product is classified as a poisonous drug or a powerful drug.

Indications

Treatment and prevention of disease caused by SARS-CoV-2 infection (COVID-19)

Dosage and administration

Treatment of COVID-19

The usual dosage in adults and pediatric individuals (≥12 years of age weighing ≥40 kg) is 300 mg of tixagevimab (genetical recombination) and 300 mg of cilgavimab (genetical recombination) administered as two separate sequential intramuscular injections.

Prevention of COVID-19

The usual dosage in adults and pediatric individuals (≥12 years of age weighing ≥40 kg) is 150 mg of tixagevimab (genetical recombination) and 150 mg of cilgavimab (genetical recombination) administered as two separate sequential intramuscular injections. Depending on the prevalence of circulating SARS-CoV-2 variants, 300 mg of tixagevimab (genetical recombination) and 300 mg of cilgavimab (genetical recombination) may be re-administered as two separate sequential intramuscular injections.

(The underlined words are added to the proposed text.)

Approval Conditions

1. The applicant is obliged to fulfill the following duties set forth in each Item of Article 28, Paragraph 3 of the Cabinet Order for Enforcement of Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.
   (1) Matters related to Item 1
   The applicant is required to conduct a use-results survey of the product and report the result.
   (2) Matters related to Item 2
   When learning about diseases, disorders, or death suspected to be caused by the product, the applicant is required to report them promptly.
   (3) Matters related to Item 3
   The applicant is required to take necessary actions to ensure that healthcare professionals who use the product can understand, and appropriately explain to patients (or their legally acceptable representatives), that the product has been granted Special Approval for Emergency and the objectives of said approval.
   (4) Matters related to Item 4
   The applicant is required to report the quantity of the product sold or provided, as necessary.

2. The product is approved with the following conditions, based on the provisions of Article 79, Paragraph 1 of the Pharmaceuticals and Medical Devices Act:
   (1) The applicant is required to develop and appropriately implement a risk management plan.
   (2) In case where there is a concern that a new variant may be in circulation, the applicant is required to promptly investigate the neutralization activity of the product against the variant and submit the results of investigation to the Ministry of Health, Labour and Welfare.
   (3) If a variant with potentially reduced susceptibility to the product is circulating, in view of the neutralization activity of the product against the new variant and the circulation of the new variant by region, the applicant is required to take necessary actions to ensure the proper use of the product, for example, by instructing physicians to use the product in eligible patients.

3. The product is approved based on Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. The approval may be withdrawn in accordance with the provision in Article 75-3 of the Act in a case where (1) the product does not conform to one or more Items of Article 14-3, Paragraph 1 of the Act or (2) the withdrawal is necessary to prevent the emergence or expansion of public health risks.

Appendix

List of Abbreviations

ACE2	Angiotensin converting enzyme 2
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cellular cytotoxicity
ADCD	Antibody-dependent complement deposition
ADCP	Antibody-dependent cellular phagocytosis
ADE	Antibody-dependent enhancement of disease
ADNKA	Antibody-dependent natural killer cell activation
ALT	Alanin aminotransferase
AST	Aspartate aminotransferase
AUC_{inf}	Area under serum concentration-time curve up to infinity
$AUC_{0\text{-x day}}$	Area under serum concentration-time curve up to x days
$AUC_{0\text{-xmonth}}$	Area under serum concentration-time curve up to x months
BA	Bioavailability
BMI	Body mass index
CI	Confidence interval
cIEF	Capillary Isoelectric Focusing
CE-SDS	Capillary gel electrophoresis-sodium dodecyl sulfate
Cilgavimab	Cilgavimab (Genetical Recombination)
Cilgavimab drug product	Drug product containing 150 mg of cilgavimab per vial
CHO	Chinese hamster ovary
C_{max}	Maximum serum concentration
COVID-19	Coronavirus disease
CQA	Critical quality attribute
C1q	Complement component 1q
CTD P	CTD relating to application for marketing approval of Evusheld for prevention of COVID-19
CTD T	CTD relating to application for marketing approval of Evusheld for treatment of COVID-19
DNA	Deoxyribonucleic acid
EC_{50}	Half maximal effective concentration
eGFR	Estimated glomerular filtration rate
ELF	Endothelial lining fluid
ELISA	Enzyme-linked immunosorbent assay
EOPCB	End of production cell bank
Evusheld	Evusheld Intramuscular Injection Set
Evusheld group	Tixagevimab + cilgavimab group
ETFE	Ethylenetetrafluoroethylene
FAS	Full analysis set
FcRn	Neonatal Fc receptor
FcγR	Fc gamma receptor
FDA	Food and drug administration in the United State
FPAS	Full pre-exposure analysis set
GFR	Glomerular filtration rate
GISAID	Global initiative on sharing avian influenza data
HCP	Host cell protein
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
HPSEC	High Performance Size Exclusion Chromatography
ICMRA	International Coalition of Medicines Regulatory Authorities
IC_{50}	50% inhibitory concentration
IgG	Immunoglobulin G
IM	Intramuscular
IV	Intravenous
K_D	Equilibrium dissociation constant
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LIVCA	Limit of in vitro cell age
MCB	Master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
Order for Enforcement of Pharmaceuticals and Medical Devices Act	Order for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Cabinet Order No. 11 of February 1, 1961)
PFU	Plaque-forming units
Pharmaceuticals and Medical Devices Act	Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of August 10, 1960)

PK	Pharmacokinetics
PMCB	Preliminary master cell bank
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
QbD	Quality by design
RBD	Receptor binding domain
RT-PCR	Reverse transcription-polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SPR	Surface plasmon resonance
S-protein	Spike protein
t_{max}	Time to maximum concentration
$t_{1/2}$	Estimate of the terminal elimination half-life
Tixagevimab	Tixagevimab (Genetical Recombination)
Tixagevimab drug product	Drug product containing 150 mg of tixagevimab per vial
V_d	Volume of distribution
V_{ss}	Volume of distribution at steady state
WCB	Working cell bank
WHO	World Health Organization
150 mg IM dose of each antibody	Intramuscular administration of the combination of tixagevimab 150 mg and cilgavimab 150 mg
300 mg IM dose of each antibody	Intramuscular administration of the combination of tixagevimab 300 mg and cilgavimab 300 mg