Report on the Deliberation Results

December 11, 2024
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Kavigale Injection Solution 300 mg
Non-proprietary Name	Sipavibart (Genetical Recombination) (JAN*)
Applicant	AstraZeneca K.K.
Date of Application	July 26, 2024

Results of Deliberation

In its meeting held on December 6, 2024, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The product is classified as a biological product. The re-examination period is 8 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

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. 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)*

Review Report

November 25, 2024
Pharmaceuticals and Medical Devices Agency

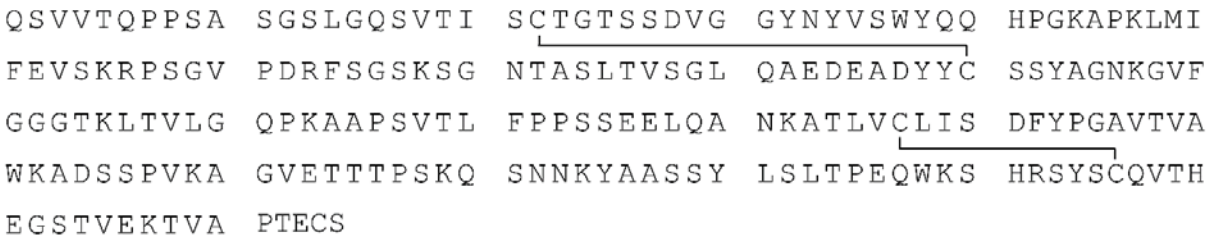
The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Kavigale Injection Solution 300 mg
Non-proprietary Name	Sipavibart (Genetical Recombination)
Applicant	AstraZeneca K.K.
Date of Application	July 26, 2024
Dosage Form/Strength	Injection in a vial (2.0 mL): Each vial contains 300 mg of sipavibart (genetical recombination).
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Sipavibart is a recombinant anti-SARS-CoV-2 spike protein monoclonal antibody derived from human IgG1, in which amino acid residues in the H-chain are substituted at 6 positions (L242F, L243E, M260Y, S262T, T264E, P339S). Sipavibart is produced in CHO cells. Sipavibart is a glycoprotein (molecular weight: ca. 148,000) composed of 2 H-chains (γ1-chains) consisting of 455 amino acid residues each and 2 L-chains (λ-chains) consisting of 215 amino acid residues each.

Structure

Amino acid sequences:

L-chain

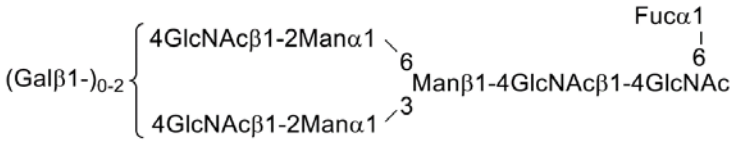


H-chain

EVQLVESGGG LVQPGRSLRL SCAASGFPFD DYAIHWVRLA PGKGLEWVSS
ISWDSGSIGY ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TALYYCAKGA
FPGYSSGWYY GLEVWGQGTT VTVSSASTKG PSVFPLAPSS KSTSGGTAAL
GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL SSVVTVPSSS
LGTQTYICNV NHKPSNTKVD KRVEPKSCDK THTCPPCPAP EFEGGPSVFL
FPPKPKDTLY ITREPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR
EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPASI EKTISKAKGQ
PREPQVYTLP PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK
TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS
LSPGK

Intrachain disulfide bonds: Shown in solid lines
Interchain disulfide bonds: C228 in H-chain- C214 in L-chain, C234 in H-chain- C234 in H-chain, C237 in H-chain- C237 in H-chain
Pyroglutamate formation (partial): E1 in H-chain, Q1 in L-chain
Glycosylation site: N305 in H chain
Partial processing: K455 in H-chain

Putative structure of main carbohydrate chain:



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

Molecular formula: $C_{6430}H_{9880}N_{1704}O_{2022}S_{40}$ (protein portion consisting of 4 chains)
(H chain) $C_{2227}H_{3412}N_{588}O_{683}S_{14}$
(L chain) $C_{988}H_{1532}N_{264}O_{328}S_{6}$
Molecular weight: Approx. 148,000

Items Warranting Special Mention

Expedited review (PSB/PED Notification No. 0802-6, dated August 2, 2024, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare)

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 prevention of disease caused by SARS-CoV-2 infection (Coronavirus disease 2019 [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 indication and dosage and administration shown below, with the following approval conditions.

Indication

Prevention of disease caused by SARS-CoV-2 infection (COVID-19)

Dosage and Administration

The usual dosage in adults and pediatric individuals aged ≥12 years weighing ≥40 kg is 300 mg of sipavibart (genetical recombination) administered by intramuscular injection in the anterolateral thigh. If intramuscular injection is difficult or inappropriate, intravenous administration should be selected.

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. 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.

Attachment

Review Report (1)

October 15, 2024

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

Product Submitted for Approval

Brand Name	Kavigale Injection Solution 300 mg
Non-proprietary Name	Sipavibart (Genetical Recombination)
Applicant	AstraZeneca K.K.
Date of Application	July 26, 2024
Dosage Form/Strength	Injection in a vial (2 mL): Each vial contains 300 mg of sipavibart (genetical recombination).

Proposed Indication

Prevention of disease caused by SARS-CoV-2 infection (COVID-19)

Proposed Dosage and Administration

The usual dosage in adults and pediatric individuals aged ≥12 years weighing ≥40 kg is 300 mg of sipavibart (genetical recombination) administered by intramuscular or intravenous injection.

Table of Contents

List of Abbreviations

See Appendix.

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

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Upon onset, it is commonly characterized by upper respiratory symptoms such as pharyngalgia and nasal discharge, along with systemic symptoms including malaise, fever, and myalgia. In patients with risk factors for severe COVID-19, such as immunocompromised state, the infection may progress to the lower respiratory tract, potentially leading to acute respiratory distress syndrome and multiple organ failure.[1)] On May 5, 2023, the World Health Organization (WHO) declared the end of the Public Health Emergency of International Concern due to COVID-19. In Japan, as of May 8, 2023, the category of COVID-19 under the Infectious Diseases Control Law[2)] was reclassified from a class of the "novel influenza or re-emerging influenza" to a "Class 5 infectious disease." Since then, the emergence of new SARS-CoV-2 variants and subsequent waves of infection have continued to be observed.

In Japan, multiple vaccines have been granted marketing approval indicated for the "prevention of disease caused by SARS-CoV-2 infection (COVID-19)." However, for individuals who may have inadequate immune response to vaccination owing to the immunocompromised state or are intolerant of vaccination due to hypersensitivity reactions, neutralizing antibody drugs (brand names, Evusheld Intramuscular Injection Set, Ronapreve for Intravenous Infusion Set 300, and Ronapreve for Intravenous Infusion Set 1332) have been approved for the "treatment and prevention of disease caused by SARS-CoV-2 infection (COVID-19)" and are used in clinical practice. However, the above neutralizing antibody drugs have shown a significant reduction in neutralization activity against circulating variants from the BQ.1 lineage onward.[3)]

Sipavibart (genetical recombination) (hereinafter referred to as sipavibart) is a human immunoglobulin G (IgG)1 monoclonal antibody against SARS-CoV-2, discovered by AstraZeneca in the UK. It neutralizes the infectivity of SARS-CoV-2 and suppresses the onset of COVID-19 by binding to the receptor binding domain (RBD) of the SARS-CoV-2 spike protein (S protein), which is essential for viral entry into host cells. Although sipavibart shares the same mechanism of action with currently approved drugs, it has been designed to exhibit neutralization activity against a broad range of variants, including the currently circulating Omicron variant.

Since December 2022, foreign phase I/III studies, including Study D7000C00001, have been conducted in immunocompromised subjects. Based on the confirmation of its efficacy and safety, the applicant has submitted a marketing application.

As of October 2024, Kavigale Injection Solution 300 mg (hereinafter referred to as Kavigale) has not been approved in any country or region. As part of the European Medicines Agency (EMA) OPEN initiative,[4)] information related to the regulatory review was shared with foreign regulatory authorities, including the EMA, during this application process.

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1) Guidelines for Diagnosis and Treatment of COVID-19, ver. 10.1 (in Japanese) (dated April 23, 2024)
2) The Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (Infectious Diseases Control Act) (Act No. 114 of 1998)
3) Package insert of Evusheld Intramuscular Injection Set, etc.
4) https://www.ema.europa.eu/en/partners-networks/international-activities/multilateral-coalitions-initiatives/opening-procedures-ema-non-eu-authorities-open-initiative (last accessed on October 11, 2024)

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Generation and control of cell substrate

Memory B cells[5] derived from a donor with a history of SARS-CoV-2 (Omicron BA.1) infection were selected for their ability to bind to the S protein of the BA.1 lineage. Based on antibodies derived from these cells, a gene expression construct for sipavibart was developed, incorporating gene fragments encoding an optimized variable region and constant region. The fragment crystallizable (Fc) region has been engineered with YTE substitutions (M252Y, S254T, and T256E[6]; *Antimicrob Agents Chemother.* 2013;57:6147-53) to prolong the serum half-life and TM substitutions (L234F, L235E, and P331S[6]; *Acta Crystallogr D Biol Crystallogr.* 2008;64:700-4) to reduce binding affinity to Fc gamma receptor (FcγR) and complement component 1q (C1q). This gene expression construct was introduced into Chinese hamster ovary (CHO) cells, and a master cell bank (MCB) and a working cell bank (WCB) were prepared from the optimal clone for sipavibart manufacturing.

Characterization and purity tests were conducted on the MCB, WCB, end-of-production cell banks (EOPCBs), and cells at the limit-of-*in-vitro*-cell-age (LIVCA) stage in accordance with International Council for Harmonisation (ICH) Q5A(R1), Q5B, and Q5D guidelines. The results showed that genetic stability during the manufacturing period was confirmed, and within the scope of the tests performed, no viral or non-viral adventitious agents were detected other than endogenous retrovirus-like particles commonly observed in rodent-derived cell lines.

The MCB and WCB are stored in [redacted]. The MCB [redacted], and the WCB [redacted].

2.1.2 Manufacturing process

The manufacturing process of the drug substance consists of cell thawing, inoculation and expansion culture, seed culture, main culture, harvest, [redacted] chromatography, [redacted] virus inactivation, [redacted] chromatography, [redacted] chromatography, virus removal filtration, [redacted], and testing/storage.

[redacted] chromatography, [redacted] virus inactivation, [redacted] chromatography, and virus removal filtration were identified as critical steps.

Process validation of the drug substance manufacturing process has been conducted at the commercial production scale.

2.1.3 Safety evaluation of adventitious agents

No biological raw materials other than the host CHO cells are used in the manufacturing process of the drug substance.

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5) *Cell.* 2022;185:2116-31
6) EU numbering (*Proc Natl Acad USA.* 1969;63:78-85)

Purity tests have been conducted on cells at the MCB, WCB, EOPCB, and LIVCA stages [see Section 2.1.1]. For unprocessed bulk obtained at the commercial production scale prior to harvest, microbial limit test, mycoplasma test, *in vitro* adventitious virus test, and transmission electron microscopy observation have been conducted. Within the scope of the examined test parameters, no viral or non-viral adventitious agents were detected. These tests for unprocessed bulk prior to harvest have been established as in-process control tests, except for transmission electron microscopy observation.

Regarding the purification process, viral clearance studies using model viruses have been conducted, demonstrating that the purification process possesses an adequate viral clearance capability (Table 1).

Table 1. Results of viral clearance studies

Manufacturing process	Viral reduction factor (log_{10})			
	Xenotropic murine leukemia virus	Pseudorabies virus	Reovirus type 3	Mouse minute virus
[redacted] virus inactivation	[redacted]			
[redacted] chromatography				
[redacted] chromatography				
Virus removal filtration				
Overall viral reduction factor	>24.92[a)]	>23.73[a)]	>16.36[a)]	>9.82

a) For the filtration process for viral removal, [redacted] was employed as [redacted] for [redacted], [redacted], and [redacted].

2.1.4 Manufacturing process development

For changes in the manufacturing process during the development of the drug substance, the comparability of pre-change and post-change drug substances has been demonstrated in accordance with the ICH Q5E guidelines. [redacted] was used in the clinical study.

2.1.5 Characterization

2.1.5.1 Structure and characteristics

The drug substance was subjected to characterization tests described in Table 2.

Table 2. Parameters for characterization

Primary/higher-order structure	Amino acid sequence, molecular weight, posttranslational modification ([redacted], oxidation, [redacted], [redacted], [redacted], [redacted]), disulfide bonds, [redacted], secondary structure, tertiary structure, thermal stability
Physicochemical properties	Size variants, charge variants, insoluble particulate matters
Carbohydrate structure	N-linked oligosaccharide profile
Biological properties	Binding activity to SARS-CoV-2 S-protein
	Binding affinity to FcγR[redacted], binding activity to FcRn
	In vitro virus neutralization activity

The main findings on biological properties are as follows:

- *In vitro* virus neutralization activity was evaluated in the following 3 studies, and all confirmed concentration-dependent neutralization activity of sipavibart:
  (a) SARS-CoV-2 neutralization assay using SARS-CoV-2 (Omicron BA.1) and [redacted] cells based on [redacted] as the indicator
  (b) Pseudovirus neutralization test by a reporter gene assay using [redacted] (pseudovirus particles) expressing the SARS-CoV-2 (Omicron BA.1) S protein and [redacted] cells expressing angiotensin-converting enzyme 2 (ACE2)

(c) Virus-like particle neutralization assay by luminescence detection using [redacted] with an 11-amino acid peptide-tagged labeled SARS-CoV-2 (Omicron variant BA.1) S protein, [redacted] cells expressing ACE2 labeled with a peptide tag-binding [redacted], and a substrate.

2.1.5.2 Product-related substances/Product-related impurities

Based on the results of the characterization analyses in Section 2.1.5.1, [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] were identified as product-related substances. High molecular weight species, fragments, Impurity A, Impurity B, Impurity C, and Impurity D were identified as product-related impurities. Among these product-related impurities, high molecular weight species and fragments are controlled by the specifications for the drug substance and drug product. Impurity C and Impurity D are controlled by the specifications for the drug product. No routine control is required for Impurity A and Impurity B because their levels have remained constantly low in the past manufacturing experiences.

2.1.5.3 Process-related impurities

Host cell-derived deoxyribonucleic acid (DNA), host cell protein (HCP), Impurity E, Impurity F, Impurity G, Impurity H, Impurity I, Impurity J, and Impurity K were identified as process-related impurities. Host cell-derived DNA, HCP, and Impurity E have been confirmed to be adequately removed during the manufacturing process. Impurity F, Impurity G, Impurity H, Impurity I, Impurity J, and Impurity K were subjected to a risk assessment and determined to be low-risk. HCP is controlled by the specifications for the drug substance.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (peptide mapping), pH, purity (capillary electrophoresis - sodium dodecyl sulfate [CE-SDS, non-reducing] and size exclusion chromatography [SEC]), capillary isoelectric focusing [cIEF], HCP, bacterial endotoxin, microbial limit, biological activity (enzyme-linked immunosorbent assay [ELISA]), polysorbate 80 content, and assay (ultraviolet-visible spectrophotometry) [see Section 2.R.1].

2.1.7 Stability of drug substance

Table 3 summarizes the main stability studies for the drug substance.

Table 3. Summary of the main stability studies for the drug substance

	Manufacturing process of drug substance	Number of batches	Storage condition	Study period	Storage form
Long-term testing	[redacted]	4	−40°C ± 10°C	[redacted] months[a)]	[redacted] container
		6	−40°C ± 5°C	[redacted] months[b)]	
Accelerated testing		4	5°C ± 3°C	[redacted] months	
		6		[redacted] months[c)]	
Stress testing		3	30°C ± 2°C/65% ± 5%RH	[redacted] months	
		6			

a) [redacted] months with 1 batch, ongoing up to [redacted] months.
b) [redacted] months with 3 batches, ongoing up to [redacted] months.
c) [redacted] months with 3 batches, ongoing up to [redacted] months.

No significant changes in quality attributes were observed throughout the duration of long-term testing and accelerated testing.

Stress testing showed a tendency toward a decrease in [redacted] and a tendency toward an increase in [redacted] in [redacted], a tendency toward a decrease in [redacted] and a tendency toward an increase in [redacted] in [redacted], and a tendency toward a decrease in [redacted] and a tendency toward an increase in [redacted] in [redacted].

Based on the above, the shelf life of [redacted] months has been proposed for the drug substance when stored in [redacted] containers at −45°C to −35°C.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an aqueous injectable preparation, with 2 mL of solution containing 300 mg of sipavibart filled in a 4 mL glass vial. The drug product contains the following excipients: L-histidine, L-histidine hydrochloride hydrate, L-arginine hydrochloride, polysorbate 80, and water for injection.

2.2.2 Manufacturing process

The manufacturing process of the drug product consists of [redacted], sterile filtration, sterile filling, [redacted], and labeling/packaging/storage/testing.

[redacted] and [redacted] were identified as critical steps.

Process validation has been conducted at the commercial production scale.

2.2.3 Manufacturing process development

Regarding the changes made to the manufacturing process during the development process of the drug product, the comparability of the pre- and post-change drug products has been confirmed in accordance with the ICH Q5E guidelines. The drug product manufactured by [redacted] was used in the clinical study.

2.2.4 Control of drug product

The proposed specifications for the drug product include strength, description, identification ([redacted]), osmolality, pH, purity (CE-SDS [non-reducing] and SEC), cIEF, bacterial endotoxin, extractable volume, foreign insoluble matters, insoluble particulate matters, sterility, biological activity (ELISA), and assay (ultraviolet-visible spectrophotometry) [see Section 2.R.1].

2.2.5 Stability of drug product

Table 4 shows the summary of the main stability studies for the drug product.

Table 4. Summary of the main stability tests on drug product

	Manufacturing process[a)]	Number of batches	Storage condition	Study period	Storage form
Long-term testing	[redacted]	3	5°C ± 3°C	18 months[b)]	Glass vial with [redacted] chlorobutyl rubber stopper
	[redacted]	3		12 months[c)]	
Accelerated testing	[redacted]	3	25°C ± 2°C/60% ± 5%RH	3 months	
	[redacted]	3		6 months	
Stress testing	[redacted]	3	30°C ± 2°C/65% ± 5%RH	3 months	
	[redacted]	3			
Photostability testing	[redacted]	1	Overall illumination of ≥1.2 million lux•h, and an integrated near ultraviolet energy of ≥200 W•h/m^2		

a) The drug substances of [redacted] and [redacted] were used for" [redacted]" and "[redacted]," respectively.
b) Ongoing up to [redacted] months.
c) 9 months with 1 batch, ongoing up to [redacted] months.

The long-term testing showed no clear changes in the quality attributes throughout the study period.

The accelerated testing and the stress testing showed a tendency toward a decrease in [redacted] and a tendency toward an increase in [redacted] in [redacted], a tendency toward a decrease in [redacted] and a tendency toward an increase in [redacted] in [redacted], and a tendency toward a decrease in [redacted] and a tendency toward an increase in [redacted] in [redacted].

The photostability testing showed that the drug product is unstable to light.

Based on the above, a shelf life of 18 months was proposed for the drug product when stored in a glass vial with [redacted] chlorobutyl rubber stopper (primary container) at 2°C to 8°C, protected from light in paper boxes.

2.3 Strategy for quality control

Based on the following evaluations, a quality control strategy was established through a combination of process parameter control, in-process control testing, and specifications. [For the 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):
  On the basis of the information obtained through the development of sipavibart and related knowledge, etc., the following CQAs were identified:
  CQAs: High molecular weight species, fragments, Impurity A, higher-order structure, Impurity B, Impurity C, Impurity D, host cell DNA, HCP, Impurity E, color, clarity, pH, protein content, polysorbate 80 concentration, [redacted], extractable volume, integrity of container-closure system, [redacted], sterility, bacterial endotoxin, viral safety, mycoplasma, identity with the target substance, potency, and neonatal Fc receptor (FcRn) binding

- Process characterization
  Based on the risk assessment of each process parameter and the process characterization, critical process parameters (CPPs) that have a significant impact on CQAs were identified, and operational control ranges for these parameters, including the CPPs, were established.

2.R Outline of the review conducted by PMDA

PMDA concluded that the quality of the drug substance and the drug product is appropriately controlled, based on the submitted data and the following evaluations.

2.R.1 Control of biological activity

SARS-CoV-2 utilizes S protein as the sole membrane protein involved in host cell entry. Sipavibart is considered to exert neutralization activity against SARS-CoV-2 by binding to the RBD of S protein, thereby inhibiting its interaction with an ACE2 receptor. Since the binding activity of sipavibart to S protein is a critical element of its mechanism of action, the applicant specifies the binding activity assay (ELISA) for S protein as the biological activity assay for the drug substance and the drug product, while considering an evaluation of neutralization activity to be unnecessary.

PMDA, however, requested the applicant to establish an *in vitro* viral neutralization assay as a test system that better reflects the overall mechanism of action of sipavibart, since the binding activity assay for S protein only evaluates an upstream component of the series of processes leading to the neutralization activity against SARS-CoV-2.

The applicant's response:
The applicant conducted characterization analyses using sipavibart and its degraded samples. In the characterization analyses, [redacted]. Therefore, the applicant proposed to specify [redacted] as specifications for the drug substance and the drug product, [redacted] for [redacted] and [redacted].

PMDA accepted the applicant's approach.

2.R.2 Novel excipient

The drug product contains L-arginine hydrochloride (excipient) in an amount exceeding that of the previous uses for intramuscular injection.

2.R.2.1 Specifications and stability

PMDA has concluded that L-arginine hydrochloride conforms to the Japanese Pharmacopoeia and that there are no issues regarding its specifications or stability.

2.R.2.2 Safety

The applicant's explanation about the safety of L-arginine hydrochloride:
From the perspective of systemic toxicity, the maximum daily dose of L-arginine hydrochloride (92.7 mg/day), based on the approved dosage and administration of the drug product (intramuscular administration), falls within the range of previously used doses for intravenous administration (120 mg/day; *Japanese Pharmaceutical Excipients Dictionary*. Yakuji Nippo, Limited, 2021;p.32-33). Regarding local toxicity, in a 3-week repeated-dose toxicity study involving intravenous and intramuscular administration (once per week) in cynomolgus monkeys, intramuscular administration of approximately 46 mg/kg of L-arginine hydrochloride (contained in sipavibart at 150 mg/kg) did not

result in findings suggestive of local irritancy at the injection site. Based on these results, there were no particular concerns.

Considering the above, the safety concern associated with this excipient is deemed to be low.

Based on the above evaluation results, PMDA has concluded that the amount of L-arginine hydrochloride used in the drug product (92.7 mg/day) is unlikely to pose a safety issue upon intramuscular administration.

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

The applicant submitted non-clinical pharmacology data on sipavibart, in the form of the results from primary pharmacodynamic studies. In the non-clinical pharmacology studies of sipavibart, antibodies listed in Table 5 were used in addition to sipavibart. The measurement results in this section are presented as mean values.

Table 5. Types of antibodies used in non-clinical pharmacology studies

AZD3152-WT	Parent antibody of sipavibart without modification of Fc region
AZD3152-TM	Antibody that shares the same Fab region as sipavibart and has the TM substitution introduced in the Fc region, but does not contain the YTE substitution.
AZD3152-YTE	Antibody that shares the same Fab region as sipavibart and has the YTE substitution introduced in the Fc region, but does not contain the TM substitution.

3.1 Primary pharmacodynamics

3.1.1 Binding characteristics to SARS-CoV-2

3.1.1.1 Binding affinity to the S protein and RBD of SARS-CoV-2 and inhibition of binding of RBD to ACE2 (CTD 4.2.1.1.1)

The binding affinity between sipavibart and S protein (trimeric ectodomain) or RBD of SARS-CoV-2[7)] was evaluated using the surface plasmon resonance (SPR) method. The equilibrium dissociation constant (K_D) for binding to S protein was 14.81 pmol/L for sipavibart and 41.39 pmol/L for cilgavimab (CIL), while the K_D for binding to the RBD was 20.95 pmol/L for sipavibart and 1,032 pmol/L for CIL.

The inhibitory activity of sipavibart against the binding of RBD to ACE2 was evaluated using ELISA. The 50% inhibitory concentration (IC_{50}) was 682.9 pmol/L for sipavibart and 966.3 pmol/L for CIL.

3.1.1.2 Epitope on RBD recognized by sipavibart and its binding mode (Reference CTD 4.2.1.1.10)

The binding mode between the antigen binding fragment (Fab) region of sipavibart and RBD of the SARS-CoV-2 Omicron BA.2 lineage S protein was analyzed by X-ray crystallography. Among the epitopes[8)] of sipavibart on the RBD, those forming polar interactions (hydrogen bonds or salt bridges) are listed in Table 6. Most of the amino acid residues of sipavibart involved in polar interactions were located in the heavy chain complementarity-determining regions (CDRH1 or CDRH3) of sipavibart.

7) SARS-CoV-2 Omicron BA.2 lineage (GenBank: ULS17723.1)

8) The binding site was defined as the amino acid residues of the RBD that have at least 1 atom located within 5 Å radius of the Fab region of sipavibart. The binding site on the RBD consists of the following 28 residues (based on the amino acid sequence of S protein of the SARS-CoV-2 original strain): R403, D405, Q409, Q414, T415, G416, K417, I418, D420, Y421, Y453, R454, L455, F456, R457, K458, S459, N460, Y473, Q474, A475, G476, S477, F486, N487, Y489, Q493, and Y505.

The sequence conservation of amino acid residues in S protein forming polar interactions with sipavibart was analyzed based on the SARS-CoV-2 genome sequences (15,084,220 entries, from December 1, 2019 to August 1, 2024) registered in the Global initiative on sharing avian influenza data (GISAID) database. The conservation rates were 98.2% for R403, 61.1% for D405, 51.0% for K417, 97.5% for L455, and 47.2% for S477, while all other residues exceeded 99.9% conservation.

Table 6. Amino acid residues forming polar interactions[a)] between sipavibart and RBD, and conservation rates of amino acid residues on RBD

Amino acid residues in RBD		Binding sites of amino acid residues in Fab of sipavibart	
Binding site[b)]	Conservation rate (%)[c)]	Heavy chain	Light chain
R403	98.2	-	E52
D405	61.1	-	N33
Q409	>99.9	-	Y34
Q414	>99.9	-	Y32
T415	>99.9	-	Y93
G416	>99.9	Y109	-
K417	51.0	Y110	Y34
D420	>99.9	Y109	-
Y421	>99.9	Y104, S105, S106	-
Y453	>99.9	-	E52, K55
L455	97.5	Y110	-
R457	>99.9	G103	-
K458	>99.9	D30, D31	-
Y473	>99.9	D31	-
S477	47.2	E1	-

-, Not applicable
a) The binding site was defined as the amino acid residues of the RBD that have at least 1 atom located within 5 Å radius of the Fab region of sipavibart.
b) Based on the amino acid sequence of the S protein of the SARS-CoV-2 original strain.
c) Calculated using 15,084,220 genome sequences of SARS-CoV-2 registered in GISAID (from December 1, 2019 to August 1, 2024)

In addition to polar interactions, hydrophobic interactions between the following residues contributed to the binding of sipavibart to the RBD: Sipavibart heavy chain residues V2, G26, F27, P28, Y32, W53, A100, F101, P102, G103, and Y104 with RBD residues F456, A475, G476, and Y489; and sipavibart light chain residues Y32, V53, and G95 with RBD residues G416 and L455.

3.1.2 Effects of YTE and TM substitutions in Fc region (Reference CTD 4.2.1.1.4)

YTE and TM substitutions have been introduced into the Fc region of sipavibart [see Section 2.1.1].

The effect of the YTE substitution on the binding affinity of sipavibart to human FcRn was evaluated using an SPR assay. Under low pH conditions (pH 6.0) simulating the environment of intracellular endosomes, the K_D of sipavibart for human FcRn was 216 nmol/L, demonstrating approximately 7-fold higher binding affinity compared to AZD3152-TM (K_D = 1413 nmol/L). On the other hand, under physiological conditions (pH 7.4), AZD3152-TM exhibited no detectable binding to human FcRn, and sipavibart displayed only minimal binding.

The effect of the TM substitution on the binding affinity of sipavibart to human FcγRs and human C1q was also evaluated using an SPR assay. Compared to AZD3152-WT, the binding affinity of sipavibart to human FcγRs (FcγRI, FcγRIIa, FcγR[redacted] and FcγR[redacted]) was reduced by 74% to 94%. The binding affinity of sipavibart to human complement C1q was reduced by 99% compared to AZD3152-WT.

3.1.3 *In vitro* antiviral activity

3.1.3.1 Neutralization activity against SARS-CoV-2 (CTD 4.2.1.1.5)

The neutralization activity (infection inhibition) of sipavibart, CIL, and cilgavimab/tixagevimab (CIL/TIX) was evaluated using the focus reduction neutralization assay. Various SARS-CoV-2 variants (clinical isolates) were treated with each study drug and subsequently VeroE6/transmembrane protease serine 2 (TMPRSS2) cells were infected with the variants.[9)] Infection was detected using SARS-CoV-2 nucleocapsid staining. Table 7 shows the results. Unlike the approved drugs (CIL/TIX), sipavibart exhibited neutralization activity against all tested variants.

Table 7. Neutralization activity against SARS-CoV-2 variants

SARS-CoV-2 lineage		EC_{50} (ng/mL)		
Pango lineage	WHO label	Sipavibart	CIL	CIL/TIX
A[a)]	-	110.9	70.4	14.8
B.1.1.7	Alpha	53.6	7.4	2.5
B.1.617.2	Delta	25.9	22.5	4.4
BA.1	Omicron	13.1	4,064.0	176.5
BA.1.1		8.3	>10,000	858.9
BA.2		32.2	25.8	43.0
BA.2.12.1		26.5	30.5	41.1
BA.5		15.3	102.1	186.7

a) D614G variant

In another assay, ACE2-expressing [redacted] cells were infected with pseudovirus particles expressing S protein of SARS-CoV-2 variants treated with sipavibart, CIL, or CIL/TIX. The neutralization activity against each pseudovirus particle was assessed using luciferase activity as an indicator. Table 8 shows the results, confirming the broad neutralization activity of sipavibart against Omicron variants.

Table 8. Neutralization activity against SARS-CoV-2 pseudovirus particles

SARS-CoV-2 lineage		EC_{50} (ng/mL)		
Pango lineage	WHO label	Sipavibart	CIL	CIL/TIX
A[a)]	-	13.5	4.9	2.6
B.1.1.7	Alpha	11.0	5.4	2.5
B.1.351	Beta	10.7	4.0	5.3
B.1.617.2	Delta	17.9	12.0	2.2
P.1	Gamma	4.6	3.5	3.6
BA.1	Omicron	5.4	2,429.5	618.4
BA.1.1		4.6	>9,000	1,728.5
BA.2		10.7	4.8	12.7
BA.2.12.1		7.9	9.1	17.2
BA.4/5		4.7	69.0	142.1
BA.2.75		25.0	156.0	60.7
BA.4.6		14.5	>9,000	>9,000
BA.4.7		4.2	>9,000	>9,000
BA.5.9		4.7	>9,000	>9,000
BA.2.75.2		9.7	>9,000	>9,000
BF.7		3.8	>9,000	>9,000
BQ.1		11.6	>9,000	>9,000
BQ.1.1		9.2	>9,000	>9,000
XBB	Omicron (recombinant)	3.8	>9,000	>9,000
XBB.1		3.6	>9,000	>9,000

a) D614G variant

9) A cell line derived from African green monkey kidney epithelial cells, with stable expression of TMPRSS2.

The impact of YTE and TM substitutions in the Fc region on neutralization activity was evaluated using a luciferase reporter assay. Sipavibart, AZD3152-TM, AZD3152-YTE, and AZD3152-WT were tested against the D614G variant. The neutralization activity was comparable among these antibodies (50% effective concentration [EC_{50}], 7.5-7.8 ng/mL), indicating that the substitutions had no effect on neutralization activity.

3.1.4 Effector functions of the Fc Region (Reference CTD 4.2.1.1.6 and CTD 4.2.1.1.9)

The effector functions mediated by the Fc region of sipavibart, including antibody-dependent cellular phagocytosis, antibody-dependent neutrophil phagocytosis, antibody-dependent cellular cytotoxicity, antibody-dependent complement deposition, antibody-dependent NK cell activation, and antibody-dependent enhancement of viral infection, were evaluated (Table 9). The results indicated that no activities suggestive of effector functions mediated by the Fc region of sipavibart were observed.

Table 9. Overview and results of the evaluation of effector functions mediated by Fc region

Effector function	Test substance	Antibody added (ng/mL)	Endpoint	Results
Antibody-dependent cellular phagocytosis	Sipavibart, AZD3152-WT, positive control, or negative control	2.3-5,000	Phagocytosis score by human monocytic THP-1 cells[a)]	The range of phagocytosis scores obtained at each concentration of sipavibart was 27.03 to 64.20, and the area under the mean phagocytosis score–antibody concentration curve was decreased by 60.6% compared to AZD3152-WT.
Antibody-dependent neutrophil phagocytosis	Sipavibart, AZD3152-WT, positive control, or negative control	30.6-67,000	Phagocytosis score by primary human neutrophils[a)]	The range of phagocytosis scores obtained at each concentration of sipavibart was 17.38 to 54.39, and the area under the mean phagocytosis score–antibody concentration curve was decreased by 70.9% compared to AZD3152-WT.
Antibody-dependent cellular cytotoxicity	Sipavibart, AZD3152-WT, positive control, negative control, positive serum, or negative serum	1.5-25,000	Cytolysis by primary human NK cells	No cytolysis was observed with either sipavibart or AZD3152-WT.
Antibody-dependent complement deposition	Sipavibart, AZD3152-WT, positive control, or negative control	45.7-100,000	Complement deposition[a)]	Complement deposition was observed with AZD3152-WT, but not with sipavibart.
Antibody-dependent NK cell activation	Sipavibart, AZD3152-WT, positive control, or negative control	9.1-20,000	Expression of CD107a, IFN-γ, and MIP-1β from primary NK cells	Induction of CD107a, IFN-γ, and MIP-1β expression was observed with AZD3152-WT, but not with sipavibart.
Antibody-dependent enhancement of viral infection	Sipavibart, sipavibart/CIL,[b)] negative control, positive serum, or negative serum	12.8×10^{-6} -3,125	Infection of Raji cells[c)] with pseudovirus particles expressing the SARS-CoV-2 S protein	The number of infected cells in both sipavibart and sipavibart/CIL groups was comparable to that in the negative control.

Positive control (antibody-dependent cellular phagocytosis, antibody-dependent neutrophil phagocytosis, antibody-dependent complement deposition, and antibody-dependent NK cell activation): REGN10989, a monoclonal antibody targeting the SARS-CoV-2 S protein with an unmodified Fc region (*Cell*. 2021;184:3949-61)
Positive control (antibody-dependent cytotoxicity): A monoclonal antibody cocktail composed of AZD3152-WT and the parent antibody of CIL with an unmodified Fc region, mixed at a 1:1 ratio
Negative control: A monoclonal antibody targeting the Ebola virus glycoprotein
Positive serum: Serum from patients who recovered from COVID-19
Negative serum: Serum from healthy subjects with no history of SARS-CoV-2 infection
a) Evaluated using fluorescently labeled beads coated with S protein
b) CIL has been confirmed not to exhibit antibody-dependent enhancement of viral infection [Report on Special Approval for Emergency on Evusheld Intramuscular Injection Set, dated August 18, 2022, see Section 3.1.3.4]
c) Human B cell line expressing FcγRIIa and not expressing ACE2

3.1.5 Induction of escape mutations (Reference CTD 4.2.1.1.8)

VeroE6/TMPRSS2 cells infected with SARS-CoV-2[10)] were subjected to 9 passages under increasing concentrations of sipavibart (0.08-10.51 μg/mL). Amino acid mutations T415I, F456L, or K458E were observed in the RBD of S protein of the virus in the culture supernatant.

The neutralization activity (EC_{50}) of sipavibart against recombinant SARS-CoV-2 viruses[10)] harboring these amino acid mutations was evaluated using the focus reduction neutralization assay. Compared to the parental strain without mutations, the neutralization activity decreased to 1/103 for T415I and to less than 1/769 for F456L and K458E.

[10)] A strain generated by (a) introduction of transcription regulatory sequence mutations, (b) deletions of open reading frames (ORFs) 3, 6, 7, and 8, (c) introduction of an enhanced green fluorescent protein (eGFP) reporter gene, and (d) introduction of amino acid mutations in the S protein of the XBB.1.5 lineage into a cDNA clone of a clinical isolate (2019-nCoV/USA_WA1/2020).

In addition to the escape mutations mentioned above, V991E amino acid mutation in the S2 domain of S protein was observed. However, this mutation was also present even without sipavibart, and no significant difference in neutralization activity was identified between the parental strain and the mutant strain (EC_{50} ratio, 1.8-fold). The applicant explained that the mutation does not qualify as an escape mutation.

3.1.6 *In vivo* antiviral activity (Reference CTD 4.2.1.1.7)

Male and female Syrian hamsters (8 animals/sex/group) received a single intraperitoneal dose of AZD3152-TM (0.67-6.0 mg) or a negative control.[11)] On the following day, SARS-CoV-2 (USA-WA1/2020, 6.0×10^3 plaque-forming unit [PFU]) was intranasally inoculated. The body weight change, lung viral load on Days 3 and 7 post-virus exposure, and pulmonary lesions (inflammation, alveolar type II epithelial cell hyperplasia, fibrin deposition or haemorrhage, endotheliitis, and necrosis) were evaluated. The results showed that AZD3152-TM at doses of ≥0.67 mg suppressed body weight loss, and a dose-dependent inhibitory effect on lung viral load and pulmonary lesions was observed.

3.2 Secondary pharmacodynamics

Sipavibart is an antibody against the SARS-CoV-2 S protein. Since no cross-reactivity was observed in the tissue cross-reactivity study [see Section 5.7.1], secondary pharmacodynamic studies were not conducted.

3.3 Safety pharmacology

Safety pharmacology was evaluated through monitoring of clinical signs in the systemic toxicity study of repeated administration of sipavibart/CIL in cynomolgus monkeys [see Section 5.1]. No effects on the central nervous, vascular, or respiratory systems were observed.

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological action of sipavibart

PMDA's view:

Based on the submitted data, the primary pharmacological action of sipavibart is considered to be the neutralization of infectivity through binding to the RBD of the SARS-CoV-2 S protein, which is crucial for viral entry into host cells. By inhibiting viral entry into the host, sipavibart is expected to exert an inhibitory effect on the replication of SARS-CoV-2 from a pharmacological perspective. With regard to antibody-dependent enhancement caused by sipavibart, no findings suggesting such an effect were observed within the scope of the evaluation conducted. Therefore, there are no particular concerns from a non-clinical pharmacology standpoint.

3.R.2 Neutralization activity of sipavibart

The applicant's explanation about the neutralization activity of sipavibart against SARS-CoV-2:

In an *in vitro* study using SARS-CoV-2 pseudovirus, sipavibart exhibited similar levels of neutralization activity against the D614G variant (lineage A), Alpha variant, Beta variant, Delta variant, and Gamma variant, and against Omicron variants (BA.1, BA.1.1, BA.2, BA.2.12.1, BA.4/5, BA.2.75, BA.4.6,

11) A human IgG1 antibody with no binding activity to SARS-CoV-2.

BA.4.7, BA.5.9, BA.2.75.2, BF.7, BQ.1, and BQ.1.1 lineages), including those that showed insufficient neutralization activity with CIL/TIX, as well as against recombinant Omicron variants (XBB and XBB.1 lineages) (see Table 8).

Furthermore, additional investigations were conducted using the same methodology to assess the neutralization activity of sipavibart against circulating variants that emerged after the previously mentioned variants. Table 10 shows the results, indicating that the neutralization activity against Omicron BA.2.86, XBB.1.5/XBB.1.9, XBB.1.16, and XBB.2.3 lineages was comparable to that observed against the D614G variant (lineage A) (Table 8).

On the other hand, a decrease in neutralization activity was observed for sipavibart against the Omicron JN.1 lineage compared to the D614G variant (lineage A) and other variants. This reduction is considered to be due to the presence of an amino acid mutation (L455S) in the RBD at L455, which forms a polar interaction with sipavibart (see Table 6). Sipavibart did not exhibit neutralization activity against variants containing the F456L amino acid mutation in the S protein, such as EG.5 and EG.5.1 lineages (Table 10). As of October 2024, the neutralization activity of sipavibart against the currently predominant KP.1, KP.3, LB.1, and ML.1 lineages has not been evaluated. Since these variants contain the F456L amino acid mutation, similar to the EG.5 and EG.5.1 lineages, sipavibart is considered unlikely to exhibit neutralization activity against circulating variants, such as the KP.1 lineage. In order to ensure the proper use of sipavibart, the package insert will include information stating that sipavibart does not exhibit *in vitro* neutralization activity against variants containing the F456L mutation.

Table 10. Neutralization activity against SARS-CoV-2 pseudovirus particles

SARS-CoV-2 lineage		EC_{50} (ng/mL)		
Pango lineage	WHO label	Sipavibart	CIL	CIL/TIX
A[a)]	-	13.5	4.9	2.6
BA.2.86	Omicron	3.8	>1,000	>1,000
JN.1		83.1	>1,000	>1,000
EG.5[b)]		>1,000	>1,000	>1,000
EG.5.1[b)]		>1,000	>1,000	>1,000
XBB.1.5/XBB.1.9	Omicron (recombinant)	5.8	>1,000	>1,000
XBB.1.16		1.3	>1,000	>1,000
XBB.2.3		3.4	>1,000	>1,000

a) D614G variant
b) Variant containing F456L mutation

PMDA's view:
The submitted data have demonstrated that sipavibart exhibits neutralization activity against a broad range of SARS-CoV-2 variants that do not contain the F456L mutation. Since sipavibart is not expected to exhibit neutralization activity against SARS-CoV-2 variants containing the F456L mutation, the appropriateness of use of sipavibart in clinical settings should be carefully assessed by physicians with updated knowledge on the presence or absence of the F456L mutation in circulating variants and the neutralization activity of sipavibart. The neutralization activity of sipavibart against emerging variants is crucial information regarding its efficacy. The applicant should continue collecting data after the marketing launch and, if new findings are obtained, the applicant should promptly provide updated information to healthcare professionals.

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

The applicant submitted results from intravenous or intramuscular administration studies of sipavibart and sipavibart/CIL using mice and monkeys. The concentration of sipavibart in mouse serum was measured by ELISA (lower limit of quantification, 31.25 ng/mL), while the concentrations of sipavibart and CIL in monkey serum were measured by liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) (lower limit of quantification, 9.0 μg/mL). Pharmacokinetics (PK) parameters are presented as mean values or mean ± standard deviation (SD), unless specified otherwise.

4.1 Absorption

4.1.1 Single-dose study (Reference CTD 4.2.2.7.1)

Table 11 shows the PK parameters following the administration of sipavibart as a single intravenous dose of 5 mg/kg to transgenic Tg32 mice expressing human FcRn (hereinafter referred to as "hFcRn-expressing mice"). The elimination half-life of sipavibart and CIL did not differ significantly.

Table 11. PK parameters following a single intravenous administration of sipavibart 5 mg/kg in hFcRn-expressing mice

	Number of animals	C_{max} (μg/mL)	AUC_{last} (μg·day/mL)	AUC_{inf} (μg·day/mL)	$t_{1/2}$ (day)	CL (mL/day/kg)	V_{ss} (mL/kg)
Sipavibart	3/time point	127	1,130	1,580	20.6	3.16	89.1
Reference, CIL[a)]	3/time point	82.2	691	1,050	17.7	4.78	121

a) Documents attached to the application of Evusheld Intramuscular Injection Set, Reference CTD 4.2.2.7.1

4.1.2 Repeated-dose study (CTD 4.2.3.2.1)

Table 12 shows the PK parameters following repeated once-weekly (intravenous or intramuscular) doses of sipavibart 150 mg/kg/CIL 150 mg/kg cynomolgus monkeys. The PK parameters of sipavibart and CIL were similar, and no clear sex differences were observed.

Table 12. PK parameters following repeated administration of sipavibart 150 mg/kg/CIL 150 mg/kg

Route of administration	Analyte	Day of measurement	Sex	N	C_{max} (mg/mL)	t_{max} (h)	$AUC_{0\text{-}72h}$ (mg·h/mL)	$AUC_{0\text{-}168h}$ (mg·h/mL)	BA[a)] (%)
i.v.[b)]	Sipavibart	Day 1	M	5	3.720 ± 0.679	0.50 [0.50, 5.50]	165 ± 15.3	334 ± 27.2	
			F	5	4.260 ± 1.120	0.50 [0.50, 5.50]	166 ± 31.9	309 ± 46.7	
		Day 15	M	5	6.770 ± 0.619	0.50 [0.50, 0.50]	368 ± 19.0	681, 761	
			F	5	6.010 ± 0.289	0.50 [0.50, 0.55]	338 ± 24.8	671, 690	
	CIL	Day 1	M	5	3.790 ± 0.484	1.00 [1.0, 6.0]	176 ± 16.1	363 ± 23.9	
			F	5	4.220 ± 0.997	1.00 [1.0, 6.0]	173 ± 21.8	329 ± 26.8	
		Day 15	M	5	6.440 ± 0.574	1.00 [1.0, 6.0]	363 ± 23.1	693, 754	
			F	5	5.430 ± 0.744	1.00 [1.0, 24.0]	320 ± 25.6	659, 659	
i.m.[c)]	Sipavibart	Day 1	M	3	2.340 ± 0.490	24.0 [24.0, 24.0]	143 ± 26.3	288 ± 42.2	92.1
			F	3	2.670 ± 0.583	24.0 [24.0, 24.0]	151 ± 25.2	304 ± 37.7	
		Day 15	M	3	4.940 ± 1.140	24.0 [24.0, 24.0]	318 ± 48.4	762	94.9
			F	3	4.000 ± 0.626	24.0 [24.0, 24.0]	260 ± 42.3	566	
	CIL	Day 1	M	3	2.130 ± 0.260	24.0 [6.00, 24.0]	135 ± 18.4	280 ± 33.0	80.9
			F	3	2.310 ± 0.297	24.0 [6.00, 24.0]	137 ± 12.6	280 ± 21.6	
		Day 15	M	3	4.630 ± 0.936	6.00 [6.00, 24.0]	305 ± 50.5	727	106
			F	3	5.050 ± 0.649	24.0 [24.0, 24.0]	331 ± 42.4	737	

t_{max} is presented as median [range]; when the number of measurements is ≤2, individual values are shown.

a) Bioavailability (BA) was calculated based on the combined results (both sexes) of $AUC_{0\text{-}168h}$ following intramuscular and intravenous administration.

b) Sipavibart and CIL were each administered by intravenous infusion over 30 minutes each.

c) Sipavibart was administered intramuscularly at 150 mg/kg to the right thigh, and CIL was administered intramuscularly at 100 mg/kg to the left thigh and at 50 mg/kg to the left biceps brachii.

4.2 Distribution

No distribution studies were conducted.

The applicant's explanation:

Following the administration of sipavibart as a single intravenous dose to hFcRn-expressing mice, the volume of distribution was 89.1 mL/kg [see Section 4.1.1]. Since this value does not differ significantly from the total blood volume of mice (84.7-96.3 mL/kg) (*J Physiol.* 1973;228:279-84), sipavibart is considered to be primarily distributed in the blood. Since IgG is known to cross the blood-placental barrier in humans (*Clin Dev Immunol.* 2012;985646), sipavibart is considered likely to cross the placenta, although the effects of YTE and TM substitutions remain unclear.

4.3 Metabolism and Excretion

No studies on metabolism or excretion were conducted.

The applicant's explanation:

Since sipavibart is an IgG monoclonal antibody and considered to be degraded into small peptides and amino acids through protein degradation pathways, no studies on metabolism or excretion were conducted. As human IgG is known to be excreted into breast milk (*Obstet Gynecol.* 2022;139:181-91), sipavibart is considered likely to be excreted into breast milk, although the effects of YTE and TM substitutions remain unclear.

4.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA considers that the non-clinical pharmacokinetic characteristics of sipavibart have been confirmed.

5. Toxicology and Outline of the Review Conducted by PMDA

Repeated-dose toxicity studies using sipavibart/CIL were conducted, and the single-dose toxicity, repeated-dose toxicity, and local tolerance of sipavibart were evaluated. A tissue cross-reactivity study using sipavibart was also conducted. Since sipavibart specifically binds to epitopes on the RBD of the SARS-CoV-2 S protein, an adventitious agent, the potential for cross-reactivity in animals is considered low. From the perspective of toxicity evaluation related to nonspecific binding, cynomolgus monkeys, which exhibit FcRn binding ability and PK similar to those of humans, were selected as the animal species for the repeated-dose toxicity study.

5.1 Single-dose toxicity

No single-dose toxicity study using sipavibart was conducted. In the repeated-dose toxicity study [see Section 5.2], no acute symptoms or fatal cases were observed following the initial intramuscular or intravenous administration of sipavibart 150 mg/kg/CIL 150 mg/kg. The approximate lethal dose of sipavibart was determined to be >150 mg/kg.

5.2 Repeated-dose toxicity

A repeated-dose toxicity study was conducted using cynomolgus monkeys, in which sipavibart 150 mg/kg/CIL 150 mg/kg was administered intravenously or intramuscularly once a week for a total

of 3 doses (Table 13). The main observed changes included elevated blood globulin levels, perivascular mononuclear cell infiltration in the meninges of the brain, and inflammatory reactions at the injection site in both dose groups. The increase in blood globulin was a minor change associated with IgG1 antibody administration and was considered toxicologically insignificant. Perivascular mononuclear cell infiltration in the meninges of the brain was multifocal and predominantly lymphocytic. As this change was not associated with tissue damage and is consistent with central nervous system changes observed as immune responses to biologic agents (*Toxicol Pathol*. 2019;47:165-73), it was considered toxicologically insignificant. The inflammatory reactions at the injection sites (mixed-cell inflammation, eosinophilic infiltration, and myocyte degeneration/necrosis in the intramuscular administration group; vascular/perivascular inflammation, perivascular degeneration/necrosis, acute thrombosis, and perivascular fibroplasia in the intravenous administration group) were also observed in the control group and were therefore attributed to the administration procedure. Based on the above, the no-observed-adverse-effect level (NOAEL) for intramuscular administration of sipavibart was determined to be 150 mg/kg.

Following 3 intramuscular administrations of sipavibart (Day 15), the C_{max} and $AUC_{0\text{-}72h}$ were 4.47 mg/mL and 289 mg·h/mL (male and female combined), respectively. Compared with the exposure level observed in the foreign phase I study (Study D7000C00001 safety cohort) in which 300 mg of sipavibart was administered intramuscularly to the anterolateral thigh ($C_{max,,}$ 0.048 mg/mL; $AUC_{0\text{-}90d,}$ 69.1 mg·h/mL), the C_{max} was 93 times higher, and the AUC was ≥4.2 times higher. Following 3 intravenous administrations of sipavibart (Day 15), the C_{max} and $AUC_{0\text{-}168h}$ were 6.39 mg/mL and 701 mg·h/mL (male and female combined), respectively. Compared with the exposure level observed in the foreign phase I study (Study D7000C00004) in which 300 mg of sipavibart was administered intravenously by infusion ($C_{max,}$ 0.129 mg/mL; $AUC_{0\text{-}90d,}$ 96.9 mg·h/mL), the C_{max} was 49 times higher, and the AUC was ≥7.2 times higher.

Table 13. Summary of repeated-dose toxicity study results

Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached Document CTD
Male and female cynomolgus monkeys	i.m.[a)] i.v.	3 weeks (once weekly) + 8-week recovery	0,[b)] 150/150[c)]	<u>Intramuscular administration:</u> Elevated blood globulin levels, mixed cell inflammation and eosinophilic infiltration in intramuscular tissue at the injection site, eosinophilic infiltration in subcutaneous tissue at the injection site, degeneration/necrosis of muscle cells at the injection site (males and females), elevated total protein in blood (males), decreased A/G ratio in blood, perivascular mononuclear cell infiltration in the meninges of the brain, and mixed cell inflammation in subcutaneous tissue at the injection site (females). <u>Intravenous administration:</u> Elevated blood globulin levels, perivascular mononuclear cell infiltration in the meninges of the brain, perivascular fibroplasia at the injection site (males and females), elevated total protein in blood, vascular/perivascular inflammation at the injection site, perivascular degeneration/necrosis at the injection site, acute thrombosis (males), and decreased A/G ratio in blood (females). Reversible	<u>Intramuscular administration:</u> Sipavibart, 150 CIL, 150 <u>Intravenous administration:</u> Sipavibart, 150 CIL, 150	4.2.3.2.1

a) Sipavibart was administered intramuscularly at 150 mg/kg to the right thigh, and CIL was administered intramuscularly at 100 mg/kg to the left thigh and 50 mg/kg to the left biceps brachii.
b) Vehicle for sipavibart (an aqueous solution containing histidine/histidine hydrochloride [20 mmol/L], arginine hydrochloride [220 mmol/L], and polysorbate 80 [0.04 w/v%], pH 6.0) and vehicle for CIL (an aqueous solution containing histidine/histidine hydrochloride [20 mmol/L], sucrose [240 mmol/L], and polysorbate 80 [0.04 w/v%], pH 6.0) were each administered intravenously and intramuscularly.
c) The doses of sipavibart and CIL are presented.

5.3 Genotoxicity

Sipavibart is a monoclonal antibody that does not cross nuclear or mitochondrial membranes and is unable to interact directly with DNA or other chromosomal materials within the nucleus. Therefore, the risk of genotoxicity is considered low, and genotoxicity studies were not conducted.

5.4 Carcinogenicity

Sipavibart targets an adventitious agent without cross-reactivity to human tissues [see Section 5.7.1]; thus, carcinogenic risk is low, and carcinogenicity studies were not conducted.

5.5 Reproductive and developmental toxicity

Since sipavibart targets an adventitious agent and does not exhibit cross-reactivity with human tissues [see Section 5.7.1], reproductive and developmental toxicity studies were not conducted. In the repeated-dose toxicity study using sipavibart [see Section 5.2], no effects on male or female reproductive organs were observed. The risk of reproductive and developmental toxicity is considered low.

5.6 Local tolerance

The local irritation of sipavibart following intramuscular and intravenous administration was evaluated in the repeated-dose toxicity study [see Section 5.2]. No local irritation was observed following intramuscular or intravenous administration of sipavibart.

5.7 Other studies

5.7.1 Tissue cross-reactivity

A tissue cross-reactivity study using frozen sections of human normal tissues and human fetal tissues was conducted for sipavibart. No cross-reactivity was observed in any of the tissues evaluated (Table 14).

Table 14. Summary of results of tissue cross-reactivity studies

Test system	Test method	Main findings	Attached document CTD
Human normal tissues	The tissue-binding activity of sipavibart at 0.5 and 2 μg/mL was evaluated by immunohistochemical staining using frozen tissue sections.	None	4.2.3.7.7.1
Human fetal tissues	The tissue-binding activity of sipavibart at 0.5 and 2 μg/mL was evaluated by immunohistochemical staining using frozen tissue sections.	None	4.2.3.7.7.2

5.R Outline of the review conducted by PMDA

From a toxicological perspective, PMDA considers that no particular safety concerns have been suggested regarding the intramuscular and intravenous administration of sipavibart.

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 sipavibart, changes were made to the manufacturing processes for both the drug substance and the drug product. The comparability of the pre-change and post-change drug substances or drug products was confirmed [see Sections 2.1.4 and 2.2.3].

The concentrations of sipavibart, CIL, and tixagevimab (TIX) in serum were measured using the LC-MS/MS[12)] (lower limit of quantification, 0.300 μg/mL in serum), while antidrug antibody (ADA) concentration in serum was measured using an electrochemiluminescence assay (lower limit of detection, 5.1-12.1 ng/mL).

6.2 Clinical pharmacology

The applicant submitted data including results from a Japanese phase I study conducted in Japanese healthy subjects, foreign clinical studies conducted in non-Japanese subjects with immunocompromised or immunocompetent conditions, and results of population pharmacokinetics (PPK) analysis.

[12)] Sipavibart, CIL, and TIX have large molecular weights and cannot be directly quantified by the LC-MS/MS method. Therefore, characteristic peptide fragments of sipavibart, CIL, and TIX generated through protein degradation were measured as surrogate markers.

6.2.1 Studies in healthy adults

6.2.1.1 Japanese phase I study (CTD 5.3.3.1.3, Study D7000C00007 [ongoing since July 2023[13)] (Data cutoff: [redacted], 20[redacted])]

Japanese healthy adults (18 subjects included in the PK analysis) received a single intramuscular injection of sipavibart at 300 mg or 600 mg in the anterolateral thigh or a single intravenous infusion of sipavibart at 1,200 mg at an infusion rate of 50 mg/min. Table 15 shows the serum concentration of sipavibart over time up to Day 91. The serum concentration of sipavibart over time following intramuscular administration demonstrated approximate dose proportionality within the evaluated dose range. No subjects were determined to be ADA-positive in serum from the time of sipavibart administration to Day 91 post-dose.

Table 15. Serum concentration of sipavibart over time following single intramuscular or intravenous administration

Measuring time point	Serum concentration (μg/mL)					
	No. of subjects	300 mg IM	No. of subjects	600 mg IM	No. of subjects	1,200 mg IV
8 h post dose	-	-	-	-	6	394.5 (23.3)
Day 3	6	35.0 (18.7)	6	82.1 (15.1)	6	309.6 (20.7)
Day 5	6	44.9 (25.4)	6	96.6 (20.0)	6	251.6 (16.6)
Day 8	6	45.7 (24.7)	6	109.7 (12.7)	6	241.3 (27.3)
Day 15	6	46.2 (17.6)	6	91.6 (18.5)	6	202.3 (20.9)
Day 29	6	43.1 (23.8)	6	82.4 (6.49)	6	170.2 (24.4)
Day 58	6	37.5 (27.6)	6	71.4 (13.8)	-	-
Day 91	6	26.6 (17.9)	6	56.2 (10.3)	-	-

Geometric mean (geometric coefficient of variation [%]); -. Not calculated; IM, Intramuscular administration; IV, Intravenous administration

6.2.1.2 Foreign phase I study (Reference CTD 5.3.5.1.2, Study D7000C00001 safety cohort [ongoing since December 2022 (data cutoff, [redacted] 20[redacted])]

In a study in healthy non-Japanese adults (40 subjects included in the PK analysis), a single dose of sipavibart and CIL at 300 mg each was administered intramuscularly in the gluteal region or the anterolateral thigh. Table 16 shows the serum concentration over time of the drug up to Day 181. The serum concentrations of sipavibart and CIL over time were similar, both exhibiting monophasic elimination. Compared with administration to the gluteal region, administration in the anterolateral thigh resulted in faster absorption, with trends toward higher C_{max} and AUC values (Table 17). The relative bioavailability of sipavibart administered in the gluteal region compared to the anterolateral thigh (based on AUC_{inf}) was 85.3%. No subjects were found to be serum ADA-positive from the time of sipavibart administration to Day 181 post-dose.

[13)] In Study D7000C00007, intramuscular administration of sipavibart at 300 mg (Cohort 1) and 600 mg (Cohort 2), as well as intravenous administration of sipavibart at 1,200 mg (Cohort 3), were planned. Safety was assessed up to Day 91, while serum sipavibart and ADA concentrations were evaluated up to Day 361. In the present application, an interim analysis was conducted to evaluate PK in Japanese subjects. Data on PK and safety up to Day 29 for Cohort 3 (and up to Day 91 for Cohorts 1 and 2) were submitted.

Table 16. Serum drug concentration over time following a single intramuscular injection of sipavibart or CIL at 300 mg in the gluteal region or anterolateral thigh

Measuring time point	Injection site: Anterolateral thigh			Injection site: Gluteal region		
	N	Sipavibart concentration (μg/mL)	CIL concentration (μg/mL)	N	Sipavibart concentration (μg/mL)	CIL concentration. (μg/mL)
Day 3	19	33.7 (39.4)	36.3 (39.3)	19	9.13 (154)	8.90 (131)
Day 5	20	43.2 (27.9)	44.4 (25.8)	19	15.7 (107)	13.3 (107)
Day 8	19	46.1 (26.2)	46.8 (25.1)	20	19.9 (75.2)	16.9 (81.6)
Day 15	20	42.9 (28.8)	43.5 (25.4)	19	22.4 (65.5)	18.5 (73.7)
Day 29	19	34.4 (27.0)	35.5 (23.3)	20	21.4 (53.9)	18.5 (61.9)
Day 58	19	31.8 (29.9)	27.8 (29.2)	20	21.9 (48.1)	16.2 (57.4)
Day 91	17	22.6 (42.3)	20.2 (45.8)[a)]	20	15.3 (54.1)	11.4 (61.6)
Day 181	16	7.46 (232)	6.43 (220)	20	6.23 (109)	4.47 (124)

Geometric mean (Geometric coefficient of variation [%])
a) Number of subjects, 16

Table 17. PK parameters following a single intramuscular injection of sipavibart 300 mg

Injection site	N	C_{max} (μg/mL)	t_{max} (day)	$t_{1/2}$ (day)	$AUC_{0\text{-}29d}$ (μg·day/mL)	$AUC_{0\text{-}91d}$ (μg·day/mL)	AUC_{inf} (μg·day/mL)	CL/F (L/day)	V_z/F (L)
Anterolateral thigh	20	48.0 (25.2)	7.47 [3.9, 53]	87.3 ± 26.5[a)]	1,068 (24.9)[b)]	2,878 (25.6)[c)]	5,618 (43.1) [a)]	0.053 (43.1)[a)]	6.33 (19.4) [a)]
Gluteal region	20	25.4 (51.7)	52.0 [4.9, 86]	91.0 ± 27.3[d)]	544.9 (65.6)	1,790 (50.0)	4,790 (47.0)[d)]	0.063 (47.0)[d)]	7.75 (15.7) [d)]

Geometric mean (Geometric coefficient of variation [%])
T_{max} is expressed as the median [minimum, maximum], and $t_{1/2}$ is expressed as the mean ± SD.
a) N = 17, b) N = 19, c) N = 18. d) N = 9

6.2.1.3 Foreign phase I study (CTD 5.3.3.1.2, Study D7000C00004 [ongoing since May 2023 (data cutoff, [redacted] 20[redacted])])

In a study in healthy non-Japanese adults (78 subjects included in the PK and ADA analyses), a single intramuscular injection of sipavibart 300 mg or 600 mg was administered in the anterolateral thigh, or a single intravenous infusion of sipavibart 300 mg, 600 mg, or 1,200 mg was administered at an infusion rate of 50 mg/min. Table 18 shows the serum concentration over time of sipavibart up to Day 91. The serum sipavibart concentrations demonstrated approximately dose-proportional pharmacokinetics within the evaluated dose range. Intramuscular administration exhibited monophasic elimination, while intravenous administration demonstrated apparent biphasic elimination. No subjects were found to be serum ADA-positive from the time of sipavibart administration to Day 91 post-dose.

Table 18. Serum sipavibart concentration over time following intramuscular or intravenous administration of sipavibart

Measuring time point	Serum concentration (μg/mL)									
	N	300 mg IM	N	600 mg IM	N	300 mg IV	N	600 mg IV	N	1,200 mg IV
20 min. post dose	-	-	-	-	3	101.6 (7.6)	-	-	11	452.1 (25.8)
40 min. post dose	-	-	-	-	3	129.2 (8.7)	-	-	11	368.1 (12.5)
60 min. post dose	-	-	-	-	3	122.1 (10.4)	-	-	11	380.1 (12.2)
4 hr. post dose	-	-	-	-	3	110.0 (7.1)	-	-	11	376.2 (15.3)
8 hr. post dose	-	-	-	-	3	103.0 (2.9)	-	-	11	355.7 (13.1)
Day 5	9	42.6 (27.6)	8	91.2 (22.6)	10	54.8 (10.3)	10	109.2 (13.1)	35	224.6 (11.2)
Day 8	10	43.1 (17.8)	8	99.9 (20.4)	9	53.0 (14.0)	9	99.4 (15.5)	37	204.7 (13.7)
Day 15	9	42.6 (11.2)	9	89.5 (16.9)	10	47.0 (11.4)	10	83.9 (20.1)	36	194.4 (18.6)
Day 31	10	39.1 (11.0)	9	71.1 (18.9)	9	44.1 (16.6)	10	91.7 (21.4)	36	169.4 (14.4)
Day 61	10	24.1 (17.7)	10	48.8 (20.4)	9	25.6 (16.0)	10	64.0 (21.1)	34	134.3 (12.2)
Day 91	10	17.4 (14.5)	10	37.5 (32.9)	9	21.6 (23.6)	9	46.0 (26.4)	34	101.8 (19.6)

Geometric mean (Geometric coefficient of variation [%]); -. Not calculated; IM, Intramuscular administration; IV, Intravenous administration

6.2.2 Investigation in immunocompromised subjects

6.2.2.1 Foreign phase II study (Reference CTD 5.3.5.1.3; Study D7000C00001 substudy [ongoing since [redacted] 20[redacted] (data cutoff, [redacted] 20[redacted])])

Immunocompromised[14] or immunocompetent foreign adult subjects, who had not experienced COVID-19 (454 subjects included in the PK analysis), received sipavibart 1,200 mg as a single intravenous infusion at a rate of 50 mg/min, or CIL 150 mg and TIX 150 mg as a single intramuscular injection in the gluteal region. Table 19 shows the serum concentration over time up to Day 91. No clear difference in serum drug concentrations was observed between immunocompromised subjects and immunocompetent subjects, though the number of the former subjects was limited. The proportion of subjects who tested positive for serum ADA from the time of sipavibart administration to Day 91 was 0.3% (1 of 300 subjects), and the antibody titer was at the lower limit of detection.

Table 19. Serum concentration over time of sipavibart and TIX/CIL in foreign adult subjects

Measuring time point	Subject population	Sipavibart 1,200 mg IV administration		CIL 150 mg IM/TIX 150 mg IM administration	
		N	Sipavibart concentration (μg/mL)	N	CIL+TIX concentration (μg/mL)
Day 29	Immunocompromised	15	115.0 (100)	4	21.5 (101)
	Immunocompetent	277	137.8 (52.4)	146	18.4 (61.8)
Day 91	Immunocompromised	14	59.9 (103)	2	7.48, 35.4
	Immunocompetent	263	71.0 (79.1)	141	14.6 (67.0)

Geometric mean (Geometric coefficient of variation [%]); In the case of 2 subjects, individual values are presented.

6.2.2.2 Foreign phase I/III study (CTD 5.3.5.1.1, Study D7000C00001 main cohort [ongoing since [redacted] 20[redacted] (data cutoff, March 2024)])

In non-Japanese subjects aged ≥12 years who had not experienced COVID-19 and were in an immunocompromised state[15] (1,347 subjects included in the PK analysis), sipavibart 300 mg was administered either as a single dose or as 2 doses with a 6-month interval via intramuscular injection, or CIL and TIX 300 mg each were administered as a single intramuscular injection (all administered in the anterolateral thigh). Table 20 shows the serum concentration over time up to Day 210. The dose-normalized serum concentrations of sipavibart over time were similar to those of CIL and TIX (combined). In subjects who received injections of sipavibart repeatedly in the anterolateral thigh at 6-month intervals, no clear drug accumulation in serum was observed. The proportion of subjects who tested positive for serum ADA from the time of sipavibart administration to Day 210 was 1.7% (1 of 59 subjects) in the single-dose group and 0.7% (4 of 545 subjects) in the 2-dose group.

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[14] The eligibility criteria included subjects meeting at least 1 of the following risk factors:
Patients with solid tumors undergoing immunosuppressive therapy, patients with haematologic malignancies, recipients of solid organ transplantation or haematopoietic stem cell transplantation, subjects receiving treatment with immunosuppressants, subjects who had undergone chimeric antigen receptor T-cell therapy, subjects who had received B-cell depletion therapy within 1 year, and subjects with moderate or severe primary or secondary immunodeficiency

[15] In addition to immunocompromised subjects included in Study D7000C00001 and its substudy (see footnote 14), subjects with HIV-infected with a CD4-positive cell count of <200/mm³ were included.

Table 20. Serum drug concentration over time following single or multiple intramuscular administration of sipavibart or CIL/TIX in subjects with immunocompromised state

Measuring time point	A single dose of sipavibart 300 mg		Multiple doses of sipavibart 300 mg[a)]		CIL 300 mg IM/TIX 300 mg IM	
	N	Sipavibart concentration (μg/mL)	N	Sipavibart concentration (μg/mL)	N	CIL+TIX concentration (μg/mL)
Day 29	47	30.5 (33.5)	529	29.8 (36.2)	564	61.1 (41.4)
Day 91	40	18.5 (40.4)	506	18.1 (50.2)	552	35.1 (56.7)
Day 181	9	9.59 (44.6)	405	8.55 (90.0)	427	15.3 (67.9)
Day 189	5	9.78 (62.2)	367	32.3 (73.0)	357	14.1 (72.6)
Day 210	5	6.36 (66.8)	299	30.8 (54.3)	296	11.3 (80.6)

Geometric mean (Geometric coefficient of variation [%])

a) Two multiple-doses administered at a 6-month interval. The measurement on Day 181 reflects the value before the second dose.

6.2.3 PPK analysis (CTD 5.3.3.5.4)

A PPK analysis (NONMEM version 7.5.0) was conducted using PK data obtained from foreign phase I studies (Study D7000C00001 safety cohort, Study D7000C00004), foreign phase II study (Study D7000C00001 substudy), and foreign phase I/III study (Study D7000C00001 main cohort), comprising 1,091 subjects and 4,039 sampling points. The final model was described using a 2-compartment model with zero-order absorption (intravenous infusion) or first-order absorption (intramuscular injection) and first-order elimination. The following covariates were selected: Body weight and diabetes mellitus for total clearance (CL) of sipavibart, body weight and race (Black and non-Black) for central compartment volume of distribution (Vc), body weight for peripheral compartment volume of distribution (Vp) and intercompartmental clearance (Q), injection site for bioavailability, sex, age (>65 years vs./65 years), body mass index (BMI) (>30 kg/m²/≤30 kg/m²), diabetes mellitus, injection site, and ethnicity (Latino or Hispanic/other) for first-order absorption rate constant (Ka) in intramuscular administration.[16)]

Based on the final model, the following predictions were obtained:

- The absolute bioavailability of sipavibart 300 mg administered intramuscularly (anterolateral thigh) was 80.7%.
- The geometric mean ratio [90% percentile interval][17)] of $AUC_{0\text{-}180d}$ (pediatric/adult) for sipavibart 300 mg administered intramuscularly (anterolateral thigh) was 1.24 [0.66, 2.28] in the pediatric population (body weight, 40-90 kg)[18)] compared to the adult population (body weight, 44.5-178.0 kg).[19)]

16) The following covariates were newly examined. The covariates selected for other parameters were set identically to those in the final PPK model constructed based on the PK data of the Evusheld (CTD 5.3.3.5.2, *Antimicrob Agents Chemother.* 2024;68:e01587-23).
- For CL, disease (solid tumor or haematologic malignancy), degree of immunosuppression, solid organ transplantation, end-stage renal failure, prior B-cell depletion therapy within 1 year, and prior anti-SARS-CoV-2 treatment, including Evusheld, within 1 year.
- For *K*a and bioavailability, injection site.

17) The ratio of $AUC_{0\text{-}180d}$ in the pediatric population relative to that in the adult population, as predicted from serum sipavibart concentrations following intramuscular administration of 300 mg of sipavibart into the anterolateral thigh, repeated 10 times in each population, based on the datasets of 1,000 subjects each in the adult and pediatric populations as shown in Footnotes 18 and 19.

18) The median body weight at age 12 years (40 kg) and the 95th percentile body weight at age 17.5 years (90.0 kg), as reported in the growth chart published by the U.S. Centers for Disease Control and Prevention (CDC) (https://www.cdc.gov/growthcharts/data/set1clinical/cj41c021.pdf [last accessed on October 11, 2024]), were defined as the lower and upper limits of the body weight range, respectively. A uniform distribution within this weight range was used to represent the body weight distribution in the pediatric population. The body weight range of subjects aged 12 to 17 years in Study D7000C00001 was 45.9 to 89.6 kg.

19) The lower (44.5 kg) and upper (178.0 kg) limits of body weight for all subjects (1,091 subjects) used in the PPK model construction were selected as the lower and upper limits of the body weight range. The weight distribution in the adult population was assumed to follow a normal distribution with a mean of 85.1 kg and a SD of 22.25 kg.

6.R Outline of the review conducted by PMDA

6.R.1 Ethnic differences in the PK of sipavibart

The applicant's explanation about the ethnic differences in the PK of sipavibart:

In each clinical study, sipavibart 300 mg was administered intramuscularly (anterolateral thigh) to Japanese and non-Japanese healthy adult subjects. Table 21 shows the PK parameters based on serum sipavibart concentration data up to Day 91. The geometric mean of $AUC_{0\text{-}91d}$ was 18.7% to 25.6% higher in Japanese subjects compared to the results from Study D7000C00004 and the Study D7000C00001 safety cohort conducted in non-Japanese subjects. This is considered to be attributable to the body weight differences between Japanese and non-Japanese subjects.[20)] The above findings suggest that there are no clinically significant differences in PK between Japanese and non-Japanese subjects.

Table 21. PK parameters following a single intramuscular administration of sipavibart 300 mg in Japanese and non-Japanese healthy subjects

Clinical study	Race	PK parameter			
		N	C_{max} (μg/mL)	N	$AUC_{0\text{-}91d}$ (μg·day/mL)
Study D7000C00007	Japanese	6	49.9 (18.2)	6	3,418 (21.9)
Study D7000C00004	Non-Japanese	10	48.6 (20.6)	9	2,722 (17.7)
Study D7000C00001 safety cohort		20	48.0 (25.2)	18	2,878 (25.6)

Geometric mean (geometric coefficient of variation [%])

PMDA accepted the applicant's explanation.

6.R.2 Rationale for the proposed dosage and administration for sipavibart

The applicant's explanation about the rationale for the proposed dosage and administration for sipavibart:

Sipavibart is a human IgG1 monoclonal antibody that shares a similar structure with the already approved drug, Evusheld (CIL 300 mg/TIX 300 mg), except for the antigen-binding site. With the assumption that the PK profiles of sipavibart and CIL + TIX are similar, the clinical development of sipavibart was conducted accordingly.

As with Evusheld, exposure to sipavibart is considered not to significantly differ between adults and pediatric subjects (≥12 years of age and weighing ≥40 kg). A foreign phase I/III study (Study D7000C00001 main cohort) was conducted in pediatric and adult subjects (≥12 years of age and ≥40 kg body weight), and the following points were confirmed:

- The similarity in the serum drug concentrations of sipavibart and CIL + TIX over time was confirmed [see Section 6.2.2.2].
- After a single intramuscular administration of sipavibart 300 mg in the anterolateral thigh, the serum concentration of sipavibart on Day 181 (8.55-9.59 μg/mL, Table 20) exceeded the serum concentration required to inhibit by 80% the entry of SARS-CoV-2 variants[21)] into the upper airway, a key tissue for preventing a viral load increase and onset of infection after SARS-CoV-2 exposure.

[20)] The body weight (median [range]) in the sipavibart 300 mg IM group was 63.3 [52.1, 79.0] kg in the Japanese phase I study (Study D7000C00007), 69.2 [56.5, 90.9] kg in the foreign phase I study (Study D7000C00004), and 72.2 [51.6, 107.4] kg in the foreign phase I study (Study D7000C00001 safety cohort), respectively.

[21)] BA.1, BA.1.1, BA.2, BA.4/5, BA.4.6, BQ.1, BQ.1.1, and BF.7 lineages

This required concentration ranged from 0.84 to 3.20 μg/mL.[22] In subjects who received sipavibart every 6 months, serum concentrations of sipavibart were maintained without cumulative buildup.

- Although the serum concentration of sipavibart in pediatric subjects was not measured in Study D7000C00001 main cohort[23] it was estimated that pediatric subjects aged ≥12 years and weighing ≥40 kg would have similar exposure to sipavibart as adults [see Section 6.2.3]. Administering the same dose to pediatric subjects as to adults does not present any issues.
- While delayed absorption upon intramuscular administration has been suggested in elderly subjects [see Section 6.2.3], no significant differences in the serum concentrations of sipavibart over time were observed between adults aged <65 years and those aged ≥65 years (Table 22). Administering the same dose to non-elderly and elderly adults is considered reasonable.

Table 22. Serum concentrations of sipavibart over time after 300 mg intramuscular administration by age group

Measuring time point	≥18 and <65 years old		≥65 years old	
	N	Sipavibart concentration (μg/mL)	N	Sipavibart concentration (μg/mL)
Day 29	344	28.1 (58.7)	232	29.2 (76.5)
Day 91	331	16.4 (75.9)	215	18.4 (78.6)
Day 181	251	7.38 (118.1)	163	8.42 (139.7)

Geometric mean (geometric coefficient of variation [%])

In this context, for the routes of administration not included in Study D7000C00001 main cohort (intravenous administration, intramuscular injection to the gluteal region), it is considered feasible to include them in the proposed dosage and administration for the following reasons:

- The serum concentration of sipavibart on Day 91 after intravenous administration of sipavibart 300 mg was 19.3% higher compared to the concentration achieved by intramuscular injection in the anterolateral thigh [see Section 6.2.1.3]. The elimination process of sipavibart is not influenced by the route of administration. Thus, intravenous administration of sipavibart 300 mg is expected to maintain the necessary serum concentration of sipavibart (0.84-3.20 μg/mL) for ≥6 months. No particular concerns regarding tolerability were noted for the intravenous administration of sipavibart 1,200 mg [see Sections 7.1.1 and 7.1.3], and no safety concerns related to an increase in exposure were observed.
- Using the PPK model [see Section 6.2.3], the serum concentration of sipavibart at 6 months after intramuscular injection of 300 mg in the gluteal region (geometric mean [90% prediction interval]) is estimated to be 6.42 [1.48, 21.30] μg/mL, and the lower limit of the predicted range is expected to exceed the necessary serum concentration of sipavibart (0.84-3.20 μg/mL).

PMDA's view:

Regarding the dosage regimen for sipavibart, administering 300 mg every 6 months by intramuscular injection in the anterolateral thigh is considered appropriate from a clinical pharmacological perspective. The appropriateness of dosage setting for pediatric and elderly patients will be further discussed in Section 7.R.6, based on clinical study results.

[22] Specified based on the IC_{80} (15.2-58.0 ng/mL) calculated from the nasal liquid/serum concentration ratio for Evusheld (1.81%) (the Report on Special Approval for Emergency on Evusheld Intramuscular Injection Set, dated August 18, 2022) and the *in vitro* IC_{50} against SARS-CoV-2 variants (BA.1, BA.1.1, BA.2, BA.4/5, BA.4.6, BQ.1, BQ.1.1, and BF.7) (3.8-14.5 ng/mL, see Section 3.1.3).

[23] The PK evaluation target in Study D7000C00001 main cohort was the first 1,200 subjects enrolled, and pediatric patients aged ≥12 and <18 years were not included.

As for intravenous administration, higher exposure than that observed in Study D7000C00001 main cohort is expected. It is clinically reasonable to consider intravenous administration as an alternative route when intramuscular injection in the anterolateral thigh is difficult. The feasibility of establishing it as an alternative route will continue to be discussed in Section 7.R.6 in light of the safety and the necessity of that setting.

The relative bioavailability of sipavibart administered by intramuscular injection in the gluteal region compared to that with the anterolateral thigh was 85.3% [see Section 6.2.1.2]. There is uncertainty in the serum concentration of sipavibart estimated from the nasal liquid concentration, which generally shows significant variability between measurements. It is important to ensure exposures that are equal to or greater than those in Study D7000C00001 main cohort for the purpose of consistent efficacy of sipavibart. Intramuscular injection in the gluteal region should not be included in the dosing regimen.

6.R.3 ADA

The applicant's explanation about the development of ADAs and their potential impact on the PK, efficacy, and safety of sipavibart:

In foreign clinical studies (Study D7000C00001 and Study D7000C00004), very few subjects tested positive for ADA in their serum after a single-dose administration of sipavibart [see Sections 6.2.1 and 6.2.2]. In Study D7000C00001 main cohort, 5 subjects who received sipavibart tested positive for ADA in their serum. However, the serum sipavibart concentrations over time in ADA-positive subjects showed a similar pattern to that of ADA-negative subjects (Table 23). Although based on a limited number of subjects, the results from ADA-positive subjects (n = 5) in Study D7000C00001 main cohort did not suggest a clear impact of ADA on the efficacy or safety of sipavibart, as shown below.

- No occurrence of COVID-19 caused by SARS-CoV-2 was observed in subjects who tested positive for ADA.
- One subject who tested positive for ADA died (cardiac arrest, Day 216). This subject tested positive for serum ADA on Day 29, but no further ADA measurements were obtained. The subject did not receive the second dose of sipavibart. This subject had multiple risk factors identified as subject demographics.[24)] Gastrointestinal and rectal haemorrhage occurred on Day 214, leading to death from shock haemorrhagic. A causal relationship to the study drug was ruled out.

Table 23. Serum concentration of sipavibart by ADA status (Study D7000C00001 main cohort)[a)]

Measuring time point	ADA-positive		ADA-negative	
	N	Sipavibart concentration (μg/mL)	N	Sipavibart concentration (μg/mL)
Day 29	4	32.1 (33.4)	489	29.7 (36.4)
Day 91	4	19.5 (76.6)	467	18.1 (50.3)
Day 181	4	6.29 (159.1)	378	8.50 (84.1)
Day 210	2	36.4, 37.6[b)]	282	31.2 (47.6)

Geometric mean (Geometric coefficient of variation [%])

a) Two multiple-doses administered at a 6-month interval. The measurement on Day 181 reflects the value before the second dose.

b) Individual values are provided.

[24)] Advanced age (7[redacted] years) and chronic diseases with multiple risk factors (end-stage renal failure, type 2 diabetes mellitus, hypertension, hypercholesterolaemia, hyperphosphataemia, haemodialysis, anaemia, parietal lobe stroke, atrial fibrillation, coronary artery disease, first-degree atrioventricular block [right bundle branch block]), as well as co-medications with inherent bleeding risks (anticoagulants such as apixaban and antiplatelet drugs like clopidogrel).

Based on the above, the risk of ADA development following administration of sipavibart is low. Even if ADA develops, it is unlikely to have a significant impact on the PK, efficacy, or safety of sipavibart.

PMDA's view:
The development of ADA following administration of sipavibart was rare, and the primary target population was patients with immunocompromised state. ADA development following sipavibart administration is, thus, unlikely to pose a clinical issue. However, the impact of ADA on the PK, efficacy, and safety of sipavibart should continue to be monitored, including data from ongoing clinical studies. Any new findings should be promptly communicated to healthcare professionals.

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

In the present application, the applicant submitted the results of clinical studies shown in Table 24 as the main efficacy and safety data.

Table 24. Summary of clinical studies

Region	Study code	Phase	Population	No. of subjects enrolled	Dosage regimen	Main endpoints [primary endpoints]
Japan	D7000C00007	I	Healthy subjects	[i.m. injection] (a) 6, (b) 6, (c) 4 [i.v. injection] (d) 6, (e) 2	[i.m. injection] A single intramuscular administration of (a) sipavibart 300 mg, (b) sipavibart 600 mg, or (c) placebo [i.v. injection] A single intravenous administration of (d) sipavibart 1,200 mg or (e) placebo	Safety, PK
Foreign	D7000C00004	I	Healthy subjects	[i.m. injection] (a) 10, (b) 10, (c) 4 [i.v. injection] (d) 10, (e) 10, (f) 40, (f) 12	[i.m. injection] A single intramuscular administration of (a) sipavibart 300 mg, (b) sipavibart 600 mg, or (c) placebo [i.v. injection] A single intravenous administration of (d) sipavibart 300 mg, (e) sipavibart 600 mg, (f) sipavibart 1,200 mg, or (g) placebo	Safety, PK
Foreign	D7000C00001	I	[Safety cohort] Healthy adults	(a) 40 (b) 16	A single intramuscular administration of (a) sipavibart 300 mg/CIL 300 mg, or (b) placebo	Safety, PK
		I/III	[Main cohort] Individuals with immunocompromised state aged ≥12 years	(a) 1,669 (b) 1,666	Intramuscular administration of (a) sipavibart 300 mg or (b) control drug (placebo or CIL 300 mg/TIX 300 mg) twice at a 6-month interval	Efficacy, safety, PK [onset of COVID-19]

7.1 Phase I studies

7.1.1 Japanese phase I study (CTD 5.3.3.1.3, Study D7000C00007 [ongoing since July 2023 (data cutoff, [redacted] 20[redacted])])

A placebo-controlled, randomized, double-blind study was conducted in Japan to evaluate the safety, etc., of sipavibart in healthy Japanese subjects aged ≥18 and ≤55 years (target sample size, 24 subjects [18 in the sipavibart group, 6 in the placebo group]).

A single intramuscular (IM) dose of sipavibart 300 mg or 600 mg or placebo was administered in the anterolateral thigh, or a single intravenous (IV) dose of sipavibart 1,200 mg or placebo was administered. An interim analysis was conducted to assess safety and PK up to Day 29 after intravenous infusion of sipavibart 1,200 mg or placebo. The results of the interim analysis were submitted for the present application. As of the interim analysis, the mean observation period was 148 days for sipavibart 300 mg IM, 129 days for sipavibart 600 mg IM, and 29 days for sipavibart 1,200 mg IV.

All of 24 randomized subjects (6 subjects each receiving sipavibart 300 mg, 600 mg, or 1,200 mg; 6 subjects receiving placebo) received the study drug and were included in the safety analysis population. No subjects discontinued the study.

Adverse events were observed in 1 subject receiving sipavibart 300 mg IM (urticaria), 2 subjects receiving sipavibart 600 mg IM (dental caries and rash erythematous in 1 subject each), and 1 subject receiving placebo (nasopharyngitis). A causal relationship to the study drug was ruled out. No deaths or serious adverse events were reported.

Based on the above, no significant concerns regarding tolerability were identified when sipavibart was administered intramuscularly at 300 mg or 600 mg or intravenously at 1,200 mg in Japanese subjects.

7.1.2 Foreign phase I study (Reference CTD 5.3.5.1.2, Study D7000C00001 safety cohort [ongoing since December 2022 (data cutoff, [redacted] 20[redacted])])

A placebo-controlled, randomized, double-blind study was conducted in the US and UK to evaluate the safety, etc., of sipavibart in combination with CIL in non-Japanese healthy subjects aged ≥18 and ≤55 years (target sample size, 56 subjects [40 in the sipavibart/CIL group, 16 in the placebo group]). In this study, interim analyses were conducted at the time points when the observation period for subjects receiving the study drug reached 29, 91, and 181 days. For the present application, the applicant submitted interim analysis results based on data up to Day 181.

A single intramuscular dose of either sipavibart + CIL (300 mg and 300 mg, respectively) or placebo was administered in the gluteal or anterolateral thigh region.

All of 57 subjects randomized (41 in the sipavibart/CIL group, 16 in the placebo group) received the study drug and were included in the safety analysis population. Four subjects discontinued the study (3 subjects in the sipavibart/CIL group, 1 subject in the placebo group). The reasons for discontinuation were lost to follow-up (3 subjects in the sipavibart/CIL group) and subject's request (1 subject in the placebo group).

Adverse events and adverse drug reactions were observed in 41.5% (17 of 41) of subjects and 7.3% (3 of 41) of subjects, respectively, in the sipavibart/CIL group and in 75.0% (12 of 16) of subjects and 18.8% (3 of 16) of subjects, respectively, in the placebo group. Table 25 shows the main events.

Table 25. Adverse events and adverse drug reactions observed in ≥2 subjects in either group (safety analysis population)

	Adverse events		Adverse drug reactions	
	Sipavibart/CIL (N = 41)	Placebo (N = 16)	Sipavibart/CIL (N = 41)	Placebo (N = 16)
Any event	12 (41.5)	12 (75.0)	3 (7.3)	3 (18.8)
Upper respiratory tract infection	5 (12.2)	0	0	0
Headache	4 (9.8)	3 (18.8)	1 (2.4)	0
Injection site pain	2 (4.9)	2 (12.5)	2 (4.9)	2 (12.5)
Oropharyngeal pain	2 (4.9)	1 (6.3)	0	0
Viral upper respiratory tract infection	1 (2.4)	3 (18.8)	0	0

Number of subjects with events (incidence [%]) Medical dictionary for regulatory activities Japanese version (MedDRA/J) ver.26.1

Death was reported in 1 subject in the sipavibart/CIL group (pneumonia).[25)] Its causal relationship to the study drug was ruled out. Serious adverse event was reported in 1 subject in the sipavibart/CIL group (hyponatremia), but its causal relationship to the study drug was ruled out.

Based on the above, no significant concerns were identified regarding the tolerability of a single intramuscular injection of sipavibart + CIL (300 mg and 300 mg respectively) in the gluteal or anterolateral thigh region.

7.1.3 Foreign phase I study (CTD 5.3.3.1.2, Study D7000C00004 [ongoing since May 2023 (data cutoff, [redacted] 20[redacted])])

A placebo-controlled, randomized, double-blind study was conducted in the US to evaluate the safety, etc., of sipavibart in non-Japanese healthy subjects aged ≥18 and ≤55 years (target sample size, 96 subjects [80 in the sipavibart group, 16 in the placebo group]).

A single intramuscular dose of sipavibart 300 mg or 600 mg or placebo was administered into the anterolateral thigh region or a single intravenous dose of sipavibart 300 mg, 600 mg, or 1,200 mg or placebo was administered at an infusion rate of 50 mg/min. In this study, an interim analysis was conducted based on data up to Day 91, and the results of this analysis were submitted for the present application.

Of the 98 randomized subjects, 96 subjects (10 each in the sipavibart 300 mg IM group, sipavibart 600 mg IM group, sipavibart 300 mg IV group, and sipavibart 600 mg IV group; 40 in the sipavibart 1,200 mg IV group; 4 in the placebo IM group; 12 in the placebo IV group) received the study drug and were included in the safety analysis population. Six subjects discontinued the study (1 in the sipavibart 300 mg IV group, 4 in the sipavibart 1,200 mg IV group, 1 in the placebo IV group). The reasons for discontinuation were lost to follow-up in 2 subjects (sipavibart 1,200 mg IV group) and subject's request in 4 subjects (1 in the sipavibart 300 mg IV group, 2 in the sipavibart 1,200 mg IV group, 1 in the placebo IV group).

The following adverse events were reported: 2 of 10 subjects (vomiting, arthralgia, and pain in extremity in 1 subject each [some subjects had multiple events]) in the sipavibart 300 mg IM group; 3 of 10 subjects (anaemia, headache, nausea, and myalgia in 1 subject each [some subjects had multiple events])

25) Events reported on Day 271.

in the sipavibart 600 mg IM group; 0 of 10 subjects in the sipavibart 300 mg IV group; 4 of 10 subjects (lymphadenopathy, insomnia, dyspnoea, toothache, non-cardiac chest pain, pain, ligament sprain, and limb injury in 1 subject each [some subjects had multiple events]) in the sipavibart 600 mg IV group; 14 of 40 subjects (nausea in 2 subjects; influenza, sinusitis, upper respiratory tract infection, headache, vertigo, nasal congestion, oropharyngeal pain, vomiting, abdominal pain, diarrhoea, rash, urticaria, fatigue, blood creatine phosphokinase increased, infusion-related reaction, and skin laceration in 1 subject each [some subjects had multiple events]) in the sipavibart 1,200 mg IV group; 0 of 4 subjects in the placebo IM group; and 1 of 16 subjects (hepatitis A, dyspnoea, rash macular, arthralgia, myalgia, musculoskeletal pain, and fatigue in 1 subject each [some subjects had multiple events]) in the placebo IV group. A causal relationship to the study drug could not be ruled out in 2 subjects in the sipavibart 600 mg IM group (headache and nausea) and 1 subject in the sipavibart 1,200 mg IV group (infusion-related reaction); however, all events had an outcome of resolved.

By the data cutoff date ([redacted], 20[redacted]; median observation period, 114.0 days for the sipavibart group, 114.0 days for the placebo group), no deaths or serious adverse events were reported.

Thus, no significant concerns were identified regarding the tolerability of sipavibart administered as a single intramuscular dose (300 mg or 600 mg) or a single intravenous dose (300-1,200 mg).

7.2 Phase I/III study

7.2.1 Foreign phase I/III study (CTD 5.3.5.1.1, Study D7000C00001 main cohort [ongoing since [redacted] 20[redacted] (data cutoff, March 2024)])

A randomized, double-blind, parallel-group study was conducted in 18 countries and regions, including the US, Australia, and Spain, to evaluate the efficacy and safety of sipavibart in non-Japanese subjects aged ≥12 years with immunocompromised state[15] (target sample size,[26] 3,200 subjects [1,600 in the sipavibart group, 1,600 in the control drug group]). Table 26 shows the main inclusion and exclusion criteria for this study.

[26] At the initiation of the main cohort ([redacted] 20[redacted]), the study protocol version 5.0 ([redacted], 20[redacted]) assumed that "the incidence of COVID-19 caused by any SARS-CoV-2 strain," a secondary efficacy endpoint, would be 3.2% in the control drug (CIL/TIX) group, and the expected hazard ratio of the sipavibart group compared to the control drug group would be 0.3. To ensure a 2-sided significance level of 5% and a statistical power of ≥90%, 40 events were required. Considering a dropout rate of 10%, the target sample size was 3,200 subjects (1,600 in the sipavibart group, 1,600 in the CIL/TIX group) to obtain the required number of events.
Subsequently, changes were made to the control drug group and primary endpoint (Table 27). In the study protocol Version 8.0 ([redacted], 20[redacted]), no changes were made to the target sample size, but the required number of events was reassessed. The incidence of COVID-19 caused by the target variant (SARS-CoV-2 without F456L mutation, expected to be susceptible to sipavibart) was estimated assuming an expected hazard ratio of 0.3 for the sipavibart group compared to the control drug group. To ensure a 2-sided significance level of 5% and a statistical power of ≥90%, the required number of events was 43. For the incidence of COVID-19 caused by all SARS-CoV-2 variants, assuming that 20% of events were due to variants containing F456L mutation (variants for which neutralization activity of sipavibart is not expected), an expected hazard ratio of 0.4 for the sipavibart group compared to the control drug group was used. To ensure a 2-sided significance level of 5% and a statistical power of ≥90%, the required number of events was 68.

Table 26. Main inclusion and exclusion criteria

Inclusion criteria	• Subjects aged ≥12 years and weighing ≥40 kg • Negative SARS-CoV-2 antigen test before administration of the study drug • Patients with at least 1 of the following immunocompromised state: ・ Patients with malignant solid tumors undergoing active immunosuppressive therapy ・ Patients with haematologic malignancies ・ Patients within 2 years post-solid organ transplantation or haematopoietic stem cell transplantation, or those with chronic graft-versus-host disease ・ Patients receiving actively immunosuppressants, alkylating agents, antimetabolites, transplant-related immunosuppressants, cancer chemotherapeutic agents classified as severe immunosuppressants, TNF inhibitors, or other immunosuppressive biologics ・ Patients who have undergone chimeric antigen receptor T-cell therapy ・ Patients within 1 year of receiving B-cell depletion therapy ・ Patients with moderate to severe primary immunodeficiency (e.g., DiGeorge syndrome) or secondary immunodeficiency (e.g., haemodialysis) ・ Patients with advanced or untreated HIV infection
Exclusion criteria	• Subjects with an acute or febrile (≥38°C) illness/infection on the day of or the day before study drug administration • Subjects diagnosed with a haemorrhagic disorder (e.g., blood coagulation factor deficiency) or with a history of significant bleeding due to intramuscular injection or venipuncture • Subjects who received immunoglobulin (including anti-SARS-CoV-2 antibody drugs), blood products, or convalescent plasma therapy for COVID-19 within 6 months prior to study drug administration • Subjects who received a SARS-CoV-2 vaccine within 3 months prior to study drug administration or were diagnosed with COVID-19 • Subjects who received prophylactic antiviral drugs for COVID-19 within 2 weeks prior to study drug administration

Sipavibart[27)] 300 mg or a control drug (placebo or CIL 300 mg/TIX 300 mg) was administered intramuscularly into the anterolateral thigh twice at 6-month intervals. In this study, the control drug and evaluation endpoints were modified under blinded conditions, as shown in Table 27. No subjects had received the second dose before the control drug was changed, and all study drugs administered in the second dose to the control drug group were placebo. An interim analysis was conducted when the median observation period for the efficacy analysis population exceeded 181 days after administration. The results of this interim analysis were submitted in the present application.

Table 27. Summary of changes in control drug groups and efficacy endpoints

Clinical study protocol version (effective date)	Control drug	Efficacy endpoint	
		Primary endpoint	Main secondary endpoint
Ver. 5.0[a)] (■ ■, 20■)	CIL/TIX	Neutralizing antibody titer against SARS-CoV-2	Incidence of COVID-19 caused by all SARS-CoV-2 variants
Ver. 6.0 (■ ■, 20■)	CIL/TIX	Incidence of COVID-19 caused by all SARS-CoV-2 variants	Neutralizing antibody titers against SARS-CoV-2
Ver. 7.0 (■ ■, 20■)	Placebo	Incidence of COVID-19 caused by all SARS-CoV-2 variants	Neutralizing antibody titers against SARS-CoV-2
Ver. 8.0 (■ ■, 20■)	Placebo	(a) Incidence of COVID-19 caused by all SARS-CoV-2 variants (b) Incidence of COVID-19 caused by targeted variants (SARS-CoV-2 without F456L mutation)	Neutralizing antibody titers against SARS-CoV-2

a) Clinical study protocol at the start of the main cohort (■ 20■)

Of the 3,349 randomized subjects (1,674 in the sipavibart group, 1,675 in the control drug group [1,111 for CIL/TIX, 564 for placebo]), 3,334 subjects (1,669 in the sipavibart group, 1,665 in the control drug group [1,104 for CIL/TIX, 561 for placebo]) were included in a full analysis set (FAS). The remaining 14 subjects who did not receive the study drug and 1 subject with duplicate enrollment were excluded.

27) In the safety cohort [see Section 7.1.2], a study was conducted on the combination of CIL and sipavibart, which demonstrated neutralizing activity against the SARS-CoV-2 Omicron variant. However, considering the *in vitro* neutralizing activity of CIL against subsequent emerging variants and concerns raised by foreign regulatory authorities, the main cohort study was conducted with sipavibart monotherapy (Study Protocol Version 5.0, dated ■ ■, 20■).

Since 2 subjects in the FAS experienced dosing errors, the safety analysis population was determined based on the actual study drug received, with 1,671 subjects in the sipavibart group and 1,663 subjects in the control drug group (1,102 for CIL/TIX, 561 for placebo). Among the FAS, 53 subjects (20 in the sipavibart group, 33 in the control drug group [22 for CIL/TIX, 11 for placebo]) tested positive for SARS-CoV-2 by reverse transcription polymerase chain reaction (RT-PCR) at baseline, and 1 subject (1 for CIL/TIX) was found to be duplicate-enrolled in another study. Excluding these cases, 3,280 subjects (1,649 in the sipavibart group, 1,631 in the control drug group [1,082 for CIL/TIX, 549 for placebo]) were included in the efficacy analysis population.

Among the subjects receiving the study drug (including 1 with duplicate enrollment), discontinuation was observed in 6.0% (100 of 1,669) of subjects in the sipavibart group and 6.4% (106 of 1,666) of subjects in the control group (8.4% [93 of 1,105] in CIL/TIX, 2.3% [13 of 561] in placebo). The main reasons for discontinuation were subject's request in 112 subjects (52 in the sipavibart group, 51 for CIL/TIX, 9 for placebo), lost to follow-up in 37 subjects (17 in the sipavibart group, 19 for CIL/TIX, 1 for placebo), and death in 32 subjects (19 in the sipavibart group, 11 for CIL/TIX, 2 for placebo). At the time point of the interim analysis, the median observation period (minimum, maximum) in the FAS was 191 (8, 360) days in the sipavibart group, 229 (5, 360) days in the CIL/TIX group, and 162 (22, 207) days in the placebo group.

Table 28 shows the relative risk reduction rate[28)] based on the occurrence of COVID-19[29)] caused by (1) all SARS-CoV-2 variants and (2) target variants (SARS-CoV-2 without F456L mutation) in the efficacy analysis population, the primary efficacy endpoints. Statistically significant differences were observed between the sipavibart and control drug groups in both primary endpoints (dual primary endpoint),[30)] demonstrating the superiority of sipavibart over the control drug.

Table 28. Relative risk reduction rate based on COVID-19 incidence (efficacy analysis population)

Causative virus	Incidence of events		Relative risk reduction rate[c)] [95% CI] (%)	Adjusted *P* level[c)]
	Sipavibart[a)]	Control drug[a) b)]		
All SARS-CoV-2 variants	7.4% (122/1,649)	10.9% (178/1,631)	34.9 [17.8, 48.4]	<0.001
Target variants (SARS-CoV-2 without F456L mutation)	3.3% (54/1,649)	5.5% (90/1,631)	42.9 [19.9, 59.3]	0.001

Incidence (%) (number of subjects with events/number of subjects evaluated)

a) Includes subjects who received the second dose of the study drug on Day 181.

b) Consists of subjects who received 1 dose of CIL/TIX or placebo; subjects who received CIL/TIX and placebo as the first and second dose, respectively (CIL/TIX-placebo); and subjects who received placebo for both doses (placebo-placebo).

c) Two-sided significance level of 5%. A Poisson regression model with robust variance, using treatment group (sipavibart vs. control drug), SARS-CoV-2 vaccination within 6 months, history of SARS-CoV-2 infection, and administration of CIL/TIX within 12 months as covariates, and the logarithm of each subject's observation period as an offset term. Multiplicity was adjusted using the Holm method.

28) Relative risk reduction rate (%) = [1 − (incidence in the sipavibart group/incidence in the control drug group)] × 100

29) The occurrence of COVID-19 was determined when both of the following criteria (a) and (b) were met:
(a) A positive SARS-CoV-2 result by RT-PCR testing
(b) Clinical criteria (i) or (ii) defined in the WHO case definition for COVID-19 (2022):
(i) At least 2 of the following: "Subjective fever," "cough," or "positive result for COVID-19 test (rapid antigen test or RT-PCR)"
(ii) Acute onset of at least 3 of the following signs or symptoms: "Subjective fever," "cough," "general weakness/fatigue," "headache," "myalgia," "sore throat," "coryza," "dyspnea," "nausea/diarrhea/loss of appetite," "conjunctivitis," "COVID-19 test positive," or "symptoms judged by a physician to be related to COVID-19"

30) For the 2 primary endpoints, multiplicity was adjusted using the Holm method. Superiority of sipavibart over the control was determined if a statistically significant difference was observed for either of the endpoints.

Figure 1 shows the results of the Kaplan-Meier curves for time to onset of COVID-19, the primary endpoint.

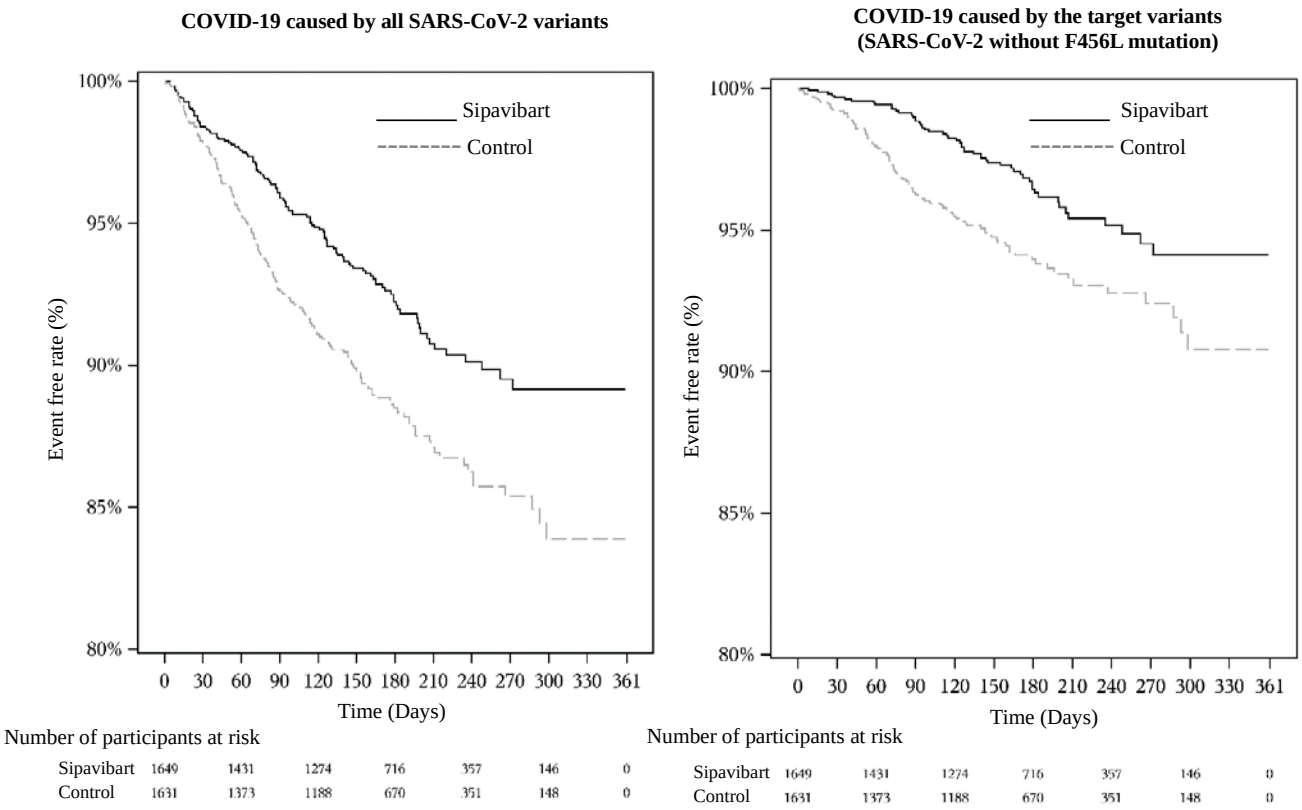

Figure 1. Kaplan-Meier curves for the cumulative event free rate of COVID-19 (efficacy analysis population)

Among the 4 Japanese subjects residing in the US who were enrolled (1 in the sipavibart group, 1 in the CIL/TIX group, 2 in the placebo group), COVID-19 was observed in 1 subject in the placebo group.

By Day 90[31)] after the first dose of the study drug, adverse events and adverse drug reactions were observed in 49.9% (833 of 1,671) of subjects and 7.4% (123 of 1,671) of subjects in the sipavibart group, 53.3% (587 of 1,102) of subjects and 10.4% (115 of 1,102) of subjects in the CIL/TIX group, and 48.1% (270 of 561) of subjects and 6.1% (34 of 561) of subjects in the placebo group, respectively. Table 29 shows the major events. By Day 90 after the second dose of the study drug, adverse events and adverse drug reactions were observed in 24.8% (220 of 886) of subjects and 3.2% (28 of 886) of subjects in the sipavibart group, 23.4% (184 of 785) of subjects and 2.4% (19 of 785) of subjects in the CIL/TIX-placebo group (first dose, CIL/TIX; second dose, placebo), and 8.5% (8 of 94) of subjects and 6.4% (6 of 94) of subjects in the placebo-placebo group (placebo administered in both the first and second doses), respectively. The event observed in ≥2% of subjects in any group was COVID-19 (2.1% [19 of 886] of subjects in the sipavibart group, 2.5% [20 of 785] of subjects in the CIL/TIX-placebo group).

31) In the clinical study of CIL/TIX, most adverse events were observed within 90 days after administration. Also, immediate post-injection reactions and administration site reactions were expected to occur within a few hours after administration. The study was therefore designed to collect adverse events and adverse drug reactions occurring within 90 days after administration of the study drug. Deaths, serious adverse events, and adverse events of special interest (serious hypersensitivity reactions, immune complex diseases, infusion-related reactions, cardiovascular events, and thromboembolic events) were collected regardless of the time of occurrence.

Table 29. Adverse events and adverse drug reactions observed in ≥2% of subjects in any group by Day 90 after the first dose of the study drug (safety analysis population)

Event	Adverse events			Adverse drug reactions		
	Sipavibart (N = 1,671)	Control drug		Sipavibart (N = 1,671)	Control drug	
		CIL/TIX (N = 1,102)	Placebo (N = 561)		CIL/TIX (N = 1,102)	Placebo (N = 561)
Any adverse event/adverse drug reaction	833 (49.9)	587 (48.1)	270 (48.1)	123 (7.4)	115 (10.4)	34 (6.1)
COVID-19	97 (5.8)	78 (7.1)	62 (11.1)	0	0	0
Cough	89 (5.3)	75 (6.8)	20 (3.6)	1 (0.1)	3 (0.3)	1 (0.2)
Headache	84 (5.0)	49 (4.4)	28 (5.0)	16 (1.0)	9 (0.8)	5 (0.9)
Fatigue	66 (3.9)	53 (4.8)	27 (4.8)	20 (1.2)	22 (2.0)	9 (1.6)
Oropharyngeal pain	66 (3.9)	28 (2.5)	15 (2.7)	1 (0.1)	0	0
Rhinorrhoea	53 (3.2)	38 (3.4)	14 (2.5)	1 (0.1)	1 (0.1)	0
Upper respiratory tract infection	46 (2.8)	17 (1.5)	21 (3.7)	0	0	0
Urinary tract infection	43 (2.6)	27 (2.5)	10 (1.8)	0	0	0
Diarrhoea	41 (2.5)	38 (3.4)	15 (2.7)	2 (0.1)	4 (0.2)	0
Nasal congestion	38 (2.3)	12 (1.1)	10 (1.8)	0	0	1 (0.2)
Nasopharyngitis	36 (2.2)	21 (1.9)	13 (2.3)	1 (0.1)	1 (0.1)	0
Pyrexia	34 (2.0)	19 (1.7)	8 (1.4)	1 (0.1)	7 (0.6)	1 (0.2)
Nausea	28 (1.7)	22 (2.0)	13 (2.3)	5 (0.3)	6 (0.5)	2 (0.4)
Injection site pain	25 (1.5)	25 (2.3)	6 (1.1)	15 (0.9)	15 (1.4)	4 (0.7)
Myalgia	24 (1.4)	19 (1.7)	15 (2.7)	7 (0.4)	5 (0.5)	4 (0.7)

Number of subjects with events (incidence [%]) MedDRA/J ver.26.1

During the observation period until the data cutoff, deaths were observed in 20 subjects in the sipavibart group (cardiac arrest in 4 subjects, septic shock in 2 subjects, and non-small cell lung cancer, rectal cancer stage IV , acute myocardial infarction, acute respiratory failure, haemoptysis, death, appendicitis perforated, pneumococcal sepsis, pulmonary fibrosis, myocardial infarction, streptococcal sepsis, cardio-respiratory arrest, pneumonia, and prostate cancer metastatic in 1 subject each), 11 subjects in the CIL/TIX group (acute respiratory failure and acute myocardial infarction in 2 subjects each, and COVID-19 pneumonia, bacteremia, urosepsis, septic shock, coronary artery disease, end stage renal disease, and myocardial infarction in 1 subject each), and 2 subjects in the placebo group (plasma cell myeloma, death). A causal relationship to the study drug was ruled out for these deaths. Among the serious adverse events (including deaths, see Table 38), events for which a causal relationship to the study drug could not be ruled out were observed in 2 subjects in the sipavibart group after the first dose (pulmonary embolism, hypertensive emergency, and acute pulmonary oedema [some subjects had multiple events]), 4 subjects in the CIL/TIX group (drug hypersensitivity, left ventricular dysfunction, hypertensive urgency, and fall), 2 subjects in the placebo group (hypersensitivity, deep vein thrombosis, and injection site necrosis [some subjects had multiple events]), and 1 subject in the CIL/TIX-placebo group after the second dose (gastroenteritis). Although sequelae were observed in the case of injection site necrosis in the placebo group, all other events resolved or were resolving.

No adverse events were observed in the 1 Japanese subject residing in the US who received sipavibart.

Based on the above findings, the prophylactic effect of sipavibart on the onset of COVID-19 was confirmed in non-Japanese immunocompromised subjects aged ≥12 years,[15)] and no particular issues with tolerability were identified.

7.R Outline of the review conducted by PMDA

7.R.1 Development strategy and clinical data package

The applicant's explanation about the development strategy and clinical data package of sipavibart:

Sipavibart has been designed as a successor to CIL/TIX (Brand name: Evusheld Intramuscular Injection Set), with the same basic structure as CIL and TIX but enhanced neutralization activity against a broader range of SARS-CoV-2 variants. In the initial clinical development of sipavibart, based on reports suggesting that SARS-CoV-2 neutralizing antibody titers could predict protective immunity against COVID-19 (*Nat Med.* 2021;27:1205-11, *N Engl J Med.* 2021;385:1184-95, etc.), the foreign phase I/III study (Study D7000C00001) was planned to evaluate the neutralizing antibody titers against SARS-CoV-2 [redacted] as an endpoint to verify the [redacted] of sipavibart 300 mg to CIL/TIX. However, following [redacted] from [redacted], the study design was modified to compare the neutralizing antibody titers of sipavibart 1,200 mg and CIL/TIX in a separate substudy (Study D7000C00001 Substudy). Consequently, for Study D7000C00001 main cohort, the secondary endpoint "occurrence of COVID-19" under blinded conditions was changed to the primary endpoint after study initiation. Since CIL/TIX lacked neutralization activity against the prevailing variants at that time, the control drug in Study D7000C00001 main cohort was switched from CIL/TIX to placebo in a blinded manner (Table 27). Furthermore, during the study period of Study D7000C00001 main cohort, SARS-CoV-2 variants containing the F456L mutation, which were expected to be resistant to sipavibart, emerged and became predominant. To cope with the situation, the intended use of sipavibart was redefined as the prevention of COVID-19 caused by variants susceptible to sipavibart. To align with this objective, an additional primary endpoint was introduced in a blinded manner to analyze the target variants (SARS-CoV-2 variants without F456L mutation). The study protocol specified that sipavibart's efficacy would be confirmed if statistically significant difference was observed between the sipavibart and control drug groups for either all variants or the target variants.

As described above, in Study D7000C00001 main cohort, these post-initiation modifications to key study parameters, including control drug, primary endpoint, and evaluation method, were implemented in a blinded manner, minimizing their impact on study outcomes. Ultimately, the study demonstrated a statistically significant reduction in the incidence of COVID-19 in both primary endpoints (the occurrence of COVID-19 caused by [1] all SARS-CoV-2 variants and [2] target variants [SARS-CoV-2 without F456L mutation]) in the sipavibart group, compared to the control drug group. Therefore, Study D7000C00001 main cohort was deemed an appropriate pivotal clinical study for the clinical data package.

Regarding the development strategy for sipavibart in Japan, the possibility of including Japanese subjects in Study D7000C00001 main cohort was explored starting around [redacted], 20[redacted], but the conclusion was reached that [redacted], [redacted] was infeasible. As an alternative, the applicant aimed to include as many Japanese residents overseas as possible in Study D7000C00001 main cohort while conducting a phase I study in healthy Japanese adults (Study D7000C00007) in Japan, as is the case of the clinical data package used for the special approval of Evusheld Intramuscular Injection Set. This approach was intended to comprehensively evaluate the efficacy and safety of sipavibart in Japanese subjects.

The applicant's additional explanation:

Based on the following considerations, there was no concern that intrinsic or extrinsic ethnic factors would affect the efficacy and safety of sipavibart, supporting the positioning of Study D7000C00001 main cohort as the pivotal study.

- Results from the Japanese phase I study (Study D7000C00007) and foreign phase I studies (Studies D7000C00004 and D7000C00001 safety cohort) indicated no clinically meaningful differences in PK between Japanese and non-Japanese subjects [see Section 6.R.1].
- Sipavibart is a specific monoclonal antibody targeting an adventitious virus, and no cross-reactivity with human tissues was observed [see Section 5.7.1].
- Except for the antigen-binding site, sipavibart shares the same basic structure with CIL and TIX. Since there have been no reports of ethnic differences in the efficacy (the prevention of COVID-19) and safety of CIL/TIX, ethnic differences are not expected for sipavibart, either.
- Despite the difference in the timing of SARS-CoV-2 variant prevalence between Japan and other countries, recent predominant variants in both regions have been Omicron variants,[32)] with no essential differences in pathogen characteristics or clinical symptoms of the infection. Thus, the neutralization activity of sipavibart against SARS-CoV-2 is expected to be similar in Japan and overseas.

PMDA's view:

For Study D7000C00001 main cohort, significant modifications were made to key study parameters such as the control drug and the primary endpoint during its conduct. By the time the study was designed in 20[redacted], however, knowledge regarding the characteristics of SARS-CoV-2 Omicron variant, the high mutation frequency of SARS-CoV-2, and the clinical symptoms of Omicron-induced COVID-19 had been accumulated. Ideally, these factors should have been thoroughly considered during the study design phase for policy evaluating sipavibart's efficacy. Considering the following factors, the impact of such protocol changes on study outcomes was limited and efficacy could be primarily evaluated based on this study:

- All major modifications were conducted in a blinded manner.
- Regarding the change in the control drug, CIL/TIX had significantly reduced neutralization activity against the prevalent variants at that time. Therefore, the efficacy of sipavibart is unlikely to have been overestimated in the control drug group consisting of subjects receiving CIL/TIX and those receiving placebo, compared to the case where all subjects in the control drug group receive placebo.
- For the change in primary endpoint, the occurrence of COVID-19 had been pre-specified as a secondary endpoint at the start of the study in Study D7000C00001 main cohort. The study had been designed with a sample size sufficient to ensure adequate power for hypothesis testing of the revised primary endpoint.
- The additional primary endpoint assessing target variants (SARS-CoV-2 without F456L mutation) was justifiable, as its results could be interpreted as demonstrating "efficacy under an ideal condition where all circulating variants were susceptible to sipavibart."

32) Japan: https://www.hokeniryo.metro.tokyo.lg.jp/kansen/corona_portal/henikabu/screening.html (last accessed on October 11, 2024)
Other countries: https://covid.cdc.gov/covid-data-tracker/#variant-proportions (last accessed on October 11, 2024)
https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports (last accessed on October 11, 2024)

Given the real-world emergence of multiple SARS-CoV-2 variants with differing neutralization activity to sipavibart and the continued reports of novel variants, discussions on the efficacy of sipavibart and the clinical relevance of the administration should focus on its overall ability to prevent COVID-19 across all SARS-CoV-2 variants, including those with the F456L mutation.

According to the clinical data package for regulatory submission in Japan, (a) sipavibart is considered to show no significant ethnic differences in PK or pharmacological activity; (b) except for the antigen-binding site, sipavibart is a human IgG1 monoclonal antibody with similar structure as that of CIL/TIX; and (c) CIL/TIX has been used in Japanese clinical settings, with no reports of ethnic differences. Thus, no significant ethnic differences are expected to exist for sipavibart. PMDA concluded that it was reasonable to evaluate the efficacy and safety of sipavibart primarily based on Study D7000C00001 main cohort conducted in foreign countries.

Given that the efficacy of sipavibart in the prevention of COVID-19 is inevitably influenced by factors such as epidemic status, contact with infected individuals, and pre-existing immunity, some uncertainty remains as to whether sipavibart will demonstrate the same efficacy in Japan as in foreign studies. Since only 4 Japanese subjects residing overseas were enrolled in Study D7000C00001 main cohort, it was difficult to evaluate ethnic differences in the efficacy and safety of sipavibart based on specific data. To undertake the development of sipavibart in Japan, enrolling Japanese subjects in Study D7000C00001 should have been a more appropriate approach for confirming its efficacy and safety in the Japanese population. Currently, the predominant SARS-CoV-2 variants in Japan include the F456L mutation, against which sipavibart lacks neutralization activity [see Section 3.R.2]. There is currently little justification for planning or conducting a clinical study in Japan to evaluate the efficacy and safety of sipavibart.

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

7.R.2 Efficacy

7.R.2.1 Prevention of COVID-19

The applicant’s explanation about the efficacy of sipavibart for preventing COVID-19 based on the results of the foreign phase I/III clinical study (Study D7000C00001) main cohort:

- For the primary endpoints, namely (1) COVID-19 caused by all SARS-CoV-2 variants and (2) COVID-19 caused by the target variants (SARS-CoV-2 without F456L mutation), a statistically significant risk reduction was observed in the sipavibart group compared to the control drug group.
- Table 30 shows the incidences of COVID-19 (all variants)-related hospitalization, severe COVID-19,[33)] and COVID-19-related death in the efficacy analysis population. Due to the small number of subjects experiencing such events, there were limitations in evaluating efficacy.

[33)] WHO Clinical Progression Scale ≥6 (requiring hospitalization and non-invasive ventilation)

Table 30. COVID-19-related hospitalization, severe cases, and deaths (efficacy analysis population)

	Incidence of events (%)	
	Sipavibart[a)]	Control drug[a) b)]
COVID-19-related hospitalization	0.6% (10/1,649)	0.6% (10/1,631)
Severe COVID-19	0.1% (2/1,649)	0.1% (2/1,631)
COVID-19-related death	0	0.1% (1/1,631)

Incidence (%) (number of subjects with events/number of subjects evaluated)
a) Includes subjects who received a second dose of the study drug on Day 181.
b) Consists of subjects who received a single dose of either CIL/TIX or placebo; subjects who received CIL/TIX and placebo at the first and second doses, respectively; and subjects who received 2 doses of placebo.

- From the initial dose to Day 180 (from the first dose of the study drug until before the second dose), the incidence of COVID-19 caused by all variants was 6.5% (107 of 1,649 subjects) in the sipavibart group and 9.8% (160 of 1,631 subjects) in the control drug group. The relative risk reduction rate [95% confidence interval (CI)] was 36.4% [18.7%, 50.3%]. The results of single-dose administration of sipavibart exhibited a trend similar to that of the primary analysis. At the time of the interim analysis (when the median observation period for the efficacy analysis population exceeded 181 days post-dose), the number of events was limited, making a detailed assessment difficult. After Day 181 (after the second dose of the study drug), however, the incidence of COVID-19 caused by all variants was 0.9% (15 of 1,649 subjects) in the sipavibart group and 1.1% (18 of 1,631 subjects) in the control drug group.
- As with the administration criteria for CIL/TIX, children aged ≥12 years and weighing ≥40 kg were eligible for enrollment. Consequently, subjects receiving immunosuppressive therapy were enrolled primarily. Table 31 shows the results of age-group analysis of the incidence of COVID-19 caused by all SARS-CoV-2 variants. The efficacy of sipavibart in elderly subjects aged ≥65 years was similar to that in non-elderly subjects aged <65 years. Although the limited number of enrolled pediatric subjects made it difficult to evaluate the incidence of COVID-19, no clear trend suggesting reduced efficacy was observed.

Table 31. Relative risk reduction rate of COVID-19 (all SARS-CoV-2 variants) by age group (efficacy analysis population)

	Incidence of events (%)		Relative risk reduction rate[c)] [95% CI] (%)
	Sipavibart[a)]	Control drug[a) b)]	
≥12 and <18 years	0 (0/8)	0 (0/7)	-
≥18 and <65 years	8.2 (86/1,045)	12.1 (125/1,037)	33.5 [12.3, 49.6]
≥65 years	6.0 (36/597)	9.0 (53/587)	36.5 [2.7, 58.5]

Incidence (%) (number of subjects with events /number of subjects evaluated); -, Non-calculable
a) Includes subjects who received a second dose of the study drug on Day 181.
b) Consists of subjects who received a single dose of either CIL/TIX or placebo; subjects who received CIL/TIX and placebo as the first and second doses, respectively; and subjects who received 2 doses of placebo.
c) A Poisson regression model with robust variance, using treatment group (sipavibart group/control drug group), subpopulation, and the interaction between treatment group and subpopulation as covariates, and the logarithm of the observation period for each case as an offset term.

PMDA's view:

The efficacy of sipavibart in prevention of COVID-19 was demonstrated in Study D7000C00001 main cohort. Due to the limited number of COVID-19-related hospitalization and of severe COVID-19, the results showed no trend toward reduced number of such events by sipavibart. Post-marketing data should therefore continue to be gathered. The efficacy of sipavibart in pediatric subjects was not clearly demonstrated in Study D7000C00001 main cohort. The use of sipavibart in pediatric subjects will be further discussed in Section 7.R.6, considering safety and PK aspects.

7.R.2.2 Efficacy against various SARS-CoV-2 variants

The applicant's explanation about the efficacy of sipavibart against various SARS-CoV-2 variants:
Sipavibart is an IgG1 antibody that specifically binds to SARS-CoV-2 S protein. However, sipavibart does not exhibit neutralization activity against some variants, particularly those whose S protein contains F456L mutation in the RBD. During the study period, the Omicron JN.1 lineage, which was prevalent at the time, contained L455S mutation in S protein, which serves as the RBD for sipavibart. A reduction in neutralization activity of sipavibart, likely due to this mutation, was observed [see Section 3.R.2]. Table 32 shows the incidence of events classified by major variant groups isolated from patients with COVID-19 in Study D7000C00001 main cohort. The results suggest that sipavibart prevented COVID-19, particularly for the target variants without F456L mutation. Although there was a trend toward reduced efficacy against the Omicron JN.1 lineage, the results still indicate the efficacy of sipavibart. For variants containing the F456L mutation, the incidence of events also tended to be lower in the sipavibart group than in the control drug group. However, given that these variants are not expected to be neutralized by sipavibart, this finding is considered incidental.

Table 32. Relative risk reduction rate of COVID-19 by major variant group (efficacy analysis population)

	Incidence of events (%)		Relative risk reduction rate[c)] [95% CI] (%)
	Sipavibart[a)]	Control drug[a) b)]	
Identified variant strains	6.1 (101/1,649)	9.4 (154/1,631)	37.6 [19.6, 51.6]
Target variants	3.3 (54/1,649)	5.5 (90/1,631)	42.9 [19.9, 59.3]
BA.2.86 + subvariants	0.1 (1/1,649)	0.6 (10/1,631)	90.9 [27.4, 98.9]
XBB + subvariants	0.4 (6/1,649)	1.2 (20/1,631)	71.6 [29.0, 88.7]
JN.1 + subvariants	2.9 (47/1,649)	3.7 (60/1,631)	25.1 [-9.7, 48.8]
Variants containing the F456L mutation	2.9 (47/1,649)	3.9 (64/1,631)	30.4 [-1.8, 52.5]

Incidence (%) (number of subjects with events/number of subjects evaluated)
a) Includes subjects who received a second dose of the study drug on Day 181.
b) Consists of subjects who received a single dose of either CIL/TIX or placebo, subjects who received CIL/TIX and placebo on the first and second dose, respectively, and subjects who received placebo twice.
c) Poisson regression model with robust variance, using treatment group (sipavibart group/control group), SARS-CoV-2 vaccination within 6 months, history of SARS-CoV-2 infection, and administration of CIL/TIX within 12 months as covariates, and the logarithm of the observation period for each case as an offset term.

Since May 2024, the predominantly circulating strains in Japan have been the Omicron KP.3 lineage and its sub-lineages, all of which contain the F456L mutation.[34)] Because sipavibart does not exhibit neutralization activity against these variants [see Section 3.R.2], its efficacy cannot be expected.

PMDA's view:
Study D7000C00001 main cohort demonstrated that sipavibart prevented COVID-19 caused by SARS-CoV-2. Although the Omicron JN.1 lineage does not contain F456L mutation, a reduction in neutralization activity of sipavibart was observed in the variant [see Section 3.R.2]. This result suggests the possibility of reduced efficacy, albeit an exploratory one. Based on the findings regarding neutralization activity, the applicant's opinion that the efficacy of sipavibart cannot be expected against variants containing F456L mutation is understandable. As of October 2024, the predominant circulating SARS-CoV-2 variants in Japan contain F456L mutation. Given the likelihood of new variants emerging in the future, the necessity of use of sipavibart should be carefully assessed, considering the prevalent variants at the time of administration.

34) https://www.niid.go.jp/niid/ja/2019-ncov/2551-cepr/12865-sars-cov-2-kp3.html (last accessed on October 11, 2024)

For the proper use of sipavibart, its neutralization activity against circulating variants is crucial information. The applicant should continuously collect information after the market launch, and new findings should be promptly provided to healthcare professionals.

7.R.2.3 Efficacy by underlying disease

The applicant's explanation about the impact of underlying disease on the efficacy of sipavibart:

Study D7000C00001 main cohort targeted subjects in an immunocompromised state, and the specific inclusion criteria (Table 26) were based on the guidelines of the U.S. National Institutes of Health (NIH) (Coronavirus Disease 2019 [COVID-19] Treatment Guidelines. National Institutes of Health, 2021). Regarding the incidence of COVID-19 caused by all SARS-CoV-2 variants in this study, the results of the analysis by underlying disease are shown in Table 33. In subpopulations other than subjects with "malignant solid tumors receiving active immunosuppressive therapy," the sipavibart group showed a tendency toward a lower incidence, similarly to the overall population. For patients with "malignant solid tumors receiving active immunosuppressive therapy," the sipavibart group showed a trend of higher event occurrence. Since (1) the number of subjects evaluated was as limited as approximately 50, (2) the confidence interval crossed zero, and (3) the serum sipavibart concentration did not differ significantly from that in patients with other underlying diseases; this was considered a coincidental bias. The limited number of "patients who received chimeric antigen receptor T-cell therapy" and "patients with advanced or untreated HIV infection" precluded the evaluation of such populations.

Table 33. Relative risk reduction rate of COVID-19 (all SARS-CoV-2 variants) by underlying disease (efficacy analysis population)

		Incidence of events (%)		Relative risk reduction rate[c)] [95% CI] (%)
		Sipavibart[a)]	Control drug[a) b)]	
Solid organ transplantation or haematopoietic stem cell transplantation	Without	7.3 (101/1,381)	10.8 (148/1,368)	34.6 [15.6, 49.3]
	With	7.8 (21/268)	11.4 (30/263)	34.3 [-15.2, 62.6]
Malignant solid tumors receiving active immunosuppressive therapy	Without	7.1 (113/1,595)	11.0 (173/1,574)	37.8 [21.0, 51.0]
	With	16.7 (9/54)	8.3 (5/57)	-87.3 [-435.1, 34.4]
Use of immunosuppressant(s)	Without	5.1 (22/435)	8.8 (36/408)	44.8 [6.1, 67.6]
	With	8.2 (100/1,214)	11.6 (142/1,223)	31.1 [10.8, 46.8]
Haematologic malignancies	Without	7.6 (105/1,387)	10.7 (150/1,401)	31.5 [12.0, 46.7]
	With	6.5 (17/262)	12.2 (28/230)	50.5 [8.4, 73.2]
Moderate to severe secondary immunodeficiency	Without	8.2 (114/1,385)	11.7 (164/1,398)	32.2 [13.8, 46.7]
	With	3.0 (8/264)	6.0 (14/233)	49.8 [-19.7, 79.0]
B-cell depletion therapy	Without	7.2 (102/1,422)	10.5 (150/1,425)	34.1 [15.1, 48.9]
	With	8.8 (20/227)	13.6 (28/206)	38.9 [-8.6. 65.6]
Chimeric antigen receptor T-cell therapy	Without	7.4 (122/1,645)	10.9 (178/1,626)	34.8 [17.8, 48.3]
	With	0 (0/4)	0 (0/5)	NC
Moderate to severe primary immunodeficiency	Without	7.4 (120/1,625)	10.8 (173/1,602)	34.4 [17.0, 48.1]
	With	8.3 (2/24)	17.2 (5/29)	46.4 [-145.4, 88.3]
Advanced or untreated HIV infection	Without	7.5 (122/1,637)	11.1 (178/1,608)	35.3 [18.3, 48.7]
	With	0 (0/12)	0 (0/23)	NC

Incidence (%) (number of subjects with events/number of subjects evaluated)

a) Includes subjects who received the second dose of the study drug on Day 181.

b) Consists of subjects who received a single dose of either CIL/TIX or placebo, subjects who received CIL/TIX and placebo on the first and second dose, respectively, and subjects who received placebo twice.

c) Poisson regression model with robust variance, using treatment group (sipavibart group/control drug group), SARS-CoV-2 vaccination within 6 months, history of SARS-CoV-2 infection, and administration of CIL/TIX within 12 months as covariates, and the logarithm of the observation period for each case as an offset term.

PMDA's view:

Regarding the subgroup analysis results by underlying disease in Study D7000C00001 main cohort, the subpopulations for some underlying diseases had a small number of subjects, making it difficult to assess

the efficacy of sipavibart. However, the analysis did not clearly suggest that underlying disease might significantly affect the efficacy of sipavibart. Sipavibart is a human IgG antibody, and no significant impact of underlying disease on its PK has been suggested currently; therefore, there is no need to exclude patients with specific underlying diseases from eligible populations for the administration of sipavibart. The applicant should continue to collect information on the impact of underlying disease on the efficacy of sipavibart after the market launch and provide information to healthcare professionals if new findings are obtained.

The appropriateness of this PMDA's judgment will be discussed at the Expert Discussion.

7.R.3 Safety

7.R.3.1 Safety profile

The applicant's explanation about the safety profile of sipavibart:

Table 34 presents the safety summary from the foreign phase I/III study (Study D7000C00001 main cohort). No significant differences were observed in the incidence of adverse events and adverse drug reactions between the sipavibart group and the control drug groups (CIL/TIX-treated subjects and placebo-treated subjects). Although the results are exploratory based on an interim analysis, the tolerability of sipavibart did not tend to worsen after the second dose.

In the sipavibart group, the most common adverse events were events related to COVID-19 and primary diseases, as well as diarrhoea and injection site pain (see Table 29). Most of them were non-serious. Table 35 shows the safety summary by age group. No particular safety concerns were suggested for elderly subjects aged ≥65 years. For the pediatric subjects aged ≥12 and <18 years, adverse events observed in each subject in the sipavibart group included urinary tract infection, systemic lupus erythematosus/lupus nephritis, rhinitis/nausea/decreased appetite/fatigue/headache/myalgia/diarrhoea/cough/oropharyngeal pain, upper respiratory tract infection, and pain in extremity. Except for pain in extremity, a causal relationship to the study drug was ruled out. Although the number of pediatric subjects was limited, no particular safety concerns have been suggested at this time.

Table 34. Safety summary by number of doses in Study D7000C00001 main cohort (safety analysis population)

	First dose (Day 1-91)			Second dose (Day 181-271)		
		Control drug			Control drug	
	Sipavibart (N = 1,671)	CIL/TIX (N = 1,102)	Placebo (N = 561)	Sipavibart (N = 886)	CIL/TIX-placebo (N = 785)	Placebo-placebo (N = 94)
Adverse events	833 (49.9)	587 (53.3)	270 (48.1)	220 (24.8)	184 (23.4)	8 (8.5)
Adverse drug reactions	123 (7.4)	115 (10.4)	34 (6.1)	28 (3.2)	19 (2.4)	6 (6.4)
Serious adverse events	120 (7.2)	85 (7.7)	37 (6.6)	41 (4.6)	34 (4.3)	0
Adverse events resulting in death	7 (0.4)	4 (0.4)	1 (0.2)	3 (0.3)	4 (0.5)	0
Adverse events leading to discontinuation	1 (0.1)	1 (0.1)	0	0	0	0

Number of subjects with events (incidence [%])

Table 35. Safety summary by age group in Study D7000C00001 main cohort (safety analysis population)

	<18 years			≥18 and <65 years			≥65 years		
	Sipavibart (N = 8)	Control drug		Sipavibart (N = 1,057)	Control drug		Sipavibart (N = 606)	Control drug	
		CIL/TIX (N = 7)	Placebo (N = 0)		CIL/TIX (N = 678)	Placebo (N = 375)		CIL/TIX (N = 417)	Placebo (N = 186)
Adverse events	5 (62.5)	6 (85.7)	0	534 (50.5)	377 (55.6)	183 (48.8)	295 (48.7)	204 (48.9)	87 (46.8)
Adverse drug reactions	1 (12.5)	2 (28.6)	0	84 (7.9)	77 (11.4)	25 (6.7)	38 (6.3)	36 (8.6)	9 (4.8)
Serious adverse events	0	1 (14.3)	0	65 (6.1)	53 (7.8)	24 (6.4)	55 (9.1)	31 (7.4)	13 (7.0)
Adverse events leading to death	0	0	0	4 (0.4)	2 (0.3)	0	3 (0.5)	2 (0.5)	1 (0.5)
Adverse events leading to discontinuation	0	0	0	0	1 (0.1)	0	1 (0.2)	0	0

Number of subjects with events (incidence [%])

Regarding the safety of sipavibart in Japanese subjects, no adverse events were observed in the 1 Japanese subject residing in the US who received sipavibart in Study D7000C00001 main cohort. In the Japanese phase I study (Study D7000C00007), only mild to moderate events were observed, but a causal relationship to the study drug was ruled out. No particular safety concerns have therefore been suggested to date [see Sections 7.1.1 and 7.2.1].

Although no serious hypersensitivity,[35)] including anaphylaxis, attributable to sipavibart has been reported in clinical studies, there is a potential risk of serious hypersensitivity, including anaphylaxis, following the administration of sipavibart, as is the case with other antibody drugs and pharmaceuticals containing protein as the active ingredient. This risk will be highlighted in the package insert.

PMDA's view:
Based on the incidence of adverse events observed in the presented clinical studies, the safety of sipavibart is considered acceptable. However, appropriate warnings must be provided regarding serious hypersensitivity, including anaphylaxis. Although safety data from Japanese subjects are limited, no particular safety concerns have been identified. Given that sipavibart is an antibody targeting an adventitious agent and does not exhibit cross-reactivity with human tissues [see Section 5.7.1], the safety profile of sipavibart is unlikely to substantially differ between Japanese and non-Japanese subjects. Nevertheless, the applicant should continue to collect safety information in Japanese subjects after the market launch and provide the information appropriately to healthcare professionals.

PMDA conducted an additional review on the risks of cardiovascular events and thromboembolic events, referencing the safety profile of the preceding product of sipavibart, CIL/TIX (brand name: Evusheld Intramuscular Injection Set) [see Section 7.R.3.2].

35) Serious adverse events and adverse events of Grade ≥3 that fall under MedDRA Standardized MedDRA query (SMQ) "Hypersensitivity" (narrow) and "Angioedema" (broad), as well as MedDRA preferred term (PT) "Idiopathic angioedema" and "Idiopathic urticaria," occurring within 30 days after administration of the study drug.

7.R.3.2 Risk of cardiovascular events and thromboembolic events

The applicant's explanation about the risk of cardiovascular events and thromboembolic events associated with sipavibart:

Table 36 shows the incidence of cardiovascular events and thromboembolic events[36)] observed from the first dose of the study drug to the data cut-off point in Study D7000C00001 main cohort. No trend suggesting a particularly higher incidence in the sipavibart group compared to the CIL/TIX group was observed. A causal relationship to the study drug could not be ruled out for peripheral swelling, pulmonary embolism, deep vein thrombosis, and acute pulmonary oedema (1 subject each) in the sipavibart group, and left ventricular dysfunction (1 subject) in the CIL/TIX group. An adverse event leading to death was observed in 1 subject in the sipavibart group (acute myocardial infarction); however, this subject had multiple risk factors, including end-stage renal failure, renal dialysis, diabetes mellitus, and hyperlipidaemia. A causal relationship to the study drug was ruled out. Other serious adverse events were reported in 44 subjects in the sipavibart group, 18 subjects in the CIL/TIX group, and 10 subjects in the placebo group. A causal relationship to the study drug could not be ruled out in 2 subjects in the sipavibart group (pulmonary embolism and acute pulmonary oedema in 1 subject each), 1 subject in the CIL/TIX group (left ventricular dysfunction), and 1 subject in the placebo group (deep vein thrombosis). All subjects who experienced cardiovascular events or thromboembolic events, including serious cases, had cardiovascular risk factors.[37)] In addition, sipavibart does not exhibit cross-reactivity with human tissues [see Section 5.7.1]. It is highly likely that the above events were due to incidental bias. At this stage, no special warnings regarding the risk of cardiovascular events and thromboembolic events are considered necessary.

[36)] Events classified under MedDRA SMQ "Myocardial infarction" (narrow), "Cardiac failure" (broad), "Embolic and thrombotic events" (narrow), "Ischemic central nervous system vascular conditions" (narrow), and "Haemorrhagic central nervous system vascular conditions" (narrow).

[37)] A history of coronary artery disease, stroke/cerebrovascular disorder/transient ischaemic attack, chronic heart failure, embolism/thrombosis, chronic kidney disease, autoimmune disease, hypertension, lipid metabolism disorders, baseline BMI ≥30 kg/m², smoking (current or past), male subjects, and age ≥65 years.

Table 36. Incidence of cardiovascular events and thromboembolic events (safety analysis population)[a)]

	Sipavibart (N = 1,671)	Control drug	
		CIL/TIX (N = 1,102)	Placebo (N = 561)
Cardiovascular events and thromboembolic events	62 (3.7)	33 (3.0)	16 (2.9)
Cardiac failure congestive	11 (0.7)	8 (0.7)	2 (0.4)
Acute myocardial infarction	10 (0.6)	5 (0.5)	2 (0.4)
Cardiac failure acute	9 (0.5)	3 (0.3)	1 (0.2)
Deep vein thrombosis	8 (0.5)	2 (0.2)	2 (0.4)
Pulmonary oedema	7 (0.4)	5 (0.5)	0
Oedema peripheral	6 (0.4)	4 (0.4)	2 (0.4)
Pulmonary embolism	6 (0.4)	0	0
Cerebrovascular accident	4 (0.2)	0	0
Peripheral swelling	3 (0.2)	1 (0.1)	1 (0.2)
Acute left ventricular failure	2 (0.1)	2 (0.2)	0
Left ventricular failure	2 (0.1)	1 (0.1)	2 (0.4)
Acute pulmonary oedema	2 (0.1)	1 (0.1)	0
Acute coronary syndrome	2 (0.1)	0	0
Myocardial infarction	2 (0.1)	0	0
Transient ischaemic attack	1 (0.1)	3 (0.3)	1 (0.2)
Troponin increased	1 (0.1)	2 (0.2)	0
Diastolic dysfunction	1 (0.1)	1 (0.1)	0
Brachiocephalic vein thrombosis	1 (0.1)	1 (0.1)	0
Coronary artery disease	1 (0.1)	0	0
Brain stem haemorrhage	1 (0.1)	0	0
Brain stem infarction	1 (0.1)	0	0
Carotid artery disease	1 (0.1)	0	0
Cerebral infarction	1 (0.1)	0	0
Cerebral microinfarction	1 (0.1)	0	0
Haemorrhage intracranial	1 (0.1)	0	0
Subdural haemorrhage	1 (0.1)	0	0
Subdural haematoma	1 (0.1)	0	0
Vascular stent occlusion	1 (0.1)	0	0
Cardiogenic shock	1 (0.1)	0	0
Cardiomegaly	1 (0.1)	0	0
Polyuria	1 (0.1)	0	0
Jugular vein thrombosis	1 (0.1)	0	0
Subclavian vein thrombosis	1 (0.1)	0	0
Thrombophlebitis	1 (0.1)	0	0
Vena cava thrombosis	1 (0.1)	0	0
Cerebral haemorrhage	1 (0.1)	0	0
Left ventricular dysfunction	0	2 (0.2)	0
Brain natriuretic peptide increased	0	1 (0.1)	0
Cardiac failure chronic	0	1 (0.1)	0
Ejection fraction decreased	0	1 (0.1)	0
Oedema	0	1 (0.1)	0
Cardiac failure	0	0	1 (0.2)
Angina unstable	0	0	1 (0.2)
Cerebral haematoma	0	0	1 (0.2)
Parietal lobe stroke	0	0	1 (0.2)

Number of subjects with events (incidence [%]) MedDRA/J ver.26.1

a) Median (range) of the observation period for safety evaluation: Sipavibart group, 183.0 days (range, 1-335); CIL/TIX, 190.0 days (range, 1-359); Placebo, 58.0 days (range, 1-207)

PMDA's View:

Regarding the cardiovascular events and thromboembolic events observed in Study D7000C00001 main cohort, similar events were observed in subjects with cardiovascular risk factors in the sipavibart group as in the CIL/TIX group. However, no risk exceeding that of CIL/TIX was suggested. Therefore, as is the case of CIL/TIX, the package insert should include precautions on administration to individuals with risk factors. The applicant should continue to collect information on cardiovascular and thromboembolic events after the market launch, and any newly obtained information should be promptly provided to healthcare professionals.

7.R.3.3 Effect of the administration route on safety

The applicant's explanation about the safety of administration routes not examined in Study D7000C00001 main cohort (intravenous administration and intramuscular administration in the gluteal region):

No impact on safety in association with the route of administration has been suggested from the following points.

- It has been confirmed that serum sipavibart concentrations following intravenous administration are higher than those following the intramuscular administration in the anterolateral thigh [see Section 6.R.2]. The safety of intravenous administration of sipavibart at a maximum dose of 1,200 mg was evaluated in Study D7000C00007 and a foreign phase I study (Study D7000C00004). In Study D7000C00007, no adverse events were observed with intravenous administration. However, in Study D7000C00004, an adverse event related to intravenous administration, specifically an "infusion related reaction," was observed. This event was mild and resolved. Infusion reaction is a cytokine-release-related event commonly observed with biological products and is known to occur independently of dose. If observed, appropriate measures such as treatment discontinuation, dose interruption, or slowing of infusion rate can be taken to manage the event, and thus, there are no particular safety concerns.
- It has been confirmed that serum sipavibart concentrations following intramuscular administration in the gluteal region are lower than those following intramuscular administration in the anterolateral thigh [see Section 6.2.1.2]. The safety of intramuscular administration of sipavibart in the gluteal region was assessed. Table 37 shows the incidence of major adverse events by administration site in Study D7000C00001 safety cohort during co-administration of sipavibart and CIL. There was no significant difference in the safety profiles between intramuscular administration in the gluteal region and that in the anterolateral thigh. Although a serious adverse event of hyponatraemia (1 subject) was observed in the sipavibart/CIL group during administration in the gluteal region, a causal relationship to the study drug was ruled out.

Table 37. Incidence of adverse events observed in ≥2 subjects in either group by administration site (safety analysis population)

	Anterolateral thigh		Gluteal region	
	Sipavibart/CIL (N = 21)	Placebo (N = 8)	Sipavibart/CIL (N = 20)	Placebo (N = 8)
Any adverse event	10 (47.6)	7 (87.5)	7 (35.0)	5 (62.5)
Headache	3 (14.3)	1 (12.5)	1 (5.0)	2 (25.0)
Upper respiratory tract infection	3 (14.3)	0	2 (10.0)	0
Injection site pain	2 (9.5)	1 (12.5)	0	1 (12.5)
Viral upper respiratory tract infection	0	3 (37.5)	1 (5.0)	0

Number of subjects with events (incidence [%]) MedDRA/J ver.26.1

PMDA considers that, compared to intramuscular administration in the anterolateral thigh, both intravenous administration and intramuscular administration in the gluteal region present a low safety concern for sipavibart and are acceptable in terms of tolerability.

The appropriateness of PMDA's above conclusion will be discussed at the Expert Discussion.

7.R.4 Clinical positioning

The applicant's explanation about the clinical positioning of sipavibart:

Prevention of COVID-19 is fundamentally based on vaccination, and multiple SARS-CoV-2 vaccines have been approved in Japan. For individuals who are intolerant of vaccination due to hypersensitivity to vaccine components or those who may have inadequate immune response owing to the immunocompromised state, SARS-CoV-2 neutralizing antibodies such as CIL/TIX are used in clinical settings to prevent COVID-19. Particularly, immunocompromised individuals have an increased risk of severe COVID-19 and hospitalization compared to immunocompetent individuals (*Lancet Reg Health Eur.* 2023; 35:100747). The administration of SARS-CoV-2 neutralizing antibodies is thus considered to be of great significance (Guidelines for Diagnosis and Treatment of COVID-19, ver. 10.1 [in Japanese], Ministry of Health, Labour and Welfare, 2024, hereinafter referred to as "Guidelines for Treatment"). However, with the emergence of BQ.1 lineage variants, a substantial decline in neutralization activity against circulating variants has been observed in conventional SARS-CoV-2 neutralizing antibodies (Package Insert of Evusheld Intramuscular Injection Set, etc.).

Sipavibart is a SARS-CoV-2 neutralizing antibody designed as a successor to CIL/TIX, with the expectation of exhibiting high neutralization activity against a broader range of Omicron variants [see Sections 2.1.1 and 3.1.3.1]. Based on the results of the foreign phase I/III clinical study (Study D7000C00001 main cohort), sipavibart is considered to provide an option, as with CIL/TIX, for preventing COVID-19 in individuals who are intolerant of vaccination or who may have inadequate immune response owing to the immunocompromised state. In Japan, CIL/TIX has been approved for the indication of the treatment of disease caused by SARS-CoV-2 infection (COVID-19) as well. Given that the primary antiviral therapy for current COVID-19 cases is oral medication due to disease seriousness and that multiple oral antiviral drugs are available as treatment options (see Guidelines for Treatment), the medical need for sipavibart as a therapeutic agent is considered low. Therefore, development efforts have been focused solely on the prevention of COVID-19.

As of October 2024, sipavibart does not exhibit neutralization activity against KP.3 lineage variants, which are currently predominant [see Section 3.R.2]. Since sipavibart is not expected to have efficacy against these variants, the package insert will include information on its neutralization activity against different variants, along with recommendations for healthcare professionals to consider the latest guidelines in evaluating the appropriateness of its administration.

PMDA's view:

Based on the findings related to the PK, efficacy, and safety of sipavibart [see Sections 6.2.2.2, 7.R.2, and 7.R.3], sipavibart is an option for preventing COVID-19 in individuals who may have inadequate immune response due to immunocompromised state. Sipavibart has demonstrated neutralization activity against broader Omicron variants compared to CIL/TIX [see Section 3.1.3.1], has shown superiority over CIL/TIX and other comparator agents in the foreign phase I/III clinical study (Study D7000C00001 main cohort), and its safety profile does not tend to significantly differ from that of CIL/TIX. Sipavibart is thus considered a potential replacement for CIL/TIX in preventing COVID-19. However, efficacy and safety evaluations have not been conducted in clinical studies for individuals who are intolerant of

vaccination due to hypersensitivity to vaccine components. The appropriateness of including this group of individuals as target population for sipavibart will be further discussed in Section 7.R.5.

Sipavibart does not exhibit neutralization activity against variants containing the F456L mutation [see Section 3.R.2], and there would be little clinical significance of administering sipavibart during a period when the variant in question constitutes the majority of circulating strains. Should variants without the F456L mutation become predominant again in the future, the efficacy of sipavibart may be expected, and there is some significance in making sipavibart available in clinical settings at this stage to ensure rapid access to medication during periods of spread of variants. To ensure proper use of sipavibart, up-to-date information on its neutralization activity against circulating variants should be provided appropriately to healthcare professionals.

The appropriateness of PMDA's conclusion will be further discussed at the Expert Discussion.

7.R.5 Indication

The applicant's explanation about the indication of sipavibart:

- In the foreign phase I/III clinical study (Study D7000C00001 main cohort), the efficacy of sipavibart in preventing COVID-19 was confirmed, and no significant concerns about its tolerability were identified. Based on the above findings and considering the approved indication of CIL/TIX, it was deemed possible to establish the indication of sipavibart as "prevention of disease caused by SARS-CoV-2 infection (COVID-19)."
- Study D7000C00001 main cohort targeted immunocompromised subjects.[15)] The specific patient population was defined with reference to the US. NIH guidelines (Coronavirus Disease 2019 [COVID-19] Treatment Guidelines. National Institutes of Health, 2021) (Table 26). Based on the above, to ensure that sipavibart is administered to eligible patients in accordance with the inclusion criteria of the clinical study, the following statement should be included in Precautions Concerning Indications. Since the efficacy of sipavibart in the prevention of COVID-19 in household members or close contacts of patients with COVID-19 has not been investigated, the pertinent information will be provided separately in the package insert.
- No clinical study has been conducted in individuals who are intolerant of vaccination due to hypersensitivity to vaccine components. Given that whether a patient is immunocompromised does not affect the PK of sipavibart [see Section 6.2.2.1] and that available measures for the prevention of COVID-19 are limited, passive immunity conferred by sipavibart could serve as an option for disease prevention. As of October 2024, CIL/TIX is supplied only to individuals who have immunodeficiency in Japan based on the Administrative Notice of the Ministry of Health, Labour and Welfare Novel Coronavirus Response Headquarters (dated September 1, 2022). There are no academic societies or other organizations in Japan that recommend the administration of CIL/TIX to individuals who are intolerant of vaccination. Hence, there is no record of CIL/TIX administration to such individuals in Japan.

Indication

Prevention of disease caused by SARS-CoV-2 infection (COVID-19)

Precautions Concerning Indications (excerpt)

Sipavibart should be used in individuals who meet 1 or more of the following criteria and who are intolerant of SARS-CoV-2 vaccination or may have inadequate immune response to SARS-CoV-2 vaccination owing to immunocompromised state:

- Patients with malignant solid tumors undergoing active immunosuppressive therapy
- Patients with haematologic malignancies
- Patients who underwent solid organ transplantation or haematopoietic stem cell transplantation within the past 2 years, or patients with chronic graft-versus-host disease
- Patients receiving actively immunosuppressive drugs (medium- or high-dose corticosteroids), alkylating agents, antimetabolites, transplant-related immunosuppressants, cancer chemotherapeutic agents classified as severe immunosuppressants (e.g., Bruton's tyrosine kinase inhibitors], TNF inhibitors, or other immunosuppressive biologics for rheumatic diseases and related conditions
- Patients who have undergone chimeric antigen receptor T-cell therapy
- Patients who received B-cell depletion therapy within the past 1 year
- Patients with moderate to severe primary immunodeficiency (e.g., DiGeorge syndrome)
- Patients with moderate to severe secondary immunodeficiency (e.g., haemodialysis)
- Patients with advanced or untreated HIV infection

PMDA's view:

Based on the considerations in Sections 7.R.1 to 7.R.4, the indication of sipavibart could be established as "prevention of disease caused by SARS-CoV-2 infection (COVID-19)," as with CIL/TIX. The primary target population for sipavibart is expected to be immunocompromised patients. The patient population described under Precautions Concerning Indications, proposed by the applicant, broadly aligns with the population specified for CIL/TIX in the Japanese guidelines (Guidelines for Treatment).[38)]

The number of individuals who are intolerant of SARS-CoV-2 vaccination due to hypersensitivity to vaccine components is very small, making clinical studies in this population challenging, which is understandable. Although most of these "individuals who are intolerant of SARS-CoV-2 vaccination" are expected to have normal immune function, considering that their PK profiles are presumed to be similar to those of immunocompromised patients, a certain level of efficacy of sipavibart in the

38) The administration of neutralizing antibody drugs is considered particularly beneficial for individuals with the following immunocompromised state:
- Patients with primary immunodeficiency syndromes presenting with antibody production failure or combined immunodeficiency.
- Patients who have received B-cell depletion therapy (e.g., rituximab) within the past 1 year.
- Patients receiving Bruton's tyrosine kinase inhibitors.
- Chimeric antigen receptor T-cell recipients.
- Recipients of haematopoietic cell transplantation who have chronic graft-versus-host disease or are taking immunosuppressive drugs for other indications
- Patients with haematologic malignancies undergoing active treatment.
- Lung transplant recipients.
- Patients who underwent solid organ transplantation (other than lung transplantation) within the past 1 year.
- Solid organ transplant recipients who have recently received T-cell or B-cell depletion therapy for acute rejection.
- Treatment-naïve HIV patients with a CD4 T-lymphocyte count of <50 cells/μL.

prevention of COVID-19 is expected. Therefore, as with CIL/TIX, the inclusion of "individuals who are intolerant of vaccination" in the eligible population for sipavibart is considered acceptable. If sipavibart is administered to this population in the post-marketing setting, information on its efficacy and safety in clinical practice in Japan should be collected.

The appropriateness of this conclusion by PMDA will be discussed at the Expert Discussion.

7.R.6 Dosage and administration

PMDA's view on the dosage and administration of sipavibart:
Based on the results of the evaluations on the PK, efficacy, and safety of sipavibart [see Sections 6.R.2, 7.R.2, and 7.R.3], the prevention of COVID-19 was confirmed in the foreign phase I/III study (Study D7000C00001 main cohort), and no particular concerns about tolerability were observed. Furthermore, the study did not suggest that the PK, efficacy, or safety of sipavibart would be significantly affected by age. Therefore, a single dose of 300 mg is appropriate for adults and pediatric individuals aged ≥12 years weighing ≥40 kg. Age (≥65 years) is considered a risk factor for cardiovascular and thromboembolic events, and appropriate precautions regarding this risk should be included in the package insert.

Regarding the route and site of administration, based on the protocol of Study D7000C00001 main cohort, intramuscular injection in the anterolateral thigh was deemed a recommended route of administration. For individuals in whom intramuscular injection is difficult, intravenous administration should be specified as an alternative route, based on the following observations: (a) The safety of sipavibart at doses up to 1,200 mg per dose was confirmed in the foreign phase I study (Study D7000C00004); (b) the infusion reactions observed in clinical studies were considered manageable; and (c) exposures comparable to or exceeding those achieved with intramuscular injection in the anterolateral thigh were expected [see Section 6.R.2]. On the other hand, intramuscular injection in the gluteal region should not be specified, as (1) it may lead to reduced drug exposure [see Section 6.R.2] and (2) efficacy at this administration route and exposure has not been established.

Based on the above, PMDA considers that the following modification should be made to the proposed dosage and administration for sipavibart. The final decision will be made based on the discussion at the Expert Discussion.

The usual dosage for adults and children aged ≥12 years weighing ≥40 kg is 300 mg of sipavibart (genetical recombination) administered by intramuscular injection <u>in the anterolateral thigh</u> ~~or intravenous injection~~. <u>If intramuscular injection is difficult or inappropriate, intravenous administration should be selected.</u> (The underline denotes additions, and strikethrough denotes deletion.)

PMDA requested the applicant to provide an explanation about the setting of multiple dosing for sipavibart, considering that the package insert of the Evusheld includes information on multiple doses.

The applicant's explanation about the dosage regimen for multiple doses of sipavibart:
In Study D7000C00001 main cohort, the dosing interval was once every 6 months to ensure that serum concentrations of sipavibart remained at levels sufficient to inhibit the cellular entry of SARS-CoV-2 variants[21)] such as BA.1 and BQ.1 by 80% [see Section 6.R.2]. The present application is based on the interim analysis of Study D7000C00001 main cohort, conducted when the median observation period for the efficacy analysis population exceeded 181 days post-dose. The final analysis results of this study, including data on the efficacy and safety of sipavibart at 6 months after the second dose, are expected to be obtained [redacted] 20[redacted]. The appropriateness of dosing interval of sipavibart will be determined based on the final analysis results.

PMDA's view on the multiple doses of sipavibart:
At present, interim analysis results from Study D7000C00001 main cohort are available, which suggest that multiple doses can maintain serum sipavibart concentrations [see Section 6.2.2.2]. Although information on the efficacy and safety of sipavibart after at least 2 doses is limited, no significant difference in efficacy and safety has been suggested between the first and the second dose [see Sections 7.R.2.1 and 7.R.3.1]. Considering the clinical positioning of sipavibart [see Section 7.R.4], continuous availability of sipavibart is desirable in the event of spread of variants susceptible to sipavibart. While a prompt re-evaluation of the appropriate dosing interval is necessary once the final analysis results of Study D7000C00001 main cohort become available, it is currently possible to administer sipavibart repeatedly at 6-month intervals.

The appropriateness of PMDA's judgment will be discussed at the Expert Discussion.

7.R.7 Post-marketing investigations

The applicant's explanation about the post-marketing investigations of sipavibart:
A post-marketing database survey will be conducted to confirm the efficacy of sipavibart in clinical practice in Japan. At present, a cohort study is planned with a study period of 7 years (target number of patients, ≥1,500 patients who received sipavibart and ≥40,000 individuals as the control [those not receiving]). The study will be conducted to evaluate the efficacy of sipavibart over 6 months post-dose in patients treated with sipavibart based on the diagnosis of COVID-19. Since the use of sipavibart is likely to be influenced by the prevalence of COVID-19 and the neutralization activity of sipavibart against circulating strains, further details of the study plan will be examined based on the latest information on future epidemic trends.

Sipavibart is structurally similar to CIL and TIX, except for the antigen-binding site, and it is a specific monoclonal antibody targeting an adventitious virus, with no observed cross-reactivity with human tissues [see Section 5.7.1]. In the foreign phase I/III study (Study D7000C00001 main cohort), the safety profile of sipavibart was similar to that of CIL/TIX [see Section 7.R.3]. Based on the above, routine pharmacovigilance activities should be conducted and additional information focusing on specific adverse drug reactions should be collected, as necessary. While cardiovascular and thromboembolic events are not considered identified risks of sipavibart, additional pharmacovigilance activities will include an assessment of such risks in the post-marketing database survey, using individuals not receiving sipavibart as the control.

PMDA's view:
Since the efficacy and safety of sipavibart have not been evaluated in Japan, its efficacy in the Japanese clinical setting should be appropriately confirmed after marketing and the obtained information should be promptly provided to healthcare professionals. In principle, the efficacy of sipavibart should be confirmed through a head-to-head comparison. The applicant's approach is understandable, but the volume of sipavibart used will be affected by future epidemic trends. The optimal evaluation method should continue to be examined after marketing.

The neutralization activity data of sipavibart against different SARS-CoV-2 variants constitute important information on its efficacy, and the latest information should continue to be provided to healthcare professionals after marketing [see Section 3.R.2].

There are no particular issues with the applicant's proposed approach for the post-marketing investigations on the safety of sipavibart. The plan for the post-marketing database survey on cardiovascular and thromboembolic events should also be further examined alongside the efficacy evaluation plan of sipavibart.

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

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

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

The new drug application data were subjected to a document-based 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.

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

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.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that sipavibart has efficacy in the prevention of disease caused by SARS-CoV-2 infection (COVID-19), and that sipavibart has acceptable safety in view of its benefits. Sipavibart has been developed as a successor to Evusheld Intramuscular Injection Set and offers an option for the prevention of COVID-19 in individuals who are intolerant of vaccination or may have inadequate immune response owing to immunocompromised state. As of October 2024, sipavibart has shown a significant decrease in neutralization activity against the predominant circulating

variants, and its efficacy against the currently dominant variants is not expected. However, should variants susceptible to sipavibart become predominant again in the future, the efficacy of sipavibart is expected. There is some significance in making sipavibart available in medical settings at this stage to ensure rapid access to medication during periods of spread of SARS-CoV-2 variants. Furthermore, the neutralization activity of sipavibart against circulating variants and its efficacy in the Japanese clinical setting should be appropriately examined after the market launch, and any information should be promptly provided to healthcare professionals when it becomes available.

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

10. Others

10.1 Serious adverse events observed in Study D7000C00001 main cohort

Table 38. Serious adverse events observed after the first or second dose of the study drug (safety analysis population)[a)]

After the first dose of the study drug (until the day before the second dose)[b)]	
Sipavibart (N = 1,671)	173 subjects (Pneumonia in 19 subjects; acute myocardial infarction in 9 subjects; cardiac failure acute in 8 subjects; COVID-19 in 7 subjects; sepsis, septic shock, atrial fibrillation, pulmonary embolism in 6 subjects each; influenza, urinary tract infection, hypervolaemia, syncope, cardiac failure congestive, and acute respiratory failure in 5 subjects each; hypotension, and acute kidney injury in 4 subjects each; urosepsis, febrile neutropenia, myocardial infarction, hypertensive emergency, dyspnoea, pulmonary oedema, colitis, cholecystitis acute, and pyrexia in 3 subjects each; COVID-19 pneumonia, cellulitis, Clostridium difficile colitis, Escherichia urinary tract infection, peritonitis, pyelonephritis, streptococcal sepsis, malignant neoplasm progression, anaemia, hyperkalaemia, cerebrovascular accident, multiple sclerosis relapse, seizure, acute coronary syndrome, cardiac arrest, coronary artery disease, ventricular tachycardia, hypertension, hypertensive crisis, acute pulmonary oedema, chronic obstructive pulmonary disease, vomiting, diabetic foot, lupus nephritis, arteriovenous fistula site complication, and post procedural haemorrhage in 2 subjects each; appendicitis, appendicitis perforated, bacterial pyelonephritis, Campylobacter gastroenteritis, Campylobacter infection, cardiac valve vegetation, colonic abscess, device related infection, diarrhoea infectious, disseminated cryptococcosis, diverticulitis, diverticulitis intestinal perforated, encephalomyelitis, Epstein-Barr virus infection, Escherichia sepsis, gastroenteritis, groin abscess, localised infection, osteomyelitis, pneumococcal sepsis, Pneumocystis jirovecii pneumonia, pneumonia bacterial, pneumonia mycoplasmal, pneumonia staphylococcal, pyomyositis, respiratory syncytial virus infection, respiratory tract infection bacterial, respiratory tract infection viral, staphylococcal bacteraemia, staphylococcal sepsis, Stenotrophomonas maltophilia pneumonia, urinary tract infection fungal, urinary tract infection pseudomonal, diffuse large B-cell lymphoma, high-grade B-cell lymphoma, non-small cell lung cancer, papillary thyroid cancer, plasma cell myeloma, rectal cancer stage IV, renal cell carcinoma, skin squamous cell carcinoma metastatic, squamous cell carcinoma of skin, uterine leiomyoma, blood loss anaemia, neutropenia, anaphylactic reaction, infusion related hypersensitivity reaction, kidney transplant rejection, dehydration, alcohol withdrawal syndrome, ataxia, brain stem haemorrhage, brain stem infarction, carotid artery disease, cerebral haemorrhage, cerebral infarction, encephalopathy, facial paralysis, focal dyscognitive seizures, haemorrhage intracranial, idiopathic intracranial hypertension, intracranial aneurysm, multiple sclerosis, glaucoma, acute left ventricular failure, atrial flutter, atrioventricular block second degree, bradycardia, cardiogenic shock, left ventricular failure, supraventricular tachycardia, aortitis, deep vein thrombosis, hypertensive urgency, jugular vein thrombosis, orthostatic hypotension, peripheral venous disease, Raynaud's phenomenon, haemoptysis, hypoxia, pleural effusion, pulmonary fibrosis, pulmonary hypertension, respiratory failure, abdominal adhesions, abdominal pain, abdominal pain upper, ascites, diarrhoea, faecaloma, femoral hernia, gastritis, gastrointestinal haemorrhage, impaired gastric emptying, inguinal hernia, large intestine perforation, nausea, oral macule, pancreatitis acute, retroperitoneal haematoma, volvulus of small bowel, cholecystitis, cholelithiasis, drug-induced liver injury, hepatic cirrhosis, jaundice cholestatic, rhabdomyolysis, systemic lupus erythematosus, cystitis haemorrhagic, end stage renal disease, renal infarct, subcapsular renal haematoma, cervical dysplasia, ovarian cyst, pelvic pain, prostatitis, asthenia, chest pain, death, non-cardiac chest pain, systemic inflammatory response syndrome, anticoagulation drug level above therapeutic, international normalised ratio increased, troponin increased, white blood cell count decreased, acetabulum fracture, ankle fracture, arteriovenous fistula thrombosis, arteriovenous graft thrombosis, complications of transplanted kidney, femoral neck fracture, femur fracture, hip fracture, pelvic fracture, post procedural bile leak, post procedural complication, radius fracture, rib fracture, spleen contusion, subcutaneous haematoma, subdural haemorrhage, tendon injury, thoracic vertebral fracture, tibia fracture, and vascular access site thrombosis in 1 subject each [some subjects had multiple events])

Table 38. Serious adverse events observed after the first or second dose of the study drug (safety analysis population) (continued)

Control drug	CIL/TIX (N = 1,102)	122 subjects (Pneumonia in 8 subjects; hypervolaemia, and hypertensive emergency in 6 subjects each; acute respiratory failure in 5 subjects; COVID-19, urinary tract infection, hyperkalaemia, and acute kidney injury in 4 subjects each; COVID-19 pneumonia, cellulitis, diverticulitis, septic shock, anaemia, mental status changes, acute myocardial infarction, atrial fibrillation, cardiac failure acute, cardiac failure congestive, and pulmonary oedema in 3 subjects each; neutropenic sepsis, sepsis, urosepsis, viral sepsis, hypoglycaemia, acute left ventricular failure, angina pectoris, hypertensive urgency, systemic lupus erythematosus, non-cardiac chest pain, and pyrexia in 2 subjects each; abscess limb, appendicitis, Aspergillus infection, bacteraemia, bronchitis bacterial, bronchitis haemophilus, catheter site cellulitis, colonic abscess, conjunctivitis, cystitis escherichia, emphysematous cystitis, endocarditis, enterococcal sepsis, erysipelas, Escherichia bacteraemia, Escherichia pyelonephritis, Escherichia sepsis, gastroenteritis, gastroenteritis viral, herpes zoster, infective exacerbation of chronic obstructive airways disease, liver abscess, lower respiratory tract infection, norovirus infection, otitis media, peritonitis, Pneumocystis jirovecii pneumonia, pneumonia influenzal, pneumonia viral, postoperative wound infection, staphylococcal bacteraemia, staphylococcal infection, Stenotrophomonas infection, brain neoplasm, central nervous system lymphoma, cholangiocarcinoma, hepatocellular carcinoma, lung adenocarcinoma, lymphoma, renal neoplasm, bicytopenia, febrile neutropenia, nephrogenic anaemia, neutropenia, anti-neutrophil cytoplasmic antibody positive vasculitis, drug hypersensitivity, kidney transplant rejection, decreased appetite, dehydration, gout, hyperglycaemia, bipolar disorder, central nervous system lupus, diabetic neuropathy, epilepsy, metabolic encephalopathy, myasthenia gravis crisis, nerve compression, neurotoxicity, seizure, syncope, transient ischaemic attack, diabetic retinal oedema, retinal vein occlusion, atrioventricular block second degree, cardiac arrest, coronary artery disease, left ventricular dysfunction, tachycardia, aortic dissection, brachiocephalic vein thrombosis, hypertension, hypertensive crisis, orthostatic hypotension, interstitial lung disease, organising pneumonia, pleural effusion, pulmonary hypertension, respiratory failure, abdominal wall cyst, colitis ulcerative, gastrointestinal haemorrhage, gastrointestinal pain, gastrointestinal polyp haemorrhage, impaired gastric emptying, large intestinal ulcer perforation, oesophagitis, stomatitis, upper gastrointestinal haemorrhage, cholecystitis chronic, hepatitis acute, jaundice cholestatic, erythema nodosum, pruritus, arthralgia, arthritis, muscular weakness, osteoarthritis, osteonecrosis, rheumatoid arthritis, spinal stenosis, azotaemia, bladder perforation, lupus nephritis, renal artery stenosis, renal failure, ureterolithiasis, urinary retention, adhesion, international normalised ratio increased, troponin increased, anaemia postoperative, arteriovenous fistula occlusion, arteriovenous fistula site complication, cystitis radiation, fall, fibula fracture, foot fracture, gastrointestinal stoma complication, graft haemorrhage, humerus fracture, hyphaema, lower limb fracture, postoperative respiratory failure, renal transplant failure, and device malfunction in 1 subjects each [some subjects had multiple events])
	Placebo (N = 561)	55 subjects (Pneumonia in 3 subjects; COVID-19 pneumonia, septic shock, acute myocardial infarction, atrial fibrillation, cardiac failure congestive, left ventricular failure, deep vein thrombosis, and hypertensive urgency in 2 subjects each; arthritis infective, bronchitis, COVID-19, cystitis, diverticulitis, fungal infection, hepatitis E, kidney infection, necrotising soft tissue infection, peritonitis, Pneumocystis jirovecii pneumonia, pneumonia bacterial, pneumonia pneumococcal, postoperative wound infection, progressive multifocal leukoencephalopathy, respiratory syncytial virus bronchitis, respiratory syncytial virus infection, sepsis, staphylococcal infection, superinfection bacterial, urinary tract infection, urinary tract infection bacterial, adenocarcinoma gastric, lymphoma, plasma cell myeloma, prostate cancer, tumour ulceration, anaemia, immune-mediated pancytopenia, nephrogenic anaemia, hypersensitivity, thyroid disorder, diabetic ketoacidosis, hyperkalaemia, altered state of consciousness, headache, myasthenia gravis, angina unstable, arteriosclerosis coronary artery, cardiac failure, cardiac failure acute, supraventricular tachycardia, dialysis hypotension, hypotension, acute respiratory failure, asthma, chronic obstructive pulmonary disease, interstitial lung disease, organising pneumonia, abdominal pain, diverticulum, duodenal ulcer haemorrhage, gastritis haemorrhagic, oedematous pancreatitis, oesophagitis, autoimmune hepatitis, cholecystitis acute, hepatitis toxic, spinal osteoarthritis, acute kidney injury, chronic kidney disease, death, injection site necrosis, arteriovenous fistula thrombosis, burns second degree, upper limb fracture, and toe amputation in 1 subject each [some subjects had multiple events])

Table 38. Serious adverse events observed after the first or second dose of the study drug (safety analysis population) (continued)

After the second dose of the study drug[c]		
Sipavibart (N = 886)		45 subjects (Hypervolaemia in 5 subjects; COVID-19, pneumonia, septic shock, cardiac failure congestive, and pulmonary oedema in 3 subjects each; sepsis, staphylococcal bacteraemia, anaemia, hyperkalaemia, cerebrovascular accident, acute myocardial infarction, atrial fibrillation, chronic obstructive pulmonary disease, and acute kidney injury in 2 subjects each; atypical pneumonia, bacterial pyelonephritis, osteomyelitis, pilonidal disease, pneumonia bacterial, pneumonia pneumococcal, pyelonephritis acute, septic pulmonary embolism, urinary tract infection, B-cell lymphoma, diffuse large B-cell lymphoma, prostate cancer, prostate cancer metastatic, electrolyte imbalance, hypoglycaemia, mental status changes, cerebral microinfarction, seizure, trigeminal neuralgia, acute right ventricular failure, cardiac arrest, cardio-respiratory arrest, left ventricular failure, hypertensive crisis, hypertensive emergency, hypertensive urgency, acute respiratory failure, bronchiectasis, dyspnoea, ascites, inguinal hernia, upper gastrointestinal haemorrhage, back pain, intervertebral disc protrusion, osteoarthritis, psoriatic arthropathy, rhabdomyolysis, weight decreased, limb injury, and unknown in 1 subject each [some subjects had multiple events])
Control drug	CIL/TIX -placebo (N = 785)	38 subjects (Hyperkalaemia and cardiac failure congestive in 5 subjects each; sepsis and acute myocardial infarction in 4 subjects each; dyspnoea in 3 subjects; pneumonia, hypervolaemia, acute respiratory failure, and small intestinal obstruction in 2 subjects each; appendicitis, arteriovenous fistula site infection, COVID-19, emphysematous pyelonephritis, gastroenteritis, influenza, pulmonary sepsis, rhinovirus infection, urinary tract infection, lung adenocarcinoma, tonsil cancer, hyperglycaemia, hypoglycaemia, atrial fibrillation, atrial flutter, atrioventricular block complete, bradycardia, left ventricular failure, myocardial infarction, myocardial ischaemia, pericarditis, supraventricular tachycardia, hypertensive emergency, hypertensive urgency, peripheral ischaemia, acute pulmonary oedema, lupus pleurisy, pleural effusion, pulmonary hypertension, pulmonary oedema, haematemesis, intestinal obstruction, lower gastrointestinal haemorrhage, back pain, lumbar spinal stenosis, acute kidney injury, end stage renal disease, nephrotic syndrome, chest pain, oedema, pyrexia, overdose, spinal compression fracture, and vascular graft occlusion in 1 subject each [some subjects had multiple events])
	Placebo -placebo (N = 94)	0 subject

a) Observation period for safety assessment (median [range]): 183.0 (1-335) days for sipavibart, 190.0 (1-359) days for CIL/TIX, and 58.0 (1-207) days for placebo

b) For subjects who did not receive a second dose of the study drug, adverse events observed up to Day 188 are shown.

c) Observation period after the second dose of the study drug (median [range]): 65.0 (1-180) days for sipavibart, 68.0 (2-180) days for CIL/TIX-placebo, and 5.0 (1-24) days for placebo-placebo

Review Report (2)

November 22, 2024

Product Submitted for Approval

Brand Name	Kavigale Injection Solution 300 mg
Non-proprietary Name	Sipavibart (Genetical Recombination)
Applicant	AstraZeneca K.K.
Date of Application	July 26, 2024

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 described in the Review Report (1) (Sections "7.R.1 Development strategy and clinical data package," "7.R.2 Efficacy," "7.R.3 Safety," "7.R.4 Clinical positioning," "7.R.5 Indication," "7.R.6 Dosage and administration," and "7.R.7 Post-marketing investigations"). The results of the Japanese phase I study (Study D7000C00007) and other studies demonstrated that there were no ethnic differences in the pharmacokinetics. Sipavibart is a specific neutralizing antibody against adventitious viral antigens and does not exhibit cross-reactivity with human tissues. Additionally, sipavibart is a human IgG1 monoclonal antibody with a structure similar to the precedent product CIL/TIX, except for its antigen-binding site, and there have been no reports suggesting ethnic differences in the efficacy and safety of CIL/TIX. Given these points, it was deemed possible to evaluate the efficacy and safety of sipavibart in Japanese subjects based on foreign clinical study results. However, the efficacy and safety of sipavibart in Japanese patients need to be appropriately confirmed in the post-marketing setting.

PMDA conducted additional evaluations on the following points and took the necessary actions.

1.1 Changes to the design of the foreign phase I/III study

All modifications to the design of the foreign phase I/III study (Study D7000C00001 main cohort) were conducted in a blinded manner, and PMDA concluded that the impact of the modifications on study results was limited. PMDA's conclusion was supported by expert advisors. At the Expert Discussion,

expert advisors commented that efficacy data obtained before and after the change of the control drug (CIL/TIX or placebo) should also be reviewed. PMDA requested the applicant to provide such information.

The applicant submitted the analysis results of the primary efficacy endpoint of Study D7000C00001 main cohort, which was the relative risk reduction rate[29)] of COVID-19[28)] caused by (1) all SARS-CoV-2 variants and (2) the target variants (SARS-CoV-2 without F456L mutation), both before and after the change of the control drug, in the efficacy analysis population (Table 39). The applicant explained that, in both cases, the incidence of events was lower in the sipavibart group than in the control drug group.

Table 39. Relative risk reduction rate of COVID-19 before and after the change of the control drug (efficacy analysis population)

Causative virus	Administration period[a)]	Incidence of event (%)			Relative risk reduction rate[d)] [95% CI] (%)
		Sipavibart[b, c)]	Control drug		
			CIL/TIX	Placebo	
All SARS-CoV-2 variants	CIL/TIX administration period	7.5 (91/1,218)	10.8 (117/1,082)		32.3 [10.8, 48.6]
	Placebo administration period	7.2 (31/431)		11.1 (61/549)	35.2 [-0.4, 58.2]
	Entire period	7.4 (122/1,649)	10.9 (178/1,631)		34.9 [17.8, 48.4]
Target variants (SARS-CoV-2 without F456L mutation)	CIL/TIX administration period	3.2 (39/1,218)	5.1 (55/1,082)		38.1 [6.6, 59.0]
	Placebo administration period	3.5 (54/431)		6.4 (35/549)	45.6 [0.0, 70.4]
	Entire period	3.3 (54/1,649)	5.5 (90/1,631)		42.9 [19.9, 59.3]

Incidence (%) (number of subjects with events/number of subjects evaluated)

a) Range of first dose dates of the study drug (CIL/TIX administration period: [redacted], 20[redacted] to [redacted], 20[redacted]; placebo administration period: [redacted], 20[redacted] to [redacted], 20[redacted])

b) Subjects who received sipavibart as the first dose during each administration period

c) For the analysis during the CIL/TIX administration period, data were used from the subject population allocated to the sipavibart group before the initiation of randomization between the sipavibart and control drug (placebo) groups; for the analysis of the placebo administration period, data were used from the subject population allocated to the sipavibart group after the initiation of randomization between the sipavibart and control drug (placebo) groups.

d) A Poisson regression model with robust variance, using treatment group (sipavibart vs. control), SARS-CoV-2 vaccination within 6 months, history of SARS-CoV-2 infection, and administration of CIL/TIX within 12 months as covariates, and the logarithm of the observation period for each case included as an offset term.

PMDA accepted the above explanation and confirmed that the efficacy of sipavibart could be evaluated primarily based on the results of Study D7000C00001 main cohort.

1.2 Indication and target patient population

At the Expert Discussion, PMDA's conclusion on indication, as described in Section "7.R.5 Indication" in the Review Report (1), was supported by the expert advisors. Additionally, the following comments were raised by the expert advisors regarding the target patient population for sipavibart:

- In Study D7000C00001 main cohort, a tendency toward increased incidence of events was observed in patients with "malignant solid tumors receiving active immunosuppressive therapy" in the sipavibart group [see "Section 7.R.2.3 Efficacy by underlying disease" in the Review Report (1)]. Given that the incidence of events was consistently lower in the sipavibart group across subjects with other underlying diseases, this was deemed an incidental finding. There is no need to exclude specific patient populations included in Study D7000C00001 main cohort from eligible populations for sipavibart administration also from a medical perspective.
- The target population for sipavibart is individuals aged ≥12 years. However, in pediatric practice, there are currently no drugs available for preventing COVID-19 in younger pediatric patients with

primary immunodeficiency and, sometimes, treatment has been challenging after disease onset. Thus, expanding the target patient population is desirable.

- For individuals who are intolerant of SARS-CoV-2 vaccination due to hypersensitivity to vaccine components, it is acceptable from a regulatory perspective to include them as eligible for sipavibart administration, as with CIL/TIX.

Taking account of comments raised in the Expert Discussion, PMDA instructed the applicant to take the following actions: (1) To include information on the subjects enrolled in clinical studies in the "Clinical Studies" section of the package insert to ensure that individuals who are eligible for treatment with CIL/TIX are also allowed to receive treatment with sipavibart and that such individuals are appropriately identified in healthcare settings; and (2) to modify the statement of "Precautions Concerning Indications" of sipavibart as shown below. The applicant has responded appropriately.

Indication
Prevention of disease caused by SARS-CoV-2 infection (COVID-19)

Precautions Concerning Indication
5.1 The target population for sipavibart should be selected based on the clinical study population and should include individuals who are intolerant of SARS-CoV-2 vaccination or may have inadequate immune response to SARS-CoV-2 vaccination owing to the immunocompromised state.
5.2 Sipavibart should be used in individuals who are not close contacts (e.g., household members or cohabitants) of patients with COVID-19. Its efficacy in close contacts of patients with COVID-19 has not been established.
5.3 Sipavibart is not expected to have efficacy against SARS-CoV-2 variants that contain the F456L mutation in the S protein, as it shows a significant reduction in neutralization activity. Furthermore, if reduced neutralization activity is observed with other mutations besides F456L, the efficacy of sipavibart may also be compromised. The appropriateness of sipavibart administration should be considered based on the latest information on circulating SARS-CoV-2 variants.
5.4 The therapeutic effect of sipavibart in patients with active COVID-19 has not been established.

The applicant's explanation about the development of sipavibart for pediatric patients aged <12 years:
In Europe, clinical development is under consideration for immunocompromised pediatric patients including from newborns soon after birth to adolescents under 18 years of age. In Japan, the number of pediatric patients aged <12 years with immunocompromised state, including primary immunodeficiency, is estimated to be fewer than 2,000 patients per year. Considering that the number of actual sipavibart recipients is expected to be limited, the applicant currently has no plans to expand the indication for patients aged <12 years.

PMDA's view:
There is no clinical experience with sipavibart in pediatric patients aged <12 years. In addition, the precedent product CIL/TIX has been approved for use in individuals aged ≥12 years and ≥40 kg both in Japan and overseas. Therefore, pediatric patients aged <12 years should not be included in the target population in the package insert at this time. Taking account of the global development status and the

medical needs in Japan for sipavibart, if it is deemed appropriate to extend the indication to pediatric patients aged <12 years in Japan, the applicant should initiate a pediatric development program in Japan promptly.

1.3 Risk management plan (draft)

In view of the evaluation in the Review Report (1) and comments from the expert advisers at the Expert Discussion, PMDA has concluded that the risk management plan for sipavibart should be modified to include the safety and efficacy specifications presented in Table 40, and that the applicant should conduct additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities presented in Table 41. PMDA instructed the applicant to conduct post-marketing investigations evaluated for these purposes.

Table 40. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Serious hypersensitivity including anaphylaxis • Infusion reaction	• Cardiovascular and thromboembolic events	• Safety of multiple doses of sipavibart
Efficacy specification		
• Efficacy of sipavibart in clinical practice in Japan • Efficacy of multiple doses of sipavibart		

Table 41. Summary of additional pharmacovigilance activities, efficacy survey and studies, and 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 • Post-marketing database survey (cardiovascular and thromboembolic events • Foreign phase I/III studies (Study D7000C00001 main cohort)	• Post-marketing database survey • Foreign phase I/III studies (Study D7000C00001 main cohort)	• Disseminate data gathered during early post-marketing phase vigilance

The applicant has explained that the post-marketing database survey (Table 42) will be conducted for each survey objective to confirm the safety and efficacy of sipavibart in clinical practice.

Table 42. Outline of post-marketing database survey (draft) [a)]

Objective	Database survey 1: To evaluate the efficacy of sipavibart in the prevention of COVID-19 in clinical practice in Japan Database survey 2: To assess the incidence of cardiovascular and thromboembolic events associated with sipavibart
Survey method	Cohort study (retrospective observational study)
Population	Subjects who may have inadequate immune response to SARS-CoV-2 vaccination owing to the immunocompromised state or who are intolerant of SARS-CoV-2 vaccination [Exposure group] Subjects receiving sipavibart [Control drug group] Subjects not receiving sipavibart (matched with the exposure group using propensity scores to adjust for differences in patient characteristics)
Survey period	7 years following the approval of sipavibart
Planned sample size	Exposure group, ≥1,500 subjects; Control drug group, ≥40,000 subjects
Definition of outcome	Database survey 1: Diagnosis of COVID-19 during the 6-month period following sipavibart administration Database survey 2: To be defined using a combination of ICD-10 codes, medical procedures, and medications

a) Two surveys are planned according to their respective objectives (details of the survey design remain under discussion).

2. Overall Evaluation

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

Indication

Prevention of disease caused by SARS-CoV-2 infection (COVID-19)

(No change from the proposed text)

Dosage and Administration

The usual dosage for adults and pediatric individuals aged ≥12 years weighing ≥40 kg is 300 mg of sipavibart (genetical recombination) administered by intramuscular injection in the anterolateral thigh ~~or intravenous injection~~. If intramuscular injection is difficult or inappropriate, intravenous administration should be selected.

(The underline denotes additions, and strikethrough denotes deletion from the proposed text.)

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. 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.

Appendix

List of Abbreviations

A/G ratio	Albumin/globulin ratio
ACE2	Angiotensin-converting enzyme 2
ADA	Antidrug antibody
AUC	Area under serum concentration-time curve
AUC_{0-X}	Area under serum concentration-time curve up to X
AUC_{inf}	Area under serum concentration-time curve up to infinity
AUC_{last}	Area under serum concentration-time curve up to last observed concentration
BMI	Body mass index
C1q	Complement component 1q
CE-SDS	Capillary electrophoresis - sodium dodecyl sulfate
CHO	Chinese hamster ovary
cIEF	Capillary isoelectric focusing
CIL	Cilgavimab
CIL/TIX	Cilgavimab/Tixagevimab
CL	Clearance
CL/F	Extravascular clearance
C_{max}	Maximum serum concentration
COVID-19	Coronavirus disease 2019
CQA	Critical quality attribute
CTD	Common Technical Document
DNA	Deoxyribonucleic acid
EC_{50}	50% effective concentration
eGFP	Enhanced green fluorescent protein
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOPCB	End-of-production cell bank
ETFE	Ethylene tetra fluoro ethylene
Evusheld	Evusheld Intramuscular Injection Set
Fab	Antigen binding fragment
Fc	Fragment crystallizable
FcRn	Neonatal Fc receptor
FcγR	Fc gamma receptor
GISAID	Global initiative on sharing avian influenza data
HCP	Host cell protein
IC_{50}	50% inhibitory concentration
ICH	International Council for Harmonisation
ICH Q5A(R1)	“Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin” (PMSB/ELD Notification No. 329, dated February 22, 2000)
ICH Q5B	Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products (PMSB/ELD Notification No. 3, dated January 6, 1998)
ICH Q5D	“Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products” (PMSB/ELD Notification No. 873, dated July 14, 2000)
IFNγ	Interferon gamma
IgG	Immunoglobulin G
*K*a	Absorption rate constant
Kavigale	Kavigale Injection Solution 300 mg
K_D	Equilibrium dissociation constant
LC-MS/MS	Liquid chromatography with tandem mass spectrometric detection
LIVCA	Limit-of-in-vitro-cell-age

MCB	Master cell bank
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MIP-1β	Macrophage Inflammatory Protein-1 β
NIH	National Institutes of Health
PFU	Plaque-forming unit
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
PT	Preferred term
RBD	Receptor binding domain
RH	Relative humidity
RT-PCR	Reverse transcription polymerase chain reaction
S protein	Spike protein
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SEC	Size Exclusion Chromatography
Sipavibart	Sipavibart (genetical recombination)
SMQ	Standardized MedDRA query
SPR	Surface Plasmon Resonance
$t_{1/2}$	Estimate of the terminal elimination half-life
TIX	Tixagevimab
t_{max}	Time to maximum concentration
TMPRSS2	Transmembrane protease serine 2
V_{ss}	Volume of distribution at steady state
V_z/F	Apparent volume of distribution at the elimination phase
WCB	Working cell bank
WHO	World Health Organization