Report on the Deliberation Results

September 27, 2021
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Xevudy for Intravenous Infusion 500 mg
Non-proprietary Name	Sotrovimab (Genetical Recombination) (JAN*)
Applicant	GlaxoSmithKline K.K.
Date of Application	September 6, 2021

Results of Deliberation

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

In its meeting held on September 27, 2021, the Second Committee on New Drugs discussed whether the product was qualified for Special Approval for Emergency under Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. The Committee concluded that the product may be approved with the conditions listed below, and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

**Japanese Accepted Name (modified INN)*

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to request that physicians administer the product only to patients considered eligible for treatment with the product who, or whose legally acceptable representatives, have been provided with the efficacy and safety information of the product in written form, and have provided written informed consent before the treatment.
3. Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act, the grace period for data submission is 4 months after the approval. If newly submitted data, etc., necessitate a change in the approved product information, the change may be ordered in accordance with the provision in Article 74-2, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.

Report on Special Approval for Emergency

September 22, 2021
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	Xevudy for Intravenous Infusion 500 mg
Non-proprietary name	Sotrovimab (Genetical Recombination)
Applicant	GlaxoSmithKline K.K.
Date of Application	September 6, 2021
Dosage Form/Strength	Injection: each vial (8 mL) contains 500 mg of Sotrovimab (Genetical Recombination).
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Sotrovimab is a recombinant anti-SARS-CoV-2 spike protein monoclonal antibody derived from human IgG1. In the H-chain, the amino acid residues at positions 438 and 444 are substituted by Leu and Ser, respectively. Sotrovimab is produced in Chinese hamster ovary cells. Sotrovimab is a glycoprotein (molecular weight: ca. 149,000) composed of 2 H-chains (γ1-chains) consisting of 457 amino acid residues each and 2 L-chains (λ-chains) consisting of 214 amino acid residues each.

Structure

Amino acid sequence:

L-chain

EIVLTQSPGT LSLSPGERAT LSCRASQTVS STSLAWYQQK PGQAPRLLIY

GASSRATGIP DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QHDTSLTFGG

GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV

DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG

LSSPVTKSFN RGEC

H-chain

QVQLVQSGAE VKKPGASVKV SCKASGYPFT SYGISWVRQA PGQGLEWMGW

ISTYQGNTNY AQKFQGRVTM TTDTSTTTGY MELRRLRSDD TAVYYCARDY

TRGAWFGESL IGGFDNWGQG TLVTVSSAST KGPSVFPLAP SSKSTSGGTA

ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS

SSLGTQTYIC NVNHKPSNTK VDKKVEPKSC DKTHTCPPCP APELLGGPSV

FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK

PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK

GQPREPQVYT LPPSRDELTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN

YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVLHE ALHSHYTQKS

LSLSPGK

Intrachain disulfide bonds: Shown in solid lines.

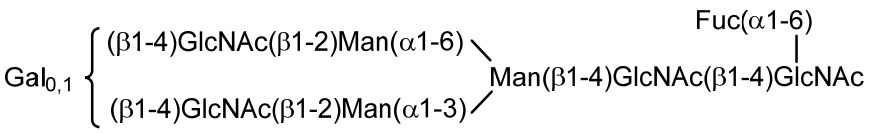
Interchain disulfide bonds: C214 (L-chain)-C230 (H-chain), C236 (H-chain)-C236 (H-chain), C239 (H-chain)-C239 (H-chain)

Pyroglutamate formation (partial): Q1 in H chain

Glycosylation site: N307 in H chain

Partial processing: G456 and K457 in H-chain

Putative structure of main carbohydrate chain:



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

Molecular formula: $C_{6492}H_{10060}N_{1744}O_{2038}S_{40}$ (protein portion composed of 4 chains)
Molecular weight: Approx. 149,000

Items Warranting Special Mention

The product is handled as a product that requires approval from the Minister of Health, Labour and Welfare prescribed in Article 14, Paragraph 1 of the Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 1 of the Act (PSEHB/PED Notification 0903-1, dated September 3, 2021, issued by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare).

Priority Review based on "Policy on regulatory review of drugs, etc. against coronavirus disease (COVID-19) (No. 2)" (PSEHB/PED Notification No. 0617-9 and PSEHB/MDED Notification No. 0617-1, dated June 17, 2021)

Reviewing Office

Office of New Drug IV

Results of Review

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

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

Indication

Disease caused by SARS-CoV-2 infection (COVID-19)

Dosage and Administration

The usual dosage in adults and pediatric patients (≥12 years of age weighing ≥40 kg) is 500 mg of Sotrovimab (Genetical Recombination) administered as a single intravenous infusion.

Approval Conditions and Other Requirements

1. The applicant is obliged to fulfill the following duties set forth in each Item of Article 28, Paragraph 3 of the Cabinet Order for Enforcement of Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 2 of the Pharmaceuticals and Medical Devices Act.

(1) Matters related to Item 1
Some of the data of clinical studies were not available for evaluation in the application review. The complete data should be submitted as soon as additional clinical data become available.

(2) Matters related to Item 2
When learning about diseases, disorders, or death suspected to be caused by the product, the applicant is required to report them promptly.

(3) Matters related to Item 3
The applicant is required to take necessary actions to ensure that healthcare professionals who use the product can understand, and appropriately explain to patients (or their legally acceptable representatives), that the product has been granted Special Approval for Emergency and the objectives of said approval.

(4) Matters related to Item 4
The applicant is required to report the quantity of the product sold or provided, as necessary.

2. The product is approved with the following conditions, based on the provisions of Article 79, Paragraph 1 of the Pharmaceuticals and Medical Devices Act:
(1) The applicant is required to develop and appropriately implement a risk management plan.
(2) The applicant is required to request that physicians administer the product only to patients considered eligible for treatment with the product who, or whose legally acceptable representatives, have been provided with the efficacy and safety information of the product in written form, and have provided written informed consent before the treatment.
(3) Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act, the grace period for data submission is 4 months after the approval. If newly submitted data, etc., necessitate a change in the approved product information, the change may be ordered in accordance with the provision in Article 74-2, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.

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

Attachment

Report on Special Approval for Emergency (1)

September 9, 2021

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	Xevudy for Intravenous Infusion 500 mg
Non-proprietary Name	Sotrovimab (Genetical Recombination)
Applicant	GlaxoSmithKline K.K.
Date of Application	September 6, 2021
Dosage Form/Strength	Injection: each vial (8 mL) contains 500 mg of Sotrovimab (Genetical Recombination).

Proposed Indication

Disease caused by SARS-CoV-2 infection (COVID-19)

Proposed Dosage and Administration

The usual dosage in adults and pediatric patients (≥12 years of age weighing ≥40 kg) is 500 mg of Sotrovimab (Genetical Recombination) administered as a single intravenous infusion.

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List of Abbreviations

See Appendix.

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

COVID-19 is a disease caused by SARS-CoV-2 infection. SARS-CoV-2 enters host cells through binding of the spike protein (S-protein) on the viral surface to angiotensin converting enzyme 2 (ACE2) on the host cells, resulting in infection (*Cell*. 2020;181:271-80). Main symptoms reported include pyrexia, cough, acute respiratory symptoms other than cough, and serious pneumonia.[1)]

In Japan, the first patient infected with SARS-CoV-2 was identified on January 15, 2020. On February 1, 2020, COVID-19[2)] was classified as a Designated Infectious Disease[3)] pursuant to the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (Infectious Diseases Control Act) and as a Quarantinable Infectious Disease[4)] pursuant to the Quarantine Act. In Japan, as of September 6, 2021, 1,571,372 people have been infected (positive for polymerase chain reaction [PCR] test). Among them, 184,732 (including 2,198 with severe disease) required hospitalization for treatment, 1,364,300 were discharged or released from medical treatment, and 16,354 died.[5)]

Sotrovimab (genetical recombination; hereinafter referred to as "sotrovimab") was discovered by Vir Biotechnology, Inc. in the US. It is a recombinant human monoclonal immunoglobulin G (IgG)1 antibody against the receptor binding domain (RBD) of SARS-CoV-2 S-protein. It inhibits the entry of SARS-CoV-2 into host cells.

In response to the Emergency Use Authorization issued by the US Food and Drug Administration (FDA) and based on the data of the foreign phase II/III study (the COMET-ICE study), etc., the applicant has submitted an application for Special Approval for Emergency of sotrovimab on the understanding that sotrovimab is qualified for approval based on Article 14, Paragraph 1 of the Pharmaceuticals and Medical Devices Act, pursuant to Article 14-3, Paragraph 1 of the Act. This report contains the result of review conducted based on the data submitted by the applicant, in accordance with the "Handling of drugs intended to be submitted for Special Approval for Emergency (Request)" (PSEHB/PED Notification 0903-1, dated September 3, 2021).

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Generation and control of cell substrate

Sotrovimab was derived based on the amino acid sequences of the light and the heavy chains from the parent antibody S309 isolated in 20[redacted] from B cells of a patient with a history of SARS-CoV infection. Using gene

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1) Symptoms of 29,601 patients reported to the National Epidemiological Surveillance of Infectious Diseases Program between February 1 and August 5, 2020 [Infectious Disease Weekly Report Japan, Vol. 22, No. 31 and 32 (combined issue): https://www.niid.go.jp/niid/images/idsc/idwr/IDWR2020/idwr2020-31-32.pdf (last accessed on September 6, 2021)]

2) Limited to the disease caused by coronavirus of genus *Betacoronavirus* that was reported as "transmissible to humans" from the People's Republic of China to WHO in January 2020.

3) The term Designated Infectious Disease means already known infectious diseases (excluding Class I Infectious Diseases, Class II Infectious Diseases, Class III Infectious Diseases, and Novel Influenza Infection, etc.) specified by Cabinet Order as a disease which would be likely to seriously affect the health of the public in the event of its spread if the provisions of the Infectious Diseases Control Act, in whole or in part, did not apply mutatis mutandis (Article 6 of the Infectious Diseases Control Act).

4) The term Quarantinable Infectious Disease means diseases specified by Cabinet Order as those which require inspection in order to prevent pathogens of infectious diseases not endemic to Japan from entering the country (Article 2, Item 3 of the Quarantine Act).

5) Ministry of Health, Labour and Welfare: https://www.mhlw.go.jp/stf/covid-19/kokunainohasseijoukyou.html (last accessed on September 6, 2021)

fragments encoding the heavy chains, the gene expression construct of the heavy and light chains of sotrovimab was engineered as follows:

(a) One amino acid mutation introduced in the heavy chain complementarity-determining region with the aim of enhancing antibody production, and
(b) Two amino acid mutations introduced in the heavy chain Fc region to increase neonatal Fc receptor (FcRn) binding affinity with the aim of extending the half-life.

The gene expression construct of sotrovimab was thus introduced into Chinese hamster ovary (CHO) cells, which were cultured in a medium containing a selective antibiotic to obtain a [redacted] bank. A master cell bank (MCB) was prepared from the optimal clone for the manufacture of sotrovimab from among the cells obtained during the preparation process of the [redacted] bank.

[redacted] bank, MCB, and end of production cell bank (EOPCB) were subjected to characterization and purity tests according to ICH Q5A (R1), Q5B, and Q5D Guidelines. Results confirmed the genetic stability during the manufacturing period. Within the range of the tests performed, no viral or non-viral adventitious agents were detected except endogenous retrovirus-like particles commonly observed in cell lines of rodent origin.

MCB is stored in the vapor phase of liquid nitrogen. There is no [redacted] MCB. The applicant explained that working cell bank (WCB) is currently undergoing qualification test and, after confirming the qualification, WCB will be used as the strain for manufacturing sotrovimab.

2.1.2 Manufacturing process

The manufacturing process for the drug substance consists of the following steps: MCB thawing, seed culture, expansion culture, manufacturing culture, harvesting, [redacted] chromatography, viral inactivation [redacted], depth filtration, [redacted] chromatography, virus removal by filtration, ultra/dia-filtration, preparation of the drug substance, final dialysis/filling, and test/storage.

[redacted] except the [redacted] are defined as critical steps.

The commercial-scale manufacturing process of the drug substance was subjected to process validation.

2.1.3 Safety evaluation of adventitious agents

No raw materials of biological origin except CHO cells, the host cells, are used in the manufacturing process of the drug substance.

Purity tests were performed on the stable pool bank, MCB, and EOPCB [see Section 2.1.1]. The pre-harvest unprocessed bulk at commercial scale was subjected to bioburden test, mycoplasma test, *in vitro* adventitious virus test, mouse minute virus test, and retrovirus tests ([redacted] with [redacted] and [redacted]). None of the tests detected contamination with either viral or nonviral

adventitious agents. The bioburden test, mycoplasma test, *in vitro* adventitious virus test, and mouse minute virus test on the pre-harvest unprocessed bulk are included as in-process control tests.

Viral clearance studies of the purification process were performed with model viruses. The results demonstrated that the purification process has a certain level of viral clearance capacity, as shown in Table 1.

Table 1. Results of viral clearance studies

Manufacturing process	Virus reduction factor (log_{10})			
	Xenotropic murine leukemia virus	Pseudorabies virus	Reovirus type 3	Minute virus of mice
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
Viral inactivation [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
Virus removal by filtration	[redacted]	[redacted]	[redacted]	[redacted]
Total virus reduction factor	>19.41	15.70	>11.68	>13.60

2.1.4 Manufacturing process development

During the development process of the drug substance, the following changes were made to the manufacturing process (each manufacturing process is referred to as Process A, Process B, Process C, Process D, and the proposed commercial process).

- Process A to Process B: Change of [redacted], optimization of [redacted]
- Process B to Process C: Introduction of MCB,[6)] changes of [redacted], formulation, etc., and optimization of [redacted] and [redacted]
- Process C to Process D: Change of [redacted], optimization of [redacted]
- Process D to proposed commercial process: Changes of [redacted], [redacted], [redacted] and [redacted] of [redacted]; and optimization of [redacted] and [redacted]

The drug product produced from the drug substance manufactured by Process B was used in the foreign phase II/III study.

In association with the above changes of the manufacturing processes, the quality attributes of drug substances were evaluated before and after the change and shown to be comparable.

In the development of manufacturing process of the drug substance, quality by design (QbD) approach was used [see Section 2.3].

2.1.5 Characterization

2.1.5.1 Structure and characteristics

Sotrovimab was subjected to characterization tests described in Table 2.

6) The [redacted] bank was used in the manufacture of batches before MCB introduction.

Table 2. Parameters evaluated in characterization tests

Primary structure/higher order structure	Amino acid sequence, N- and C-terminal amino acid sequences, posttranslational modification (pyroglutamylation, oxidation, deamidation, Asn succinimidization, Asp isomerization), disulfide bonds, free thiol groups, secondary structure, tertiary structure
Physicochemical properties	Molecular weight, heat stability, absorption coefficient, size variants, charge variants
Carbohydrate structure	N-linked carbohydrate chain profile
Biological properties	Binding activity to SARS-CoV-2 S-protein
	Binding affinity to FcγRIIa, FcγRIIIa, FcRn, and C1q
	Neutralization activity
	ADCC activity, ADCP activity

As for biological properties, binding activity to S-protein was investigated by [redacted].

Binding affinity to Fc gamma receptor (FcγR)IIa, FcγRIIIa, and FcRn was investigated by [redacted]. Binding affinity to Complement 1, q subcomponent (C1q) was investigated by [redacted]. Binding affinity to FcRn was found to be approximately [redacted] times higher than the affinity of usual IgG1 to FcRn, owing to the introduction of [redacted].

The neutralization activity was assayed using [redacted] engineered to express S-protein[7)] ([redacted]) and a [redacted] introduced with [redacted].

Antibody-dependent cellular cytotoxicity (ADCC) activity and antibody-dependent cellular phagocytosis (ADCP) activity were assayed by [redacted] using [redacted] cells stably expressing S protein as the target cells and [redacted] ([redacted] cells) as the effector cells.

2.1.5.2 Product-related substances/product-related impurities

Variant A, Variant B, and Variant C were identified as product-related substances based on the results of characterization tests in Section 2.1.5.1. Variant D, Variant E, Variant F, Variant G, and Variant H were identified as product-related impurities. Variant D, Variant E, and Variant I are controlled by the specifications for the drug substance and the drug product. Variant F, Variant G, and Variant H are controlled appropriately during the manufacturing process.

2.1.5.3 Process-related impurities

Host cell protein (HCP), Impurity A, Impurity B, Impurity C, Impurity D, and Impurity E were identified as process-related impurities. HCP, Impurity A, Impurity B, and Impurity D have been demonstrated to be adequately removed by the manufacturing process. Impurity C and Impurity E were subjected to safety risk assessment and concluded to have only negligible risk at the residual concentrations. HCP is controlled by the specifications of the drug substance.

7) [redacted]

2.1.6 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (capillary isoelectric focusing [cIEF], peptide mapping), pH, sugar chain profile, purity (cIEF, size exclusion high performance liquid chromatography [SE-HPLC], capillary gel electrophoresis-sodium dodecyl sulfate (CE-SDS) [non-reducing, reducing]), HCP, endotoxin, microbial limits, biological activity (ELISA), and assay (ultraviolet-visible spectrophotometry).

The applicant explained that the drug substance used for the manufacture of the drug product to be distributed early after the market launch would be controlled by the specifications that were applied to the drug substance used in clinical studies, based on the current status of the quality control [see Section 2.R.1].

2.1.7 Stability of drug substance

Table 3 shows a summary of the main stability tests on the drug substance.

Table 3. Summary of the main stability tests on drug substance

Test	Manufacturing process	Number of batches	Storage condition	Study period	Storage package
Long-term	Process A and Process B[a)]	3	± °C	months	bottle and cap
Accelerated		3	± °C	months	
Stress		3	± °C/ ± % RH	months	
Long-term	Process D	2	± °C	months[b)]	
		1	± °C	months[b)]	bag[c)]
Accelerated		2	± °C	months	bottle and cap
Stress		2	± °C/ ± % RH	months	
Long-term	Proposed commercial process[d)]	4	± °C	months[e)]	bag[c)]
Accelerated		4	± °C	months[f)]	
Stress		4	± °C/ ± % RH	months	
		4	± °C/ ± % RH	months	

a) 1 batch of process A-derived drug substance and 2 batches of process B-derived drug substance. The process A- and B-derived drug products differ from the drug substance manufactured by the proposed commercial process in the concentration of the active ingredient, etc.
b) These stability tests (ongoing) are continued for months.
c) bag with lining
d) Of the 4 batches manufactured using the proposed commercial process, 2 were also subjected to the stability test using a bottle and cap as the primary container.
e) The stability test (ongoing) is continued for months.
f) The stability test (ongoing) is continued for months.

The long-term test (°C and °C) did not show any clear changes in quality attributes throughout the study period.

The accelerated test showed a tendency of slight decrease in in and in ( ) in the process A- and B-derived drug substances; and a tendency of decrease in and an increase in Variant D in in the process D-derived drug substance.

The stress test (bag, °C) showed a tendency of decrease in and increase in Variant D in , decrease in in ( ), a tendency of decrease in the of

and [redacted] in [redacted] ([redacted]), and tendencies of decrease in [redacted] and increase in [redacted] in [redacted].

At the same measuring time point as in the stress test ([redacted]°C), the stress test ([redacted]°C) showed more marked changes in the quality attributes observed by [redacted], [redacted] ([redacted]), and [redacted].

The applicant proposed the shelf life of [redacted] months for the drug substance when stored at ≤[redacted]°C in [redacted] bag as a primary container, [redacted].

2.2 Drug product

2.2.1 Description and composition of drug product and formulation

Sotrovimab is available as 1 glass vial (10 R) containing sotrovimab 500 mg per 8 mL solution (aqueous injection). The drug product contains excipients: L-histidine, L-histidine hydrochloride hydrate, sucrose, polysorbate 80, L-methionine, and water for injection.

2.2.2 Manufacturing process

The manufacturing process of the drug product consists of thawing/pooling of the drug substance, preparation of prescription buffer, dilution of the drug substance/mixing of the bulk drug product, bioburden removal by filtration, sterile filtration, filling/capping, inspection, storage, packaging/labeling, and test/storage.

[redacted] of the [redacted], [redacted], [redacted] of the [redacted] of the [redacted], [redacted], and [redacted] are defined as critical steps.

The commercial-scale manufacturing process of the drug product is subjected to process validation.

2.2.3 Manufacturing process development

The following are main changes in the manufacturing process during the development of the drug product (each process is referred to as Process I, Process II, and proposed commercial process).

- Process I to II: Changes of [redacted], concentration of the active ingredient, [redacted], formulation, etc., and addition of [redacted]
- Process II to proposed commercial process: Changes of [redacted], [redacted], [redacted] of [redacted]

The drug product manufactured by Process I was used in the foreign phase II/III study.

When the manufacturing process was changed from Process I to II and from Process II to proposed commercial process, the quality attributes of the pre-change and post-change drug products were evaluated and shown to be comparable.

2.2.4 Control of drug product

The proposed specifications for the drug product include strength, description, identification (cIEF, peptide mapping), osmotic pressure, pH, purity (cIEF, SE-HPLC, CE-SDS [non-reducing, reducing]), endotoxin, extractable volume, foreign insoluble matter, insoluble particulate matters, sterility, polysorbate 80, biological activity (ELISA), and assay (ultraviolet-visible spectrophotometry).

The applicant explained that the product to be distributed early after the market launch would be controlled by the specifications that were applied to the product used in clinical studies, based on the current status of the quality control, as is the case with the drug substance [see Section 2.R.1].

2.2.5 Stability of drug product

Table 4 shows the main stability tests on the drug product.

Table 4. Summary of main stability tests of drug product

Test	Manufacturing process	Number of batches	Storage condition	Study period	Storage package
Long-term	Drug substance: Process A: 1 batch Process B: 2 batches	3	5 ± 3°C	12 months[a)b)]	Glass vial with chlorobutyl rubber stopper
Accelerated		3	25 ± 2°C/60 ± 5% RH	6 months	
Stress	Drug product: Process I	3	40 ± 2°C/75 ± 5% RH	6 months	
Long-term	Drug substance: Process D	2	5 ± 3°C	6 months[c)]	
Accelerated		2	25 ± 2°C/60 ± 5% RH	6 months	
Stress	Drug product: Process II	2	40 ± 2°C/75 ± 5% RH	3 months	
Long-term	Drug substance: Proposed commercial process	6	5 ± 3°C	4 months[d)e)]	
Accelerated		6	25 ± 2°C/60 ± 5% RH	4 months[d)f)]	
Stress		6	40 ± 2°C/75 ± 5% RH	3 months[g)h)]	
Photostability	Drug product: Proposed commercial process	1	Total illuminance ≥1.2 × 10^6 lux•h, total near ultraviolet radiation energy ≥200 W•h/m^2, [redacted]°C/[redacted]%RH		

The concentrations of the active ingredient, etc., in the Process I-derived drug product are different from those in the proposed commercial product.

a) Up to [redacted] months for 2 batches and up to [redacted] months for 1 batch
b) The stability test (ongoing) is continued for [redacted] months on 2 batches manufactured using the process B-derived drug substance.
c) The stability test (ongoing) is continued for [redacted] months.
d) [redacted] month in 1 batch, [redacted] months in 2 batches, and [redacted] month in 3 batches
e) The stability test (ongoing) is continued for [redacted] months.
f) The stability test (ongoing) is continued for [redacted] months.
g) [redacted] months in 1 batch, [redacted] months in 2 batches, and [redacted] month in 3 batches
h) The stability test (ongoing) is continued for [redacted] months.

The long-term test did not show any clear changes in quality attributes in the drug products of either manufacturing processes throughout the study period.

The accelerated test showed tendencies of decrease in [redacted] in [redacted], decrease in [redacted] in [redacted] ([redacted]), decrease in [redacted] and increase in [redacted] in [redacted], in both Process I- and II-derived drug products.

The stress test on Process I-derived drug product showed tendencies of decrease in [redacted] and increase in the Variant D in [redacted]; decrease in [redacted] in [redacted] ([redacted]); decrease in the [redacted] of [redacted] and [redacted] in [redacted] ([redacted]); and decrease in [redacted], increase in [redacted], and tendency of decrease in [redacted] in [redacted]. The stress test on Process II-derived drug product and the proposed commercial product showed tendencies of decrease in [redacted] and increase in Variant D in [redacted]; decrease in [redacted] in [redacted] ([redacted]); tendency of decrease in the sum of [redacted] and [redacted] in [redacted] ([redacted]); and decrease in [redacted], increase in [redacted], and tendency of decrease in [redacted] in [redacted].

The photostability test showed that the drug product was photo-unstable.

The applicant proposed a shelf life of 12 months for the product when stored in a glass vial with chlorobutyl rubber stopper as the primary container at 2°C to 8°C and placed in a carton to protect from light.

2.3 QbD

QbD approach was used in the development of the drug substance and the drug product, and the strategy for quality control was developed by the following investigations.

- Identification of critical quality attribute(CQA)s:

  Regarding the product-related impurities, process-related impurities, and general quality attributes, the following CQAs were identified based on the information obtained during the process of the development of sotrovimab and related findings:

  CQA of drug substance: [redacted], adventitious viruses, microbiological safety, [redacted], Variant D, Variant E, Variant I, Variant F, Variant G, Variant H, HCP, Impurity A, Impurity B, Impurity C, Impurity D, and polysorbate 80.

  CQA of drug product: [redacted], microbiological safety, [redacted], sterility, [redacted], Variant D, Variant E, Variant I, Variant F, and polysorbate 80

- Process characterization

  The acceptable ranges were identified based on the identification of the process parameters affecting CQA and process performance by risk assessment, etc.

- Establishment of the controlling methods

The method for controlling the quality attributes of the drug product was established by the combination of the process parameters control, in-process control, and specifications based on the knowledge on the process including the above process characterization and on the risk assessment on the quality attributes of the product [see Sections 2.1.5.2 and 2.1.5.3 for the control of product-related impurities and process-related impurities].

2.R Outline of the review conducted by PMDA

Because of the short development period of sotrovimab, some information is lacking as described below. Nevertheless, PMDA concluded that the quality of the drug substance and the drug product is appropriately ensured.

2.R.1 Specifications

The applicant's explanation about the specifications of the drug substance and the drug product:

The drug substance and the drug product are controlled by the specifications described in Sections 2.1.6 and 2.2.4 (specifications for marketing). However, the product to be distributed early after the market launch will be controlled by the specifications for the drug substance and the drug product applied for the product used in clinical studies, etc. (specifications for clinical studies), based on the current status of the quality control. The specifications for clinical studies are different from those for marketing in the following points:

(a) ELISA, instead of [redacted], is used as the [redacted] for the drug substance and the drug product.
(b) [redacted] is not included for the drug substance
(c) [redacted] in [redacted] for the drug substance and the drug product are broader than [redacted] for marketing.

The specifications for marketing will be changed during the period from [redacted] of 20[redacted] to [redacted] of 20[redacted], albeit yet to be defined.

An assay for [redacted] neutralization activity is currently being developed as a biological activity assay. The biological activity assay of the drug substance and the drug product will be changed from ELISA to [redacted] neutralization activity as soon as the specification for the assay is established.

The specifications for the drug substance and the drug product will be reviewed after accumulation of the manufacturing history of ≥[redacted] each of the drug substance and the drug product, or [redacted], whichever comes earlier, based on the additional data obtained before the timing of the review.

PMDA's view:

Under ordinary situations, the early distribution batches should be controlled by the specifications for marketing, including the specification for biological activity based on virus-neutralization activity. However, the applicant's policy for setting the specifications for the drug substance and the drug product is acceptable, for the following reasons: (a) the product is urgently needed in clinical practice, and (b) given the applicant's

strategy for controlling the quality attributes, it is possible to constantly manufacture the product with consistent quality, and the quality of the drug substance and the drug product is assured to a certain extent even with the specifications for clinical studies. PMDA instructed the applicant to revise the specifications based on the manufacturing history, etc., at the planned timing and to take appropriate regulatory actions. The applicant agreed to take appropriate actions, and PMDA accepted the applicant's response.

2.R.2 Determination of the storage method and the shelf-life

Since sotrovimab is a protein product, the shelf-life of the drug substance and the drug product should be determined based on the results of long-term studies of ≥3 batches under real-time, real-conditions, in accordance with "Stability Testing of Biotechnological/Biological Products" (PMSB/ELD Notification No. 6, dated January 6, 1998). The proposed shelf-life is 12 months for both the drug substance and the drug product. However, stability studies of the drug substance and drug product are ongoing [see Sections 2.1.7 and 2.2.5], and the [redacted]-month data of long-term storage tests under real-time, real-conditions reflecting the commercial scale manufacture are currently unavailable either for the drug substance or the drug product. PMDA asked the applicant to explain the stability of the drug substance and the drug product.

The applicant's explanation:

Drug substance:

During the process of the development, the primary container was changed from [redacted] to [redacted], and the [redacted] was changed from [redacted]°C to [redacted]°C. Prior to these changes, possible effect of the [redacted] and the [redacted] of the [redacted] on the quality of the drug substance was evaluated, and it was confirmed that these changes did not affect the quality of the drug substance. These results suggest that it is acceptable to apply the results of the stability studies conducted using [redacted] to the determination of the shelf-life of the drug substance. Results of stability studies thus far conducted do not show any clear change in the quality of the drug substance batches in long-term storage tests, and results of accelerated tests also suggest that the quality is maintained at a certain level up to [redacted] months. On the basis of these results, the applicant considers that it is acceptable to determine the shelf-life as "[redacted] months at [redacted]°C in [redacted] as the primary container, [redacted]."

Drug product:

The formulation and the strength were changed during the development process. However, since comparison of Process I-derived product and Process II-derived product showed similar stability profiles, it is considered acceptable to predict the stability of the proposed drug product based on the results of the stability tests on Process I-derived drug product. Long-term storage tests did not show any change in the quality attributes of either drug product, from which the applicant considers that the drug product conforms to the specifications for at least 12 months when stored at 2 to 8°C.

PMDA's view:

The explanation of the applicant is acceptable to a certain extent, because sotrovimab is urgently needed in clinical practice, and because there is a risk that the supply of sotrovimab to Japan may be delayed due to

its global distribution. Therefore, at present, there is no choice but to determine the storage method and the shelf-life as proposed based on the submitted data. Results of the currently ongoing stability studies should be confirmed promptly at each measuring time point and, if any tendency of deviation from the expected results is noted, appropriate actions should be taken promptly. PMDA asked the applicant to address the above issues and the applicant agreed to take appropriate actions. PMDA accepted the applicant's response.

On the basis of the above, PMDA concluded that the following shelf-lives of the drug substance and the drug product was acceptable:
The drug substance: [redacted] months when stored at ≤[redacted]°C in [redacted] as the primary container.
The drug product: 12 months when stored at 2°C to 8°C in a glass vial with chlorobutyl rubber stopper as the primary container, placed in a carton to be protected from light.

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

Results of primary pharmacodynamic studies, secondary pharmacodynamic studies, and pharmacodynamic interaction studies were submitted as the nonclinical pharmacological data of sotrovimab. Sotrovimab and other antibodies listed in Table 5 were used in these nonclinical pharmacological studies. In this section, values are expressed in means unless specified otherwise.

Table 5. Antibodies used in nonclinical pharmacology studies

S309	The parent antibody of sotrovimab. It is identical with sotrovimab except the following changes introduced into sotrovimab: N55Q[a)] in the complementarity-determining region and LS mutation (M438L and N444S)[b)] in Fc region.
VIR-7832	Fab region is identical with that of sotrovimab. XX2 mutations (G236A, A330L, and I332E)[c)] are introduced into Fc region of sotrovimab. It is confirmed that there is no difference in the structure or the binding specificity to SARS-CoV-2 between sotrovimab and VIR-7832
VIR-7831-WT	Fab region is identical with that of sotrovimab. LS mutations (M438L and N444S)[b)] are not introduced in Fc region of sotrovimab.
GH-S309	Chimeric antibody containing the variable region of S309 and Fc region of hamster IgG2a [d)]

a) Introduced to increase the amount of antibody production.
b) Prolongation of the half-life of the antibody and increased distribution in respiratory mucous membrane are expected.
c) Enhancement of effector function and immune modulation are expected.
d) It is reported that the effector function of hamster IgG2 resembles that of human IgG1 (*J Immunol Methods*. 1982;52:63-72)

3.1 Primary pharmacodynamics

3.1.1 Binding characteristics to SARS-CoV-2

3.1.1.1 Binding affinity to S-protein and RBD (CTD 5.3.5.4: 2020N456937)

The binding affinity of sotrovimab to S-protein and RBD was investigated by ELISA, SPR, and flow cytometry. ELISA confirmed the binding of sotrovimab to RBD monomer with half maximal effective concentration (EC_{50}) of 20.40 ng/mL. SPR confirmed the binding of sotrovimab to RBD monomer with the equilibrium dissociation constant (K_D) of 0.21 nmol/L (approx. 31 ng/mL). Flow cytometry using CHO cells engineered to express S-protein trimer confirmed the binding of sotrovimab to S-protein trimer expressed on the cell surface.

3.1.1.2 Epitope mapping (CTD 5.3.5.4: 2020N456987, 2021N481340)

The epitope was identified based on the determination of the structure of the complex of Fab region of S309 and RBD by X-ray crystallography. Table 6 shows the results, which demonstrated that ≥99.75% of all 23 amino acid residues consisting the epitope (≥99.99% for 16 amino acid residues among them) were conserved,

as based on the amino acid sequence of S-protein registered on Global Initiative on Sharing Avian Influenza Data (GISAID) database (data obtained as of July 16, 2021). The applicant's explanation: The complementarity-determining region of sotrovimab is identical with that of S309 except N55Q. Since it was confirmed by crystallography that N55 residue does not interact with RBD, it is considered that S309 and sotrovimab recognize the identical epitope.

Table 6. Amino acid residues that interact in the binding of sotrovimab to RBD

Amino acid residue in RBD[a)]	Amino acid residues in sotrovimab	
	Heavy chain	Light chain
I332	T30, T74	—
T333	T30	—
N334	W105, T30, Y54	—
L335	W105, T30, P28, S31	—
C336	W105	—
P337	W105, F106	—
G339	L110, Y100	—
E340	W105, L110, S31, A104, Y100, E108, G107, G103, F106	—
V341	F106	—
N343	L110, I111, Y100, S109	—
A344	L110, I111, S109, E108	—
T345	I111, L110, S109	S33, H92, S30, T32
R346	E108, S109	S33, H92, T94, T32, D93
N354	E108	—
K356	F106, E108	—
R357	F106	—
I358	F106	—
S359	W105	—
N360	W105	—
C361	W105	—
N440	—	S31
L441	I111	T32
R509	I111	T32

—: Not applicable
a) NCBI reference sequence: YP_009724390.1

3.1.1.3 Competition against the binding of S protein or RBD with ACE2 (reference CTD 4.3: *Nature.* 2020;583:290-5)

The competitive activity of S309 against the binding of RBD monomer or S-protein trimer with ACE2 was investigated by bio-layer interferometry. Results showed that S309 does not compete with either of these bindings. Crystal structure analysis by cryo-electron microscopy showed that Fab region of S309 binds to a region different from ACE2-binding region on RBD.

3.1.2 *In vitro* antiviral activity

3.1.2.1 SARS-CoV-2-neutralization activity (CTD 5.3.5.4: 2020N456924, 2020N457420)

SARS-CoV-2 (isolate: USA-WA1/2020) was treated with sotrovimab, and following the incubation of thus-treated virus with Vero E6 cells for 24 hours, the neutralization activity of sotrovimab was investigated by SARS-CoV-2 nucleocapside staining which detects intracellular viral infection. Sotrovimab showed a concentration-dependent neutralization activity against SARS-CoV-2 with EC_{50} and 90% effective concentration (EC_{90}) of 100.1 ng/mL and 186.3 ng/mL, respectively.

Replication-incompetent vesicular stomatitis virus[8] (pseudovirus particles) engineered to express S-protein of SARS-CoV-2 (WuhanCoV) was treated with sotrovimab and incubated with Vero E6 cells and, after cultivation for 17 hours, the neutralization activity of sotrovimab was investigated by luciferase reporter assay which detects intracellular viral infection. Sotrovimab showed a dose-dependent neutralization activity against pseudovirus particles with EC_{50} and EC_{90} of 24.06 ng/mL and 107.72 ng/mL, respectively.

3.1.2.2 Neutralization activity against mutant strains

3.1.2.2.1 Studies with pseudovirus particles (CTD 5.3.5.4: 2020N456987, 2021N466446, 2021N470273, 2021N470274, 2021N471870, 2021N475740, 2021N476139, 2021N477024, 2021N477635, 2021N478962, 2021N481341, 2021N481931)

Replication-incompetent vesicular stomatitis virus (pseudovirus particles) engineered to express S-protein with amino acid mutations[9] was treated with sotrovimab or S309 and incubated with Vero E6 cells and, after cultivation for 17 hours or for 20 to 24 hours, the neutralization activity of sotrovimab was investigated by luciferase reporter assay which detects intracellular viral infection. Compared with the neutralization activity of sotrovimab against the reference strain, the neutralization activity decreased against pseudovirus particles with mutations introduced in P337, E340, and K356 within the epitope of sotrovimab (P337H/D614G [5.13-fold], P337K/D614G [>304-fold], P337L/D614G [>192-fold], P337R/D614G [>192-fold], P337T/D614G [10.62-fold], E340A [>100-fold], E340K [>297-fold], E340G/D614G [18.21-fold], E340Q/D614G [>50-fold], and K356T/D614G [5.9-fold])[10].

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8) Prepared by replacing a gene for glycoprotein of vesicular stomatitis virus with the gene for S-protein of SARS-CoV-2.

9) The following amino acid mutations were selected from among mutations observed with high frequency in GISAID (>1% as of May 14, 2020), amino acid mutations observed in the epitope of sotrovimab, amino acid mutations with low sensitivity to monoclonal antibodies targeted at S-protein of SARS-CoV-2 as is the case with sotrovimab (bamlanivimab, casirivimab, and imdevimab) (*Science*. 2020;369:1014-18, *Cell*. 2021;184:1171-87, etc.), and amino acid mutations observed in *in vitro* studies on escape mutations [see Section 3.1.3]:
L5F/D614G, S13I/W152C/L452R/D614G, L18F/D614G, L54F/D614G, deletion 69-70/S477N/D614G, G261D/Y453F, I332V/D614G, I332T/D614G, T333I/D614G, T333K/D614G, N334K/D614G, N334H/D614G, N334Y/D614G, N334S/D614G, L335F, L335S/D614G, P337L/D614G, P337R/D614G, P337S/D614G, P337H/D614G, P337T/D614G, P337K/D614G, G339S/D614G, G339D/D614G, G339C/D614G, G339V/D614G, E340A, E340K, E340G/D614G, E340Q/D614G, E340D/D614G, V341I/D614G, N343S/D614G, A344S, A344T/D614G, A344V/D614G, T345S/D614G, T345N/D614G, R346K/D614G, R346I/D614G, R346S/D614G, R346T/D614G, R346G/D614G, N354D, N354K/T95I, N354S/D614G, N354H/D614G, N354I/D614G, K356A, K356R/D614G, K356N/D614G, K356M/D614G, K356T/D614G, R357K/D614G, R357I/D614G, I358L, I358V/D614G, I358F/D614G, S359N, S359G/D614G, S359R/D614G, S359T/D614G, N360S/D614G, N360Y/D614G, V367F, E406W, K417E, N439K/D614G, N440D, N440K/D614G, N440Y/D614G, N440S/D614G, N440T/D614G, N440I/D614G, L441F/D614G, L441I/D614G, L441R/D614G, L441V/D614G, K444Q, V445A, G446V/D614G, L455F/D614G, G476S, S477N/D614G, T478I/D641G, V483A, E484K/D614G, E484Q/D614G/Q779H, G485R/D614G, F486V, Y489H, F490S, F490L/D614G, Q493K, S494P/D614G, D614G, D614G/D936Y, R682W, and V1128F.

10) Value in square brackets indicates fold change in the neutralizing activity ("EC_{50} [geometric mean] in variant"/"EC_{50} [geometric mean] in reference strain [D614 or D614G mutation])

Table 7 shows the neutralization activity of sotrovimab against main variants such as variants of concern (VOC) and variants of interest (VOI)[11] which was not significantly different from the neutralization activity against the reference strain.

Table 7. Neutralization activity against VOC and VOI

Strain	Amino acid mutations tested	Fold change in neutralization activity[a]	Submission data CTD
B.1.1.7 (Alpha)	Deletion H69, deletion V70, deletion Y144, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H	2.3	CTD 5.3.5.4: 2021N470273
		2.3	CTD 5.3.5.4: 2021N477024
B.1.1.7 (Alpha) + E484K	Deletion H69, deletion V70, deletion Y144, E484K, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H	1.7	CTD 5.3.5.4: 2021N478962
B.1.351 (Beta)	L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, A701V	0.6	CTD 5.3.5.4: 2021N470273
	L18F, D80A, D215G, R246I, deletion 242-244, K417N, E484K, N501Y, D614G, A701V	0.7	CTD 5.3.5.4: 2021N477024
P.1 (Gamma)	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F	0.35	CTD 5.3.5.4: 2021N470273
	L18F, T20N, P26S, D138Y, R190S, K417N, E484K, N501Y, D614G, T1027I, V1176F	0.6	CTD 5.3.5.4: 2021N477024
B.1.617.2 (Delta)	T19R, G142D, E156G, deletion F157, deletion R158, L452R, T478K, D614G, P681R, D950N	1.0	CTD 5.3.5.4: 2021N478962
B.1.525 (Eta)	Q52R, A67V, deletion H69, deletion V70, deletion Y144, E484K, D614G, Q677H, F888L	0.9	CTD 5.3.5.4: 2021N477024
B.1.526 (Iota)	L5F, T95I, D253G, E484K, D614G, A701V	0.6	CTD 5.3.5.4: 2021N477024
B.1.617.1 (Kappa)	T95I, G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H	0.7	CTD 5.3.5.4: 2021N475740
C.37 (Lambda)	G75V, T76I, deletion 246-252, L452Q, F490S, T859N	1.5	CTD 5.3.5.4: 2021N481931
B.1.621 (Mu)	—	—	—
B.1.617.3[b]	—	—	—
B.1.427[c], B.1.429[c]	S13I, W152C, L452R, D614G	0.7	CTD 5.3.5.4: 2021N470273
		0.9	CTD 5.3.5.4: 2021N477024
B.1.619[c]	I210T, N440K, E484K, D614G, D936N, S939F, T1027I	1.3	CTD 5.3.5.4: 2021N478962

a) EC_{50} (geometric mean) against variants/EC_{50} (geometric mean) against reference strain (D614 or D614G mutation)
b) Designated as VOI by US CDC (as of September 6, 2021)
c) Designated as "Currently designated Alerts for Further Monitoring" by WHO (as of September 6, 2021)
—: No data available

[11] Variants identified as VOI or VOC by WHO as of September 6, 2021 [https://www.who.int/en/activities/tracking-SARS-CoV-2-variants (last accessed on September 6, 2021)], National Institute of Infectious Diseases as of August 28, 2021 [https://www.niid.go.jp/niid/images/epi/corona/43/covid19-43-2.pdf (last accessed on September 6, 2021)], and US CDC as of September 6, 2021 [https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html (last accessed on September 6, 2021)]
The definitions of VOI and VOC by WHO are as follows. The definitions by National Institute of Infectious Diseases and US CDC reflect the epidemic situation in each country.

VOI: A SARS-CoV-2 isolate is a VOI if it:
(a) Is phenotypically changed compared to a reference isolate or has a genome with mutations that lead to amino acid changes associated with established or suspected phenotypic implications, and (b) has been identified to cause community transmission/multiple COVID-19 cases/clusters, or has been detected in multiple countries; OR
(c) Is otherwise assessed to be a VOI by WHO in consultation with the WHO SARS-CoV-2 Virus Working Group.

VOC: A VOI is a VOC if, through a comparative assessment, it has been demonstrated to be associated with:
(a) • Increase in transmissibility or detrimental change in COVID-19 epidemiology; OR
• Increase in virulence or change in clinical disease presentation; OR
• Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics, OR
(b) Has been assessed to be a VOC by WHO in consultation with the WHO SARS-CoV-2 Virus Working Group.
[https://www.who.int/publications/m/item/covid-19-weekly-epidemiological-update (last accessed on September 6, 2021)]

3.1.2.2.2 Study with SARS-CoV-2 (CTD 5.3.5.4: 2021N475485)

SARS-CoV-2 strains B.1.1.7 (Alpha), B.1.351 (Beta), and P.1 (Gamma) were treated with sotrovimab and incubated with Vero E6 cells and, after cultivation for 6 hours, neutralization activity was investigated by SARS-CoV-2 nucleocapside staining which detects intracellular viral infection. Table 8 shows the results.

Table 8. Neutralization activity against SARS-CoV-2 variants

Strain[a)]	EC_{50} (ng/mL)[b)]	Fold change in neutralization activity[c)]
Wild type	58.13	—
B.1.1.7 (Alpha)	187.15	3.0
B.1.351 (Beta)	71.89	1.2
P.1 (Gamma)	73.11	1.6

—: Not applicable

a) Isolate used among each strain: Wild type (isolate: USA-WA1/2020), strain B.1.1.7(isolate: UK/VUI/3/2020), strain B.1.351(isolate: hCoV-19/SouthAfrica/KRISP-K005325/2020), and strain P.1 (isolate: hCoV-19/Japan/TY7-503/2021)

b) Geometric mean

c) "EC_{50} (geometric mean) against variants"/"EC_{50} (geometric mean) against wild-type strain"

3.1.2.3 Studies on effector functions (CTD 5.3.5.4:2020N456792)

Binding affinity of sotrovimab to human FcγRIIa (low-affinity polymorphism R131 and high-affinity polymorphism H131), FcγRIIb, and FcγRIIIa (low-affinity polymorphism F158 and high-affinity polymorphism V158) was investigated by SPR. Sotrovimab was found to bind to all FcγRs investigated. In addition, sotrovimab was shown to bind to human C1q, a component of complement, by bio-layer interferometry.

Human T cell line (Jurkat cells) expressing human FcγRIIa (high-affinity polymorphism H131), FcγRIIb, or FcγRIIIa (low-affinity polymorphism F158 and high-affinity polymorphism V158) was co-cultivated with S-protein-expressing CHO cells in the presence of sotrovimab (0.006-10,000 ng/mL), and FcγR activation was investigated by luciferase reporter assay. Sotrovimab activated FcγRIIa (high-affinity polymorphism H131) and FcγRIIIa (high-affinity polymorphism V158) and weakly activated FcγRIIIa (low-affinity polymorphism F158) and inhibitory receptor FcγRIIb.

Using human donor-derived natural killer (NK) cells containing homozygotic, high-affinity (V/V158) or low-affinity (F/F158) FcγRIIIa, ADCC activity of sotrovimab (0.075-40,000 ng/mL) against S-protein-expressing CHO cells was investigated by lactate dehydrogenase (LDH) assay. Sotrovimab showed ADCC activity against NK cells derived from all donors tested.

Human peripheral mononuclear cells were co-cultivated with S-protein-expressing CHO cells in the presence of sotrovimab (0.32-5,000 ng/mL), and ADCP activity was investigated using the phagocytosis rate as the index.[12)] Sotrovimab was shown to have ADCP activity.

12) Percentage of human monocytes engulfing S-protein-expressing cells.

3.1.3 *In vitro* study on escape mutation (CTD 5.3.5.4: 2020N456627)

Vero E6 cells were infected with SARS-CoV-2 (isolate: USA-WA1/2020) in the presence of a high-concentration of VIR-7832 (1, 2, 5, or 10 μg/mL[13)]) and passaged for 10 generations. Cytopathic effect (loss of neutralization activity) was not observed at any concentration, with no focus formation, an index of viral titer, in the culture supernatant.

Vero E6 cells were infected with SARS-CoV-2 (isolate: USA-WA1/2020) in the presence of a low-concentration of VIR-7832 (0.05 μg/mL[14]). After confirming the cytopathic effect of >50%, cells were passaged for 8 generations in the presence of the same or higher concentrations (0.1, 0.2, 0.5, and 1 μg/mL) of VIR-7832, and culture supernatant at each generation was subjected to assay for viral focus formation. When the neutralization activity of VIR-7832 against the detected virus decreased to <50% of the activity against the wild type, the gene sequence of S-protein was determined. Results showed 215-216KLRS insertion, 675-679 deletion, and amino acid mutations E340A, R682W, and V1128F. The 675-679 deletion had already been reported in the passages of SARS-CoV-2 in Vero E6 cells (*Lancet Infect Dis*. 2020;20:656-7), and 215-216KLRS insertion was detected in SARS-CoV-2 (isolate: USA-WA1/2020) before treatment with VIR-7832 at an allele frequency of 60.9%.

3.1.4 *In vivo* antiviral activity

Sotrovimab, VIR-7831-WT, and GH-S309 were administered to Syrian hamsters and their antiviral activity against the wild type and variants of SARS-CoV-2 was investigated. Table 9 shows the results. The applicant explained that since VIR-7831-WT reaches the maximum serum concentration (C_{max}) at 24 to 36 hours after intraperitoneal administration, administration 1 day before viral exposure reflects therapeutic effect and administration 2 days before viral exposure reflects prophylactic effect.

Table 9. *In vivo* antiviral activity

Animal species (number of animals/group)	Dosage regimen, method for viral exposure	Summary of main results	Submission data CTD
Syrian hamsters (7 males/group)	VIR-7831-WT 0 (vehicle), 0.05, 0.5, 5, 15, 30 mg/kg[a)] or the control antibody 30 mg/kg was administered intraperitoneally 1 or 2 days before intranasal inoculation of SARS-CoV-2 (isolate: USA-WA1/2020, 1.31×10^5 $TCID_{50}$/animal)	<u>Administration 1 day before viral exposure</u> Body weight (4 days after viral exposure): Reduced body weight loss was observed in VIR-7831-WT groups (≥5 mg/kg) compared with the vehicle group or the control antibody group. Viral load and titer in pulmonary tissue (4 days after viral exposure): Reduced viral load (≥5 mg/kg) and reduced viral titer (≥0.5 mg/kg) were observed in VIR-7831-WT groups compared with the control antibody group. <u>Administration 2 days before viral exposure</u> Body weight (4 days after viral exposure): Reduced body weight loss was observed in VIR-7831-WT groups (≥5 mg/kg) compared with the control antibody group.	CTD 5.3.5.4: 2020N457284

[13)] Approximately 10, 20, 50, or 100 times the concentration of EC_{50} of neutralizing activity (geometric mean: 100.75 ng/mL) of VIR-7832 against SARS-CoV-2 (isolate: USA-WA1/2020)

[14)] Approximately 0.5 times the concentration of EC_{50} of neutralizing activity (geometric mean: 100.75 ng/mL) of VIR-7832 against SARS-CoV-2 (isolate: USA-WA1/2020)

Animal species (number of animals/group)	Dosage regimen, method for viral exposure	Summary of main results	Submission data CTD
		Viral load and titer in pulmonary tissue (4 days after viral exposure): Reduced viral load (≥5 mg/kg) and reduced viral titer (≥0.5 mg/kg) were observed in VIR-7831-WT groups compared with the control antibody group.	
Syrian hamsters (4 females/group)	GH-S309 0.1, 0.4, 1.5, 4 mg/kg or the control antibody 4 mg/kg was administered intraperitoneally 2 days before intranasal inoculation of SARS-CoV-2 (BetaCov/Belgium/GHB-03021/2020, 2×10^6 $TCID_{50}$/animal)	Viral load and titer in pulmonary tissue (4 days after viral exposure): Reduced viral load was observed in GH-S309 group (4 mg/kg). No significant difference was observed in viral titer. Histopathological examination of the lung (necropsied 4 days after viral exposure): Pathological score[b)] of lung injury improved in GH-S309 group (4 mg/kg) compared with the control antibody group.	CTD 5.3.5.4: 2021N471868
Syrian hamsters (6 males/group)	Sotrovimab 0 (vehicle), 0.05, 0.5, 5, 15 mg/kg or the control antibody 15 mg/kg was administered intraperitoneally 2 days before intranasal inoculation of SARS-CoV-2 (USA-WA1/2020, 7.4×10^4 $TCID_{50}$/animal)	Body weight (4 days after viral exposure): Reduced body weight loss was observed in sotrovimab groups (≥5 mg/kg) compared with the control antibody group. Viral load and titer in pulmonary tissue (4 days after viral exposure): Reduced viral load and titer were observed in sotrovimab groups (≥0.5 mg/kg) compared with the control antibody group.	CTD 5.3.5.4: 2021N471990
Syrian hamsters (3 each of males and females/group)	Sotrovimab 0 (physiological saline), 0.5, 5, 30 mg/kg or the control antibody 30 mg/kg was administered intraperitoneally 1 day before intranasal inoculation of strain B.1.1.7 (Alpha) SARS-CoV-2 (isolate: UK/VUI/3/2020, 1.58×10^6 $TCID_{50}$/animal)	Body weight (4 days after viral exposure): Reduced body weight loss was observed in sotrovimab groups (≥5 mg/kg) compared with the control antibody group.	CTD 5.3.5.4: 2021N475485
Syrian hamsters (6 females/group)	Sotrovimab 0.5, 2, 5, 15 mg/kg or the control antibody 15 mg/kg was administered intraperitoneally 2 days before intranasal inoculation of strain B.1.351 (Beta) SARS-CoV-2 (isolate: hCoV-105 19/Belgium/rega-1920/2021, 1×10^4 $TCID_{50}$/animal)	Viral load and titer in pulmonary tissue (4 days after viral exposure): Reduced viral load (≥0.5 mg/kg) and reduced viral titer (≥2 mg/kg) were observed in sotrovimab groups compared with the control antibody group.	CTD 5.3.5.4: 2021N480075

a) The 15 mg/kg group received sotrovimab 2 days before viral exposure only, and the 30 mg/kg group received sotrovimab 1 day before viral exposure only.
b) Sum of the severity scores (rating scale of 0-3) of the lung injury (congestion, intra-alveolar hemorrhage, apoptotic bodies within bronchial wall, necrotizing bronchitis, perivascular edema, bronchopneumonia, perivascular inflammation, peribronchial inflammation, and vasculitis)

3.2 Secondary pharmacology

3.2.1 *In vitro* antibody-dependent enhancement (ADE) (CTD 4.2.1.2: 2020N456687)

SARS-CoV-2 (isolate: USA-WA1/2020) was cultivated with various cells expressing FcγR (human monocyte-derived dendrocytes [moDC], human peripheral mononuclear cells [PBMC], human monocyte-derived cell line [U937]) or with Vero E6 cells in the presence of sotrovimab (0, 0.00143, 0.0143, 0.143, or 143 ng/mL[15)]). Viral entry and replication were observed only in Vero E6 cells, whereas no enhancement of viral entry or replication was observed in FcγR-expressing cells in the presence of sotrovimab. Addition of sotrovimab did

15) The neutralizing activity of sotrovimab against SARS-CoV-2 was investigated at the concentration range from around EC_{50} (100.1 ng/mL, see Section 3.1.2.1) to approximately 1/100,000 times the EC_{50}. There is a report that FcγR-dependent ADE was observed below the antibody concentrations required for the sufficient neutralizing activity (*Immunol Rev*. 2015;268:340-64).

not increase the production of cytokines and chemokines (interferon [IFN-γ], interleukin (IL)-10, IL-6, IL-8, interferon inducible protein-10 (IP-10)/CXCL-10, monocyte chemoattractant protein-1 (MCP-1)/CCL2, and tumor necrosis factor [TNF-α]) in the culture supernatant of any cells investigated.

3.3 Pharmacodynamic interaction

3.3.1 *In vitro* effect of co-administration of sotrovimab with remdesivir (CTD 4.2.1.4:2020N456694)

Recombinant SARS-CoV-2 virus[16)] was treated with sotrovimab 3 to 2,160 ng/mL and remdesivir 50 to 12,353 ng/mL, and after cultivation in Vero E6 cells for 24 hours, the combined effect of the neutralization activity was investigated by luciferase reporter assay that detects intracellular viral infection. The synergistic effect evaluated by MacSynergyII program[17)] was 24.17 μ (mol/L)^2%, showing an additive effect, and no competitive effect.

3.4 Safety pharmacology

Safety pharmacology was evaluated based on the clinical symptoms in a 2-week repeated intravenous toxicity study in cynomolgus monkeys [see Section 5.2]. The applicant explained that sotrovimab did not cause any effect on the cardiovascular, respiratory, or central nervous system.

3.R Outline of the review conducted by PMDA

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

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

Sotrovimab has been shown to exert its neutralization activity against SARS-CoV-2 by binding to the epitope on RBD different from ACE2-binding site [see Sections 3.1.2.1 and 3.1.2.2]. It has been shown *in vitro* that sotrovimab does not compete with ACE2 in its binding to RBD [see Section 3.1.1.3]. The mechanism in which the binding of sotrovimab to RBD leads to neutralizing effect is unknown. However, one or a combination of mechanisms of bivalent binding specific to IgG (binding to S-protein trimer, steric hindrance, or aggregation of viral particles [*J Gen Virol*. 2002;83:2091-108]) is suggested to contribute to the SARS-CoV-2-neutralization activity of sotrovimab since S309, the parental antibody of sotrovimab, demonstrated a complete neutralizing effect against pseudovirus particles, while the neutralization activity of Fab region of S309 was approximately 80% at best (*Nature*. 2020;583:290-5).

In an *in vitro* study, sotrovimab induced NK cell-mediated ADCC activity and monocyte-mediated ADCP activity against S-protein-expressing cells [see Section 3.1.2.3]. On the other hand, GH-S309, a chimeric antibody prepared by introducing Fc region of hamster IgG2a into S309, the parental antibody of sotrovimab, showed a higher binding affinity to hamster spleen cells than sotrovimab. In a study with a hamster model of SARS-CoV-2 infection, antiviral activity was similar between the group receiving GH-S309 and the group receiving VIR-7831-WT, an antibody without LS mutation (M438L and N444S) in Fc region of sotrovimab

16) Prepared by replacing Open Reading Frame (ORF)-7 gene of SARS-CoV-2 (isolate: USA-WA1/2020) with nanoluciferase gene.

17) The synergistic effect was defined as additive if synergistic amount [μ (mol/L)^2 %] was <25, weakly synergistic if 25 to <50, moderately synergistic if 50 to <100, and potently synergistic if >100 (*Antiviral Res*. 1990;14:181-205).

[see Section 3.1.4]. These results suggest that the contribution of Fc-region-mediated effector function is minor compared with the neutralization activity of sotrovimab against SARS-CoV-2.

PMDA's view:
Sotrovimab has been shown to have neutralization activity against SARS-CoV-2, suggesting the efficacy against COVID-19 from the pharmacological point of view.

3.R.2 Neutralization activity against variants

The applicant's explanation about the neutralization activity of sotrovimab against variants:
In vitro studies did not show any decrease in the neutralization activity of sotrovimab against variants of concern (VOC) or against variants of interest (VOI)[18] tested [see Section 3.1.2.2], and *in vivo* studies confirmed the neutralization activity of sotrovimab in hamsters infected with strain B.1.1.7 (Alpha) or B.1.351 (Beta) [see Section 3.1.4]. *In vitro* studies using pseudovirus particles engineered to express S-protein with various amino acid mutations showed decreased neutralization activity of sotrovimab against virus particles with amino acid mutations P337 (H/K/L/R/T), E340 (A/K/G/Q), or K356T in the sotrovimab-binding epitope [see Section 3.1.2.2.1]. However, P337, E340, and K356 are retained in ≥99.99% of the amino acid sequences of S-protein registered in the latest GISAID database (as of July 16, 2021). At present, these results suggest that there is no variant that affects the neutralization activity of sotrovimab.

PMDA's view:
At present, sotrovimab is expected to have neutralization activity against the VOC and VOI evaluated. Whether sotrovimab has neutralization activity against novel variants is an important information regarding the efficacy. Relevant information should be collected continuously after the market launch, and new findings should be promptly provided to healthcare professionals. Clinical efficacy against variants is discussed in Section 7.R.1.

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

The applicant's explanation about ADE by sotrovimab:
When the titer of a virus-targeted antibody is below the exposure level showing neutralization activity, there is a possibility that the binding of the antibody to the virus or to FcγR-expressing cells leads to enhanced viral intrusion into cells or that formation of antibody-antigen complex enhances cytokine production (*Nat Rev Immunol*. 2020;20:633-43, *Cell*. 2021;184:4203-19). Since the extrapolability of these findings to clinical situations has not been established, caution is required to their interpretation. In the *in vitro* studies [see Section 3.2.1] and in the hamster model of SARS-CoV-2 [see Section 3.1.4], increase in the viral load or histopathological aggravation was not observed in any of the group receiving sotrovimab, VIR-7831-WT, or GH-S309, compared with the control group, failing to show results suggestive of ADE. The applicant considers that sotrovimab is unlikely to cause ADE based on the above results of the nonclinical studies.

[18] Variants defined as VOC or VOI by WHO as of September 6, 2021 [https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/ (last accessed on September 6, 2021)], National Institute of Infectious Diseases as of August 28, 2021 [https://www.niid.go.jp/niid/images/epi/corona/57/covid19-57.pdf (last accessed on September 6, 2021)], and US CDC as of September 6, 2021 [https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html (last accessed on September 6, 2021])

PMDA considers that the applicant's explanation is acceptable from the viewpoint of nonclinical pharmacology.

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

Pharmacokinetics (PK) of sotrovimab was investigated in monkeys. Serum concentration of sotrovimab in monkeys was measured by ELISA (lower quantitation limit: 50 ng/mL), and anti-drug antibodies (ADA) by electrochemiluminescence immunoassay.

4.1 Absorption

4.1.1 Single dose study (CTD 4.2.2.2)

Table 10 shows PK parameters following a single intravenous infusion of sotrovimab 5 mg/kg in monkeys (3 each of males and females) over 1 hour. ADA was negative in all animals studied.

Table 10. PK parameters following a single intravenous infusion of sotrovimab 5 mg/kg in monkeys

Sex	C_{max} (μg/mL)	t_{max} (days)	$t_{1/2}$ (days)	V_{ss} (mL/kg)	CL (mL/day/kg)	AUC_{last} (day·μg/mL)	AUC_{inf} (day·μg/mL)
Male	127±10.4	0.0451 [0.0451, 0.0451]	18.8±3.71	85.6±2.36	3.41±0.706	1,320±195	1,510±310
Female	114±12.1	0.0451 [0.0451, 0.0451]	16.7±7.02	93.7±15.0	4.33±1.01	1,070±160	1,200±293

Mean ± SD; t_{max} is median value [range]

4.1.2 Repeated-dose study (CTD 4.2.3.2)

Table 11 shows PK parameters following 2-week repeated-dose intravenous infusion of sotrovimab once every week to monkeys (5 each of males and females). No difference was observed in PK parameters between ADA-positive and ADA-negative animals.

Table 11. PK parameters in 2-week repeated intravenous infusion of sotrovimab 5 mg/kg once weekly to monkeys

Dose (mg/kg)	Duration of infusion	Sex	C_{max}(μg/mL)		t_{max}(h)		AUC_{tau} (day·μg/mL)		Number of ADA-positive animals
			Week 1	Week 2	Week 1	Week 2	Week 1	Week 2	
50	0.2	M	1,150±103	1,540±176	1.2 [0.3, 2.2]	1.2 [0.3, 1.2]	3,940±370	6,580±621	0/5
		F	1,120±80.8	1,550±74.4	0.3 [0.3, 1.2]	0.3 [0.3, 1.2]	3,900±114	5,920±332	3/5
150	0.6	M	3,710±432	5,080±535	0.7 [0.7, 1.6]	1.6 [0.7, 1.6]	13,400± 1,780	20,800± 2,320	2/5
		F	3,160±123	4,390±369	0.7 [0.7, 1.6]	1.6 [0.7, 4.6]	11,400± 758	18,500± 1,600	3/5
500	2.0	M	10,700± 1,470	13,300± 2,220	4.0 [2.1, 4.0]	2.1 [2.1, 3.0]	36,600± 2,160	50,400± 5,630	2/5
		F	10,300± 1,590	13,600± 3,230	3.0 [2.1, 4.0]	2.1 [2.1, 3.0]	33,000± 5,330	45,800± 7,500	1/5

Mean ± SD; t_{max} in median [range]

4.2 Distribution

No distribution study was conducted.

The applicant's explanation:
Following a single intravenous dose of sotrovimab in monkeys, the distribution volume of sotrovimab at steady state [see Section 4.1.1] was not significantly different from the plasma volume of monkeys (44.8 mL/kg), suggesting that extravascular distribution of sotrovimab is minimal. Human IgG1 is known to cross the blood-placental barrier (*Front Immunol*. 2017;8:1294), suggesting that the IgG1 product of sotrovimab may cross the placenta.

4.3 Metabolism and excretion

No studies on metabolism and excretion have been conducted.
The applicant's explanation:
Since sotrovimab is an antibody drug and is considered to be eliminated through the protein degradation pathway, no studies on metabolism or excretion were conducted according to "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" (PFSB/ELD Notification No. 0323-1 dated March 23, 2012). Since human IgG is known to be excreted in milk (*Nutrients*. 2011;3:442-74), the IgG1 product of sotrovimab may be excreted in milk.

4.R Outline of the review conducted by PMDA

PMDA concluded that no particular problems were noticed in the results of the nonclinical pharmacokinetic studies submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant conducted repeated-dose toxicity studies, local tolerance studies, and tissue cross-reactivity studies as toxicity studies of sotrovimab. Sotrovimab specifically binds to S-protein of SARS-CoV-2, an adventitious agent. It is therefore unlikely to cross-react with components in animals. Nevertheless, to investigate the nonspecific binding, cynomolgus monkeys were used in the repeated dose toxicity study, and minipigs were used for the evaluation of local tolerance.

5.1 Single dose toxicity

No single dose toxicity study was conducted on sotrovimab. In the repeated-dose toxicity study that evaluated sotrovimab [see Section 5.2], there were no acute symptoms or death after the first dose of 500 mg/kg by intravenous administration. The approximate lethal dose was >500 mg/kg.

5.2 Repeated dose toxicity

A 2-week repeated-dose intravenous toxicity study was conducted in cynomolgus monkeys (Table 12). No systemic toxicity was observed. The no observed adverse effect level was determined to be 500 mg/kg, and the exposure (AUC_{0-t}) to sotrovimab after the first administration at the no observed adverse effect level was 34,800 μg•day/mL.

Table 12. Summary of results of repeated-dose toxicity study

Animal	Route of administration	Treatment period	Dose (mg/kg)	Main findings	No observed adverse effect level (mg/kg)	Submission data CTD
Male and female cynomolgus monkeys	i.v.	2 weeks (once/week) + 105-day recovery period	0[a)], 50, 150, 500	None Recovery period None	500	CTD 4.2.3.2: 2021N468234

a) Vehicle: 20 mmol/L histidine buffer (pH 6.0) containing 8% (w/v) sucrose, 5 mmol/L L-methionine, and 0.04% (w/v) polysorbate 80

5.3 Genotoxicity

Sotrovimab is a monoclonal antibody that does not pass through the nuclear or mitochondrial membrane, and is unable to directly interact with DNA or other chromosomal substances in the nucleus. It is thus considered to pose no genotoxicity concern, and no genotoxicity study was conducted.

5.4 Carcinogenicity

Sotrovimab is administered for only a short duration in humans. In addition, it targets an adventitious agent and does not cross-react with human tissues [see Section 5.7.1]. It is therefore unlikely to be carcinogenic, and no carcinogenicity study was conducted.

5.5 Reproductive and developmental toxicity

Sotrovimab targets an adventitious agent and does not cross-react with human tissues [see Section 5.7.1]. Therefore, no reproductive toxicity study was conducted. No effect on male and female reproductive organs was observed in the repeated dose toxicity study on sotrovimab [see Section 5.2].

5.6 Local tolerance

Local tolerance to intravenous administration of sotrovimab was evaluated in the repeated intravenous toxicity study [see Section 5.2]. No local irritation was observed. Local tolerance in intramuscular injection of sotrovimab was evaluated in a local tolerance study in minipigs. No local irritation was observed (Table 13).

Table 13. Summary of results of local tolerance study

Animal	Method	Main findings	Submission data CTD
Female minipigs (Göttingen)	Sotrovimab: 4 mL (62.5 mg/mL) administered into the right neck muscle Vehicle: 4 mL administered into the left neck muscle of the same animal	None	CTD 4.2.3.6: 2021N470452

Vehicle: 20 mmol/L histidine buffer (pH 6.0) containing 7.0% (w/v) sucrose, 5 mmol/L L-methionine, and 0.04% (w/v) polysorbate 80

5.7 Other studies

5.7.1 Tissue cross-reactivity

Tissue cross-reactivity was investigated for sotrovimab using frozen sections of normal tissues of humans and cynomolgus monkeys. No cross-reactivity was observed in any of the tissues evaluated (Table 14). In addition, binding of sotrovimab to 66 types of proteins secreted or expressed on the cell membrane surface of human embryos and fetuses was evaluated. No binding was observed in any of the proteins investigated (CTD 4.2.3.7: 2021N468478).

Table 14. Summary results of tissue cross-reactivity studies

Test system	Method	Results	Submission data CTD
Human normal tissues	Binding of sotrovimab 1 and 5 μg/mL to tissues was evaluated by immunohistochemical staining (avidin-biotin method) using frozen tissue sections.	No cross-reactivity	CTD 4.2.3.7: 2020N456662
Cynomolgus monkey normal tissues	Binding of sotrovimab 1 and 5 μg/mL to tissues was evaluated by immunohistochemical staining (avidin-biotin method) using frozen tissue sections.	No cross-reactivity	CTD 4.2.3.7: 2020N457086

5.R Outline of the review conducted by PMDA

PMDA's view:

No particular safety problems are suggested in administering sotrovimab to humans from the toxicological point of view.

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

6.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

During the development process of sotrovimab, changes were made to the manufacturing process and site of the drug substance and to the formulation and manufacturing site of the drug product. After each change, the comparability of quality attributes was demonstrated between the pre-change and post-change drug substances and between the pre-change and post-change drug products [see Sections 2.1.4 and 2.2.3].

Sotrovimab concentration in human serum and ADA were measured by electrochemiluminescence immunoassay (lower quantitation limit for sotrovimab: 100 ng/mL).

6.2 Clinical pharmacology

The applicant submitted the results of a foreign phase II/III study (the COMET-ICE study) in patients with COVID-19 and results of population pharmacokinetics (PPK) analysis. PK parameters are expressed in means unless specified otherwise.

6.2.1 Foreign phase II/III study (CTD 5.3.5.1: the COMET-ICE study [ongoing since August 2020]; data cut-off on April 27, 2021)

A single dose of sotrovimab 500 mg was infused intravenously over 1 hour to patients ≥18 years of age with COVID-19, and PK was investigated. Table 15 shows PK parameters in the introductory part (9 PK-evaluable patients). Serum concentration 28 days after dosing ($C_{28\ day}$) (mean ± SD) in the expanded part (363 PK-evaluable patients) was 25.8 ± 8.3 μg/mL.

ADA was positive in 10 of 391 patients in the sotrovimab group.

Table 15. PK parameters following a single dose intravenous infusion of sotrovimab 500 mg in non-Japanese patients with COVID-19 (The COMET-ICE study, introductory part)

C_{max} (μg/mL)	$C_{28\ day}$ (μg/mL)	t_{max} (days)	$t_{1/2}$ (days)	V_{ss} (L)	CL (mL/day)	$AUC_{0\text{-}28\ day}$ (day·μg/mL)	AUC_{last} (day·μg/mL)	AUC_{inf} (day·μg/mL)
219±100	37.2±2.9	0.04 [0.04, 0.05]	49.3±7.3	8.1±0.9	125±22	1,529±147[a)]	3,714±537	4,116±694

Mean ± SD; t_{max} in median [range]
a) N = 8

6.2.2 PPK analysis (CTD 5.3.3.5)

Using PK data of sotrovimab (1,466 measuring time points in 476 patients; data cut off on April 27, 2021) in patients with COVID-19 obtained from the COMET-ICE study, PPK analysis (SAS 9.4) was conducted. The PPK model was described by a 2-compartment model with first-order elimination with allometric scaling based on body weight and body mass index (BMI). Body weight and BMI were identified as covariates for total body clearance (CL), inter-compartmental clearance (Q), volume of distribution of the central compartment (V1), and volume of distribution of the peripheral compartment (V2).[19)]

Using the above PPK model, PK parameters were estimated a posteriori in patients with COVID-19 receiving a single intravenous dose of sotrovimab 500 mg in the COMET-ICE study.

Table 16. PK parameters in foreign patients with COVID-19 receiving a single dose intravenous infusion of sotrovimab 500 mg (the COMET-ICE study, post hoc estimate)

C_{max}(μg/mL)	$t_{1/2}$ (days)	V_{ss}(L)	CL (mL/day)	$AUC_{0\text{-}28\ day}$(day·μg/mL)
123±41	45.0±4.8	12.0±4.4	200±100	1,077±279

Mean ± SD

6.R Outline of the review conducted by PMDA

6.R.1 Difference in PK of sotrovimab between Japanese and non-Japanese populations

The applicant's explanation about the difference in PK of sotrovimab between Japanese and non-Japanese populations:

No data are available on PK of sotrovimab in Japanese population. However, ethnic factors are unlikely to affect PK significantly due to the following reasons: (a) Since sotrovimab is an antibody against an adventitious agent, the elimination process of sotrovimab is unlikely to differ among different ethnicities, and (b) intrinsic factors such as renal and hepatic function test values were not identified as covariates in PPK analysis [see Section 6.2.2].

Currently, a phase I study (Study 217653)[20)] in healthy adults (Japanese and Caucasians) is ongoing to investigate PK, safety, etc., of a single intravenous infusion or intramuscular injection of sotrovimab 500 mg.

19) The following parameters were investigated as candidates for covariates: Age, body weight, BMI, height, total bilirubin, ALT, AST, direct bilirubin, albumin, eGFR, country (USA, Canada, Brazil, Spain), race (White, Black, African American, Asian, American Indian, Alaska Natives, other), ethnicity (Hispanic and Latin American, non-Hispanic and non-Latin American), sex, presence/absence of ADA on Day 29 after randomization, time from the onset of symptom, presence/absence of congestive heart failure, presence/absence of chronic kidney disease, presence/absence of diabetes mellitus, use/non-use of dexamethasone within past 28 days, and baseline viral load.

20) The study consisted of Part 1 for intravenous infusion and Part 2 for intramuscular injection, and enrolled approximately 8 each of Japanese and Caucasian subjects in the sotrovimab group and 2 each of Japanese and Caucasian subjects in the placebo group. The target sample size was 40 evaluable subjects.

Patient enrollment had been completed on August 3, 2021, and data of intravenous infusion are expected to become available in October 2021.

PMDA's view:
At present, no PK data of sotrovimab in Japanese subjects are available. However, the applicant's explanation that PK of sotrovimab is unlikely to differ significantly between Japanese and non-Japanese based on the following reasoning is acceptable: (a) Sotrovimab is an antibody against an adventitious agent and (b) since sotrovimab undergoes metabolism and is degraded into amino acids as are the cases with IgG antibodies in the body, the elimination process is unlikely to be different among different ethnicities.

As soon as the results of the ongoing phase I study (Study 217653) investigating PK, safety, etc., in healthy adults (Japanese and Caucasians) become available, appropriateness of the dosage regimen in Japanese subjects should be evaluated, and new findings should be provided promptly to healthcare professionals.

6.R.2 Rationale for the proposed dosage and administration for adult patients

The applicant's explanation about the rationale for proposing the dosage and administration as a single dose intravenous infusion of sotrovimab 500 mg:

- The target sotrovimab concentration in serum was investigated by referring to the lung/serum ratio (approx. 0.25) of IgG antibody concentration in animals (*Cancer Res*. 1994;54:1517-28). Serum sotrovimab concentration necessary to obtain intrapulmonary sotrovimab concentration in excess of EC_{90} against SARS-CoV-2 was calculated to be ≥1.32 μg/mL from the maximum level of EC_{90} (0.33 μg/mL) against SARS-CoV-2. Taking the sensitivity of the virus to sotrovimab into account, the target sotrovimab concentration in serum was set at 13.2 μg/mL.
- From the PK data in monkeys, it was predicted that serum sotrovimab concentration exceeds the above target concentration up to Day 28 after single dose intravenous infusion of sotrovimab 500 mg to humans. Accordingly, a single dose intravenous infusion of sotrovimab 500 mg was employed as the dosage regimen in the COMET-ICE study. In this study, the serum sotrovimab concentration on Day 28 was 37.2 μg/mL in the introductory part and 25.8 μg/mL in the expanded part, exceeding the target concentration [see Section 6.2.1].

The protocol for the foreign phase II/III study (the COMET-ICE study) had specified that sotrovimab be administered over 1 hour. In the BLAZE-4 study (NCT04634409) administering sotrovimab in combination with bamlanivimab, another IgG antibody targeted at S-protein of SARS-CoV-2, to unhospitalized patients with mild to moderate COVID-19, serious adverse events, infusion-related reactions, etc., were not observed in patients receiving sotrovimab 500 mg over 30 minutes in combination with bamlanivimab [see Section 7.R.2]. Accordingly, the proposed dosage and administration for sotrovimab was infusion over 30 minutes.

PMDA's view:
The applicant's explanation about the rationale for the dosage and administration in adult patients is acceptable from the aspect of the clinical pharmacology. The appropriateness of the proposed dosage and administration is discussed further, taking account of the efficacy and safety in clinical studies [see Section 7.R.5].

6.R.3 Rationale for the proposed dosage and administration for pediatric patients

The applicant's explanation for proposing the dosage and administration for pediatric patients aged ≥12 years weighing ≥40 kg as "a single dose intravenous infusion of sotrovimab 500 mg":
Although PK data of sotrovimab in pediatric patients have not been available, body weight of pediatric patients aged ≥12 years weighing ≥40 kg largely overlaps the body weight range in adults, suggesting that a similar extent of exposure as in adults is achieved in pediatric patients. Sotrovimab has a binding capacity specific to S-protein of SARS-CoV-2, an adventitious agent, and does not cross-react with human tissues [see Section 5.7.1]. These results suggest that sotrovimab does not pose any safety or efficacy concern different from that in adults.

A phase III study (the COMET-TAIL study)[21] in ≥12-year-old patients with mild to moderate COVID-19 with risk factors for severe COVID-19 is currently ongoing and, as of [redacted], patient enrollment has been completed (including [redacted] pediatric patients aged ≥12 and <18 years). Results of the study are [redacted] available in [redacted]. Also, a clinical study in <18-year-old patients with COVID-19 is being planned.

PMDA's view:
At present, data of clinical studies in pediatric patients are unavailable. However, PMDA understands, to a certain extent, the applicant's explanation that treating pediatric patients aged ≥12 years of age weighing ≥40 kg with the same dosage and administration as that in adults is unlikely to pose any particular safety or efficacy concern. The current outbreak of COVID-19 also warrants the applicant's proposal to use the above dosage in pediatric patients. The Emergency Use Authorization of the US stipulates that the dosage in pediatric patients aged ≥12 years and weighing ≥40 kg should be the same as that in adults.

As soon as the results of the ongoing phase III study (the COMET-TAIL study) in adults and pediatric patients aged ≥12 years, etc., become available, the appropriateness of the above dosage and administration in pediatric patients should be evaluated, and new findings should be promptly provided to healthcare professionals.

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

The applicant submitted the results of clinical study shown in Table 17 as the main efficacy and safety data.

[21] The study includes sotrovimab 500 mg intravenous infusion group, sotrovimab 500 mg intramuscular injection group, and sotrovimab 250 mg intramuscular injection group. The target sample size is 1,020 (340 per group).

Table 17. Summary of clinical studies

Data category	Region	Study identifier	Phase	Population	No. of subjects enrolled	Dosage regimen	Main evaluation items
Evaluation	Foreign	COMET-ICE	II/III	Patients with COVID-19	(a) 528 (b) 529	(a) Sotrovimab group: Sotrovimab 500 mg was administered as a single intravenous dose. (b) Placebo group: Placebo was administered as a single intravenous dose.	Efficacy Safety PK

7.1 Foreign phase II/III study (CTD 5.3.5.1: the COMET-ICE study [ongoing since August 2020], data cut-off on April 27, 2021)

A placebo-controlled, randomized, double-blind, parallel-group study in ≥18-year-old patients with COVID-19 (target sample size: 20 in introductory part [10 per group], 1,360 in expanded part [680 per group][22)]) was conducted to investigate the efficacy and safety of sotrovimab at 57 study sites in 5 countries (US, Brazil, Spain, Canada, and Peru). Table 18 shows the main inclusion/exclusion criteria of the study. Patients with risk factors for severe COVID-19 not requiring oxygen therapy were eligible for the study.

Table 18. Main inclusion/exclusion criteria

Inclusion criteria	1. Has a SARS-CoV-2-positive diagnostic test (by RT-PCR, antigen test, etc., using a sample collected within 7 days before enrollment) 2. Has symptoms consistent with COVID-19 within 5 days before enrollment 3. Maintains O_2 saturation ≥94% on room air 4. Has at least one of the following risk factors for severe COVID-19: ・ ≥55 years old ・ Diabetes requiring drug therapy ・ Obesity (BMI >30 kg/m^2[a)] or 35 kg/m^2[b)]) ・ Chronic renal impairment (eGFR <60 mL/min/1.73 m^2) ・ Congestive heart failure (NYHA class ≥II) ・ Chronic obstructive pulmonary disease (chronic bronchitis, chronic obstructive pulmonary disease, or emphysema accompanied by exertional dyspnea) ・ Moderate to severe asthma (patients requiring inhaled corticosteroids for controlling symptoms or those prescribed with oral corticosteroid within 1 year before enrollment)
Exclusion criteria	1. Patients currently hospitalized or determined by the investigator as likely to require hospitalization in the next 24 hours or as likely to die in the next 7 days 2. Patients with symptoms consistent with severe COVID-19 (defined as shortness of breath at rest, respiratory distress, or requiring oxygen therapy) 3. Patients with severely immunodeficient condition 4. Patients who have received vaccine against COVID-19 before randomization or those who are scheduled to receive the vaccine within 4 weeks after the study drug administration

a) Clinical study protocol ver. 1 (July 27, 2020)
b) Clinical study protocol, 1st revision (December 22, 2020)

A single dose of sotrovimab 500 mg or placebo was infused intravenously over 1 hour.

Upon confirmation of safety up to Day 15 after sotrovimab administration by the independent data monitoring committee (IDMC) in the introductory part, the study was to proceed to the expanded part. When approximately 41% and approximately 64% of the target number of subjects made Day 29 visit, 2 interim analyses were to be conducted to decide early termination for efficacy or for futility. As a result of the first interim analysis (data cut-off on March 4, 2021), IDMC recommended study discontinuation for fulfilling the pre-defined efficacy

22) Assuming that the percentage of patients who reach the primary endpoint "hospitalization for >24 hours for acute phase control of the disease or death for any reason within 29 days after randomization" is 10% in the sotrovimab group and 16% in the placebo group, the number of subjects necessary for ensuring the statistical power of approximately 90% with a significance level of 5% (2-sided) was calculated to be 1,360 (680 per group).

criteria. In response to the recommendation, the study was terminated early for efficacy and further randomization was cancelled. After all randomized patients had completed Day 29 visit or prematurely discontinued, the final analysis (data cut-off on April 27, 2021) was conducted.[23)]

In the first interim analysis (data cut-off on March 4, 2021), 583 patients (291 in the sotrovimab group, 292 in the placebo group) randomized on or before January 19, 2021 were included in the efficacy analysis set. Table 19 shows the percentage of subjects who reached the primary endpoint "hospitalization for >24 hours for acute phase control of the disease or death for any reason within 29 days after randomization (hereinafter referred to "event".[24)]" A statistically significant difference was observed between the sotrovimab group and the placebo group.

Table 19. Results of interim analysis for the primary endpoint (efficacy analysis set: data cut-off on March 4, 2021)

	Sotrovimab	Placebo
Incidence of events	1% (3 of 291 subjects)	7% (21 of 292 subjects)
Risk ratio [97.24% CI][a)]	0.15 [0.04, 0.56]	
P value[a)b)]	0.002	

Missing values were imputed by multiple imputation.

a) Poisson regression model with treatment group, time from symptom onset (≤3 days, 4-5 days), age (≤70, >70), and sex as covariates

b) A 2-sided significance level of 0.02758. The significance level of the entire study was 0.05 (2-sided). Hwang-Shih-DeCani (γ=1) alpha-spending function by the Lan-DeMets method was used to adjust for the multiplicity of the hypothesis testing in the interim analysis.

In the final analysis (data cut-off on April 27, 2021), 1,057 randomized subjects (528 in the sotrovimab group, 529 in the placebo group) were included in the intent-to-treat (ITT) population and subjected to efficacy analysis. A total of 1,049 subjects who were randomized and received the study drug (523 in the sotrovimab group, 526 in the placebo group) were included in the safety analysis set. The causes of discontinuation within 29 days after randomization were death in 4 subjects (4 in the placebo group), adverse events in 1 subject (1 in the placebo group), lost to follow-up in 1 subject (1 in the placebo group), physician's discretion in 2 subjects (2 in the sotrovimab group), and subject's request in 18 subjects (8 in the sotrovimab group, 10 in the placebo group).

Table 20 shows the percentage of subjects who reached the primary efficacy endpoint "hospitalization for >24 hours for acute phase control of the disease or death for any reason within 29 days after randomization (event)," showing a tendency similar to that observed in the interim analysis. Figure 1 shows Kaplan-Meier curves of the cumulative incidence of events of the primary endpoint.

Table 20. Results of final analysis of primary endpoint (ITT population: data cut-off on April 27, 2021)

	Sotrovimab	Placebo
Incidence of events	1% (6 of 528 subjects)	6% (30 of 529 subjects)
Risk ratio [95% confidence interval] [a)]	0.21 [0.09, 0.50]	
P value [a)]	<0.001	

Missing values were imputed by multiple imputation.

a) Poisson regression model with treatment group, time from symptom onset (≤3 days, 4-5 days), age (≤70, >70), and sex as covariates

23) Since the study was terminated early for efficacy as a result of the interim analysis, the results of the primary endpoint in the interim analysis was handled as the main data for evaluating the success or failure of the study. Since the results of the final analysis contain the results of a greater number of subjects than those of the interim analysis, PMDA also focused on the results of the final analysis in its evaluation.

24) The study drug was to be administered on the day of the randomization.

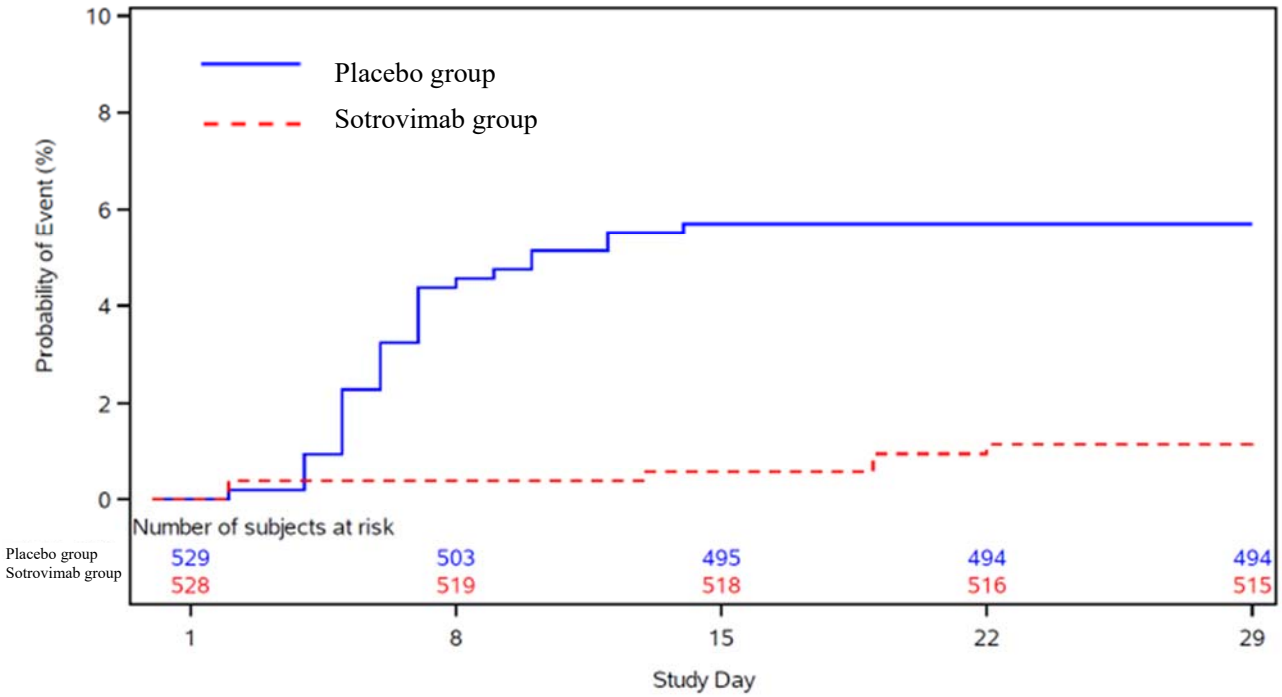

Fig. 1 Cumulative incidence of primary endpoint (ITT population: data cut-off on April 27, 2021)

Viral load was evaluated mainly on Day 8 after randomization. The change in the viral load (nasopharyngeal swab) from baseline to Day 8 after randomization (data cut-off on April 27, 2021, least squares mean [95% confidence interval] $\log_{10}$ copies/mL)[25] was −2.589 [−2.708, −2.470] in the sotrovimab group and −2.357 [−2.475, −2.240] in the placebo group, with the between-group difference of −0.232 [−0.399, −0.065]. Table 21 shows the change over time in the viral load (nasopharyngeal swab) from baseline to Day 29 after randomization.

Table 21. Change over time in viral load (nasopharyngeal swab) (data cut-off on April 27, 2021)

	Sotrovimab		Placebo	
	No. of subjects	Viral load[a] ($\log_{10}$ copies/mL)	No. of subjects	Viral load[a] ($\log_{10}$ copies/mL)
Baseline	358	6.554±1.625	375	6.652±1.673
Day 5	314	4.690±1.457	319	5.168±1.741
Day 8	294	4.039±1.207	305	4.284±1.346
Day 11	307	3.689±1.004	315	3.827±1.145
Day 15	274	3.371±0.665	289	3.428±0.834
Day 22	288	3.055±0.376	286	3.177±0.567
Day 29	295	3.023±0.395	306	3.040±0.400

Mean ± SD

a) Detection limit 3.17 $\log_{10}$ copies/mL, lower quantitation limit 3.35 $\log_{10}$ copies/mL. Value below detection limit was assumed to be "0.5 × detection limit." Value below the quantitation limit was assumed to be "lower quantitation limit − 0.5 × (lower quantitation limit − detection limit)." These values were then $\log_{10}$ transformed.

[25] The change in viral load was analyzed in the randomized subjects whose viral load in nasopharyngeal swab sample collected on the day of the study drug administration at the central laboratory was confirmed to be quantifiable. In the present application, data from approximately 90% of subjects in the analysis set were submitted (358 in the sotrovimab group, 375 in the placebo group, data cut-off on April 27, 2021).

Adverse events were observed in 22% (114 of 523) of subjects in the sotrovimab group and in 23% (123 of 526) of subjects in the placebo group (data cut-off on April 27, 2021). Table 22 shows the incidence of adverse events and adverse drug reactions with an incidence of ≥1% in either group.

Table 22. Adverse events and adverse drug reactions with an incidence of ≥1% in either group (safety analysis set: data cut-off on April 27, 2021)

Event	Adverse events		Adverse drug reactions	
	Sotrovimab (n = 523)	Placebo (n = 526)	Sotrovimab (n = 523)	Placebo (n = 526)
Total	114(22)	123(23)	8(2)	9(2)
Diarrhoea	8(2)	4(<1)	0	0
COVID-19 pneumonia	5(<1)	22(4)	0	2(<1)
Nausea	5(<1)	9(2)	1(<1)	1(<1)
Headache	4(<1)	11(2)	1(<1)	0

Number of subjects (%), MedDRA(Version 23.1)

Adverse events leading to death were observed in 4 subjects in the placebo group (COVID-19 pneumonia in 2, pneumonia and respiratory failure in 1 subject each). A causal relationship to the study drug was denied for all of them.

Serious adverse events were observed in 11 subjects in the sotrovimab group (COVID-19 pneumonia in 3, diverticulitis in 2, diabetes mellitus, non-small cell lung cancer, small intestinal obstruction, adenocarcinoma pancreas, diabetic foot, and myocardial ischaemia in 1 subject each) and in 32 subjects in the placebo group (COVID-19 pneumonia in 20, pneumonia in 3, COVID-19 and acute kidney injury in 2 subjects each, acute respiratory failure, pulmonary embolism, respiratory distress, respiratory failure, gastrooesophageal reflux disease, obstructive pancreatitis, dehydration, hypovolaemia, cardio-respiratory arrest, and peripheral artery thrombosis in 1 subject each [some subjects had more than 1 event]). Causal relationship to the study drug could not be ruled out for COVID-19 pneumonia in 2 subjects in the placebo group. The outcome was recovery in both of them.

An adverse event leading to treatment discontinuation was observed in 1 subject in the placebo group (nausea), but its causal relationship to the study drug was denied.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

7.R.1.1 Efficacy in patients with COVID-19

The applicant's explanation about the efficacy of sotrovimab in patients with COVID-19:

In the COMET-ICE study, the efficacy endpoint was "the percentage of subjects hospitalized for >24 hours for acute phase control of the disease or death for any reason within 29 days after randomization." COVID-19 causes not only respiratory pathologies such as hypoxemia but also a wide range of pathologies in multiple organ systems (*JAMA*. 2020;324:782-93). The above endpoint allows comprehensive assessment of the pathologic conditions related to COVID-19, and is thus a clinically important endpoint. Table 23 shows the

results. In the interim analysis, a statistically significant difference was observed between the sotrovimab group and the placebo group, and a similar trend was observed also in the final analysis.

Table 23. Results of the primary endpoint in foreign phase II/III study (the COMET-ICE study) (reproduced from Tables 19 and 20)

	Interim analysis (data cut-off on March 4, 2021)		Final analysis (data cut-off on April 27, 2021)	
	Sotrovimab	Placebo	Sotrovimab	Placebo
Incidence of events	1% (3 of 291 subjects)	7% (21 of 292 subjects)	1% (6 of 528 subjects)	6% (30 of 529 subjects)
Risk ratio [confidence interval][b)]	0.15 [0.04, 0.56]		0.21 [0.09, 0.50]	
P value[b)]	0.002[c)]		<0.001	

Missing values were imputed by multiple imputation.

a) The pre-defined efficacy criteria were met in the interim analysis, resulting in the early termination of the study.

b) Poisson regression model with treatment group, time from symptom onset (≤3 days, 4-5 days), age (≤70, >70), and sex as covariates. 97.24% CI in the interim analysis and 95% CI in the final analysis.

c) A 2-sided significance level of 0.02758. The significance level of the entire study was 0.05 (2-sided). Hwang-Shih-DeCani (γ=1) alpha-spending function by the Lan-DeMets method was used to adjust for the multiplicity of the hypothesis testing in the interim analysis.

As for the effect of SARS-CoV-2 variants, the main SARS-CoV-2 strains observed in the countries of the study during the conduct of the COMET-ICE study were the wild strain, strains B.1.1.7 (Alpha) and P.1 (Gamma). Table 24 shows the number of subjects with SARS-CoV-2 showing mutations related to VOC or VOI among 275 subjects from whom samples were available for base sequence analysis of SARS-CoV-2 (137 in the sotrovimab group, 138 in the placebo group).[26)] The number of subjects with events of the primary endpoint "hospitalization for >24 hours for acute phase control of the disease or death for any reason" was 1 in the sotrovimab group (strain B.1.427/B.1.429) and 1 in the placebo group (strain B.1.1.7 [Alpha]). *In vitro* studies did not show any decrease in the neutralization activity of sotrovimab against VOC or VOI tested [see Section 3.R.2].

[26)] Nasopharyngeal swab samples that fulfill the following criteria were obtained from all subjects randomized and treated with the study drug and were subjected to analysis (detection limit: 4.5 $\log_{10}$ copies/mL). In the present application, data from approximately 38% of the subjects in the analysis set were submitted (137 in the sotrovimab group, 138 in the placebo group, data cut-off on May 18, 2021).

(a) Baseline (Day 1) samples in all subjects. Day 5 sample could be used in place in case the baseline sample was unavailable for use.

(b) Post-baseline samples obtained from subjects who had quantifiable viral load on Day 8 allowing base sequence analysis

- Evaluable samples obtained at the latest visit after baseline were used for base sequence analysis.
- In case a post-baseline sample was unavailable for use, a sample collected before or after the evaluation time point could be used in place.

Table 24. Subjects infected with SARS-CoV-2 containing mutations related to VOC or VOI in the COMET-ICE study (data cut-off on May 18, 2021)

Strain	Amino acid mutations tested	Sotrovimab (n = 137)	Placebo (n = 138)
B.1.1.7 (Alpha)	Deletion H69, deletion V70, deletion Y144, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H	5	6
B.1.351 (Beta)	L18F, D80A, D215G, R246I, deletion L242, deletion A243, deletion L244, K417N, E484K, N501Y, A701V	0	0
P.1 (Gamma)	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, H655Y, T1027I, V1176F	0	0
B.1.427/B.1.429	S13I, W152C, L452R	5	7
B.1.526 (Iota)	L5F, T95I, D253G, S477N or E484K, A701V	0	0
B.1.617.1 (Kappa)	T95I, G142D, E154K, L452R, E484Q, P681R, Q1071H	0	0
B.1.617.2 (Delta)	T19R, G142D, E156G, deletion F157, deletion R158, L452R, T478K, P681R, D950N	0	0
—	N501Y	1	1
—	L452R	0	2
—	S477N	3	4

Number of subjects
—: Not applicable

The above results demonstrate the efficacy of sotrovimab in patients with COVID-19 who have risk factors for severe COVID-19 but do not require oxygen therapy. The efficacy of sotrovimab in patients with COVID-19 without risk factors for severe COVID-19 has not been demonstrated.

Although Japanese patients with COVID-19 were not enrolled in the COMET-ICE study, the efficacy of sotrovimab can be expected in Japanese patients, based on the results of the study, taking into account that (a) diagnostic criteria for COVID-19, pathology, and risk factors for severe COVID-19 are similar between Japan and other countries, and there is no significant difference in the treatment guidelines with a focus on oxygen therapy and the types of drugs that can be used,[27] (b) sotrovimab is an antibody against an adventitious agent, and (c) PK of sotrovimab is unlikely to differ significantly between Japanese and non-Japanese subjects [see Section 6.R.1].

PMDA's view:
The applicant's explanation is acceptable that the data of the COMET-ICE study have demonstrated the efficacy of sotrovimab in patients with COVID-19 who have risk factors for severe COVID-19 but do not require oxygen therapy. Given that sotrovimab is a therapeutic agent urgently needed in clinical practice, it is acceptable that clinical data in Japanese patients with COVID-19 are unavailable at present. PMDA has concluded that sotrovimab is expected to demonstrate efficacy, to a certain extent, in Japanese patients with COVID-19, taking into account that (a) there is no significant difference in the diagnostic criteria for COVID-19, pathology, risk factors for severe COVID-19, treatments, etc., between Japan and other countries, (b) sotrovimab is an antibody against an adventitious agent and does not cross-react with human tissues, and (c) PK of sotrovimab is unlikely to differ significantly between Japanese and non-Japanese subjects [see Section 6.R.1].

[27] NIH Coronavirus Disease 2019 (COVID-19) Treatment Guidelines, Clinical Practice Guidelines for Novel Coronavirus Infection (COVID-19), ver. 5.3, Ministry of Health, Labour and Welfare (August 31, 2021)

As soon as the results of the ongoing phase I study (Study 217653) investigating PK, safety, etc., in healthy adults (Japanese and Caucasians) become available, information including effects on the efficacy and safety should be provided promptly to healthcare professionals. Information on the effect of anti-SARS-CoV-2 antibody on the efficacy of sotrovimab, which is being investigated in the COMET-ICE study, should be collected continuously after the market launch, and new findings should be provided to healthcare professionals appropriately.

The COMET-ICE study did not detect any significant decrease in the efficacy of sotrovimab against variants, neither did *in vitro* studies detect any decrease in the neutralization activity of sotrovimab against VOC and VOI tested [see Section 3.R.2]. These results suggest that sotrovimab has efficacy against these variants at present, although there are only limited clinical data available.

Information on the efficacy of sotrovimab on variants should be collected continuously after the market launch and provided appropriately to healthcare professionals.

7.R.1.2 Effect of epitope mutation on efficacy

The applicant's explanation about the possibility that viruses containing epitope mutations are induced or selected by sotrovimab administration and about the efficacy of sotrovimab in patients infected by these viruses:

In the COMET-ICE study, base sequence of SARS-CoV-2 could be analyzed at baseline in 259 subjects (127 in the sotrovimab group, 132 in the placebo group) and after baseline in 80 subjects (45 in the sotrovimab group, 35 in the placebo group). The gene sequence encoding S-protein of these virus strains was analyzed using the next-generation sequencing approach (data cut-off on May 18, 2021).[26)]

Epitope mutations were observed after baseline in 22.2% (10 of 45) of subjects in the sotrovimab group and in 0% (0 of 35) of subjects in the placebo group. One subject (E340K) reached the primary endpoint "hospitalization for >24 hours for acute phase control of the disease or death for any reason within 29 days after randomization." Mutations (allele frequency) observed in the sotrovimab group were E340K (99.7%-99.9%) in 4 subjects, S359G (8.2%, 12.2%) in 2 subjects, A344V (6.2%), R346G (5.2%), K356R (7.5%), and C361T (6.0%) in 1 subject each.

Among subjects with both baseline and post-baseline base sequence data, 20.0% (7 of 35) of subjects in the sotrovimab group and in 0% (0 of 29) of subjects in the placebo group showed new epitope mutation. The mutations observed in the sotrovimab group were E340K and S359G in 2 subjects each, A344V, K356R, and C361T in 1 subject each.

Epitope mutations were observed at baseline in 3.9% (5 of 127) of subjects in the sotrovimab group and in 3.0% (4 of 132) of subjects in the placebo group. None of these subjects reached the endpoint "hospitalization for >24 hours for acute phase control of the disease or death for any reason within 29 days after randomization."

Mutations (allele frequency) observed in the sotrovimab group were C361T (5.1%, 5.5%) in 2 subjects, L335S (6.7%), C336R (11.1%), and E340A (99.7%) in 1 subject each.

PMDA's view:
Although the currently available information is limited, an *in vitro* study demonstrated a decreased neutralization activity of sotrovimab against the virus with E340K mutation among epitope mutations observed after baseline [see Section 3.1.2.2.1]. The possibility that viruses with epitope mutations are induced or selected by sotrovimab should be carefully monitored. Information on the occurrence of variants resistant to sotrovimab should be collected continuously after the market launch, and new findings should be provided promptly to healthcare professionals.

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

7.R.2 Safety

The applicant's explanation about the safety profile of sotrovimab:
Table 25 shows the summary of safety in the foreign phase II/III study (the COMET-ICE study). The incidence of events did not tend to be higher in the sotrovimab group than in the placebo group.

Table 25. Summary of safety in foreign phase II/III study (the COMET-ICE study)
(safety analysis set: data cut-off on April 27, 2021)

	Sotrovimab (n = 523)	Placebo (n = 526)
Adverse events	114 (22)	123 (23)
Adverse drug reactions	8 (2)	9 (2)
Serious adverse events	11 (2)	32 (6)
Adverse events leading to death	0	4 (<1)
Adverse events leading to discontinuation	0	1 (<1)

Number of subjects (%)

In the sotrovimab groups of the ongoing or completed foreign clinical studies (the COMET-PEAK study, the ACTIV-3 study, and the BLAZE-4 study),[28)] serious adverse events were observed in 1 subject in the intravenous infusion group (COVID-19 pneumonia) and in 3 subjects in the intramuscular injection group (COVID-19 pneumonia, coronavirus pneumonia, dehydration, bilateral pneumonia, and acute hypoxic respiratory failure in 1 subject each [some subjects had more than 1 event]) in the COMET-PEAK study (part B); and in 7 subjects (anaphylaxis, cytokine release syndrome, respiratory failure, respiratory distress,

28) ・The COMET-PEAK study (NCT04779879) in unhospitalized patients with mild to moderate COVID-19: In Part A, sotrovimab Process I- or Process II-derived formulation 500 mg was infused intravenously as a single dose (infusion time: 60 minutes). In Part B, sotrovimab Process II-derived formulation 500 mg was infused intravenously (infusion time: 15 minutes) or injected intramuscularly as a single dose. Sotrovimab was administered to 30 subjects in Part A (8 in Process I-derived formulation group, 22 in Process II-derived formulation group) and to 166 subjects in Part B (84 in intravenous infusion group, 82 in intramuscular injection group) (Part A: data cut-off on June 8, 2021; Part B: data cut-off on July 1, 2021).
・The ACTIV-3 study (NCT04501978) in hospitalized patients with COVID-19: Sotrovimab Process I-derived formulation 500 mg was infused intravenously as a single dose (infusion time 60 min). Sotrovimab was administered to 182 subjects (data cut-off on March 18, 2021).
・The BLAZE-4 study (NCT04634409) in unhospitalized patients with mild to moderate COVID-19: In treatment group 7, sotrovimab Process II-derived formulation 500 mg + bamlanivimab 700 mg were infused intravenously as a single dose (infusion time: 30 minutes each with an interval of ≥30 minutes in between). Sotrovimab + bamlanivimab were administered to 101 subjects (data cut-off on March 17, 2021).

hypercalcaemia, hypoxia, and haemolytic anaemia in 1 subject each) in the ACTIV-3 study[29]. Causal relationship to the study drug could not be ruled out in 3 subjects of the ACTIV-3 study (anaphylaxis, cytokine release syndrome, and respiratory distress). The outcome was recovery in all of them. No serious adverse events were observed in the BLAZE-4 study. In the ACTIV-3 study, serious adverse events in 11 subjects in the sotrovimab group (pulseless electrical activity in 2 subjects, acute respiratory failure, cardio-respiratory arrest, cardiogenic shock, respiratory failure, lung neoplasm malignant, multiple organ dysfunction syndrome, COVID-19, COVID-19 pneumonia, and death in 1 subject each) led to death. All of these serious adverse events except those in 2 subjects (lung neoplasm malignant and multiple organ dysfunction syndrome) were considered to be caused by COVID-19.

In the foreign phase II/III study (the COMET-ICE study), infusion related reactions[30] including hypersensitivity were observed in 1% (6 of 523) of subjects in the sotrovimab group and in 1% (6 of 526) of subjects in the placebo group (Table 26). All events observed in the sotrovimab group were Grade 1 or 2, and their causal relationship to the study drug was denied. The outcome was recovery in all of them.

Table 26. Infusion related reactions including hypersensitivity observed in foreign phase II/III study (the COMET-ICE study) (Safety analysis set: data cut-off on April 27, 2021)

Events	Adverse events		Adverse drug reactions	
	Sotrovimab (n = 523)	Placebo (n = 526)	Sotrovimab (n = 523)	Placebo (n = 526)
Total	6 (1)	6 (1)	0	3 (<1)
Pyrexia	3 (<1)	1 (<1)	0	0
Chills	2 (<1)	0	0	0
Dizziness	1 (<1)	3 (<1)	0	1 (<1)
Pruritus	0	1 (<1)	0	1 (<1)
Rash	0	1 (<1)	0	1 (<1)
Infusion related reaction	1 (<1)	0	0	0
Dyspnoea	1 (<1)	1 (<1)	0	0

Number of patients (%)

The following information was obtained from the ACTIV-3 study: Infusion related reactions[31] were observed in 10% (18 of 182) of subjects in the sotrovimab group and in 8% (14 of 178) of subjects in the placebo group. Among them, Grade 4 events were observed in 2 subjects in the sotrovimab group (anaphylaxis, bronchospasm, and breath shortness in 1 subject each [1 subject had more than 1 event]) and in 1 subject in the placebo group (other reactions). Causal relationship to the study drug could not be ruled out for any of Grade 4 events observed in the sotrovimab group. They were serious adverse events. In the BLAZE-4 study, there was no infusion related reaction.[32]

29) In the ACTIV-3 study, serious symptoms (including death) known to occur as complications of COVID-19 were predefined not to be reported as serious adverse events, except clinical organ failure, serious infection, and those considered to causally related to the study drug.

30) The following events that occurred within 24 hours after start of the study drug administration:
Events coded as "anaphylactic reaction (wide)" or "hypersensitivity (narrow)" in Standardized MedDRA Query (SMQ), and events defined based on the customized PT list derived from infusion related reactions that occurred within 24 hours after the start of infusion, as reported with other approved monoclonal antibodies.

31) The following events observed during, or within 2 hours after, the study drug administration:
Angioedema, anaphylaxis, bronchospasm, chills, diarrhoea, headache, pyrexia, hypotension, pruritus, myalgia, rash (except urticaria), nausea, breath shortness, tachycardia, throat irritation/tightening, vomiting, urticaria, dizziness, change in reality perception, confusion, mental status changes, and other events recognized as infusion related reactions by the investigator, etc.

32) Events coded as MedDRA SMQ "anaphylactic reactions (wide)," "angioedema (wide)," or "hypersensitivity (wide)."

Although there are no experiences of administering sotrovimab to Japanese patients with COVID-19, it is possible to evaluate, to a certain extent, the safety of the treatment in Japanese patients with COVID-19 based on the results of the COMET-ICE study, for the following reasons: (a) There is no significant difference in the diagnostic criteria for COVID-19, pathology, risk factors for severe COVID-19, treatment methods, etc., between Japanese and non-Japanese patients, and (b) Sotrovimab is an antibody against an adventitious agent.

After the Emergency Use Authorization in the US up to August 19, 2021, there were spontaneous reports of 1 case of serious adverse event (COVID-19 pneumonia) in the US and 3 cases of serious adverse events (COVID-19 pneumonia) and 1 case of an adverse event (rash) in the United Arab Emirates. However, there have been no events that affect the benefit-risk balance of sotrovimab evaluated based on the results of the COMET-ICE study and other clinical studies.

On the basis of the above, the applicant considers that the safety profile of sotrovimab is acceptable. Since sotrovimab is a protein product and caused hypersensitivity (including anaphylaxis) in clinical studies, the package insert will include a precautionary statement regarding the risk of such reactions.

PMDA's view:
The safety risk of sotrovimab in patients with COVID-19 is manageable provided that appropriate caution is given, in view of the information on hypersensitivity (including anaphylaxis) obtained in the COMET-ICE study, etc. The safety profile of sotrovimab in Japanese patients is unlikely to be significantly different from that in non-Japanese patients because sotrovimab is an antibody against an adventitious agent, although it is difficult to reach a definite conclusion due to the lack of experience of administering sotrovimab to Japanese patients with COVID-19. Information on the safety in Japanese patients, including that obtained from the ongoing clinical studies, should be collected continuously after the market launch and provided appropriately to healthcare professionals.

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

7.R.3 Clinical positioning

The applicant's explanation about the clinical positioning of sotrovimab:
In Japan, remdesivir, dexamethasone, and baricitinib have been approved as therapeutic agents against COVID-19, and used in patients with moderate (I and II) to severe disease according to the profile of each drug. Also, co-administration of casirivimab and imdevimab is approved and used in patients with mild to moderate I disease who have risk factors for severe COVID-19.[33)] In the COMET-ICE study, sotrovimab was shown to have efficacy and safety in patients with Covid-19 who have risk factors for severe COVID-19 but do not require oxygen therapy. Patients not requiring oxygen therapy in the COMET-ICE study correspond to those with mild to moderate I COVID-19 according to the Clinical Practice Guidelines for Novel Coronavirus

[33)] Package insert, Clinical Practice Guidelines for Novel Coronavirus Infection (COVID-19), ver. 5.3 (August 31, 2021)

Infection (COVID-19), ver. 5.3 (August 31, 2021). Accordingly, sotrovimab would be a treatment option for patients with mild to moderate I COVID-19 who have risk factors for severe COVID-19.

PMDA's view:
On the basis of the review in Sections 7.R.1 and 7.R.2, PMDA considers that sotrovimab provides a treatment option for patients with mild to moderate I COVID-19 who have risk factors for severe COVID-19. The intended population will be discussed in Section 7.R.4.

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

7.R.4 Indication

The applicant's explanation about the indication and the intended population for sotrovimab:
The COMET-ICE study demonstrated the efficacy and safety of sotrovimab in patients with COVID-19 who have risk factors for severe COVID-19 but do not require oxygen therapy. Accordingly, the indication should be disease caused by SARS-CoV-2 infection (COVID-19), and the package insert should advise that sotrovimab is intended only for patients who have risk factors for severe COVID-19 but do not require oxygen therapy.

PMDA's view:
On the basis of the review in Sections 7.R.1 and 7.R.2, the following indication of sotrovimab is acceptable: Disease caused by SARS-CoV-2 infection (COVID-19). The intended population of sotrovimab should be patients with COVID-19 who have risk factors for severe COVID-19 but do not require oxygen therapy, taking account of the inclusion/exclusion criteria of the COMET-ICE study.

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

7.R.5 Dosage and administration

The applicant's rationale for the proposed dosage and administration:
On the basis of the results of nonclinical studies etc., the dosage regimen of the COMET-ICE study was a single intravenous administration of sotrovimab 500 mg [see Section 6.R.2], and results confirmed the efficacy and safety against disease caused by SARS-CoV-2 infection (COVID-19) [see Sections 7.R.1 and 7.R.2]. Accordingly, the appropriate dosage and administration should be a single intravenous administration of sotrovimab 500 mg. It is considered appropriate to use the same dosage regimen in pediatric patients aged ≥12 years and weighing ≥40 kg as that in adults, taking account of the results of clinical pharmacology studies [see Section 6.R.3].

PMDA's view:
The following dosage and administration for adults and pediatric patients aged ≥12 years and weighing ≥40 kg is acceptable: a single intravenous administration of sotrovimab 500 mg. As soon as the results of the ongoing phase I study (Study 217653) on PK, safety, etc., in healthy adults (Japanese and Caucasians) and the clinical

study in adults and pediatric patients aged ≥12 years become available, the appropriateness of the dosage and administration in Japanese adults and pediatric patients aged ≥12 years and weighing ≥40 kg should be evaluated, and new findings should be provided promptly to healthcare professionals.

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

7.R.6 Post-marketing investigations

The applicant plans to conduct a use-results survey (target sample size, 630; follow-up period, 28 days) in addition to the usual pharmacovigilance activities, in order to confirm the safety, etc., in clinical practice after the market launch.

PMDA's view:

In order to confirm the safety, etc., the applicant should conduct a use-results survey in Japanese patients with COVID-19 after the market launch for the following reasons: (a) There is no experience with sotrovimab in Japanese patients with COVID-19; and (b) Hypersensitivity (including anaphylaxis) occurred after sotrovimab administration (see Section 7.R.2).

The above conclusions 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 inspection is currently ongoing. Results and the conclusion of PMDA will be reported in Report on Special Approval for Emergency (2).

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

The inspection is currently ongoing. Results and the conclusion of PMDA will be reported in Report on Special Approval for Emergency (2).

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

On the basis of the data submitted, PMDA has concluded that sotrovimab has efficacy in the treatment of COVID-19, and that sotrovimab has acceptable safety in view of its benefits. Sotrovimab is clinically meaningful because it offers a new treatment option for patients with COVID-19.

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

Report on Special Approval for Emergency (2)

September 21, 2021

Product Submitted for Approval

Brand Name	Xevudy for Intravenous Infusion 500 mg
Non-proprietary Name	Sotrovimab (Genetical Recombination)
Applicant	GlaxoSmithKline K.K.
Date of Application	September 6, 2021

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 Report on Special Approval for Emergency (1) (Sections "7.R.1 Efficacy," "7.R.2 Safety," "7.R.3 Clinical Positioning," "7.R.4 Indication," "7.R.5 Dosage and Administration," and "7.R.6 Post-marketing investigations").

1.1 Neutralization activity against variants (CTD 5.3.5.4: 2021N483004)

New study data on the neutralization activity against variants were submitted after finalization of the Report on Special Approval for Emergency (1).

Replication-incompetent vesicular stomatitis virus (pseudovirus particles) engineered to express S-protein with amino acid mutations was treated with sotrovimab and incubated with Vero E6 cells and, after cultivation for 20 to 24 hours, the neutralization activity of sotrovimab was investigated by luciferase reporter assay which detects intracellular viral infection. Table 27 shows the results. The neutralization activity against the variants was not significantly different from the activity against the wild-type strain.

PMDA instructed the applicant to provide the above information to healthcare professionals in the form of the package insert. The applicant agreed.

Table 27. Neutralization activity against VOC, VOI, etc.

Strain	Amino acid mutations tested	Fold change in neutralization activity[a)]	Submission data CTD
AY.1 (Delta[b)])	T19R, T95I, G142D, E156G, deletion F157, deletion R158, W258L, K417N, L452R, T478K, D614G, P681R, D950N	1.1	CTD 5.3.5.4: 2021N483004
AY.2 (Delta[b)])	T19R, V70F, G142D, E156G, deletion F157, deletion R158, A222V, K417N, L452R, T478K, D614G, P681R, D950N	1.3	CTD 5.3.5.4: 2021N483004

a) EC_{50} (geometric mean) against variant/EC_{50} (geometric mean) against wild-type strain
b) AY.2 is a strain derived from strain B.1.617.2 and is handled as a substrain of Delta (as of September 15, 2021).

1.2 Risk management plan (draft)

In view of the discussions presented in Section "7.R.6 Post-marketing investigations" in Report on Special Approval for Emergency (1) and comments from the expert advisors at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for sotrovimab should include the safety specifications presented in Table 28, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 29 and 30.

Table 28. Safety and efficacy specifications in the risk management plan (draft)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Serious hypersensitivity reactions such as anaphylaxis Infusion reaction	None	None
Efficacy specification		
None		

Table 29. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Use-results survey	None	• Disseminate data gathered during early post-marketing phase vigilance • Provide information to patients and enhance their understanding before starting treatment (through an informed consent form and a brochure for patients)

Table 30. Outline of use-results survey (draft)

Objective	To collect information on the safety and efficacy of sotrovimab in clinical use
Survey method	Central registry system
Population	Patients with COVID-19 who have risk factors for severe COVID-19 but do not require oxygen therapy
Observation period	From sotrovimab administration (Day 1) up to Day 29 (28 days from the next day of sotrovimab administration)
Planned sample size	630 enrolled patients
Main survey items	Patient characteristics, past treatments, vaccination status against COVID-19, sotrovimab administration status, concomitant drugs, body temperature, SpO_2, clinical symptoms, admission to high care unit or intensive care unit, hospitalization status, pregnancy, and adverse events

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

2.1 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 compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products

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

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

The new drug application data (CTD 5.3.5.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration 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 drug substance is classified as a poisonous or powerful drug.

Indication

Disease caused by SARS-CoV-2 infection (COVID-19)

Dosage and Administration

The usual dosage in adults and pediatric patients (≥12 years of age weighing ≥40 kg) is 500 mg of Sotrovimab (Genetical Recombination) administered as a single intravenous infusion.

Approval Conditions

1. The applicant is obliged to fulfill the following duties set forth in each Item of Article 28, Paragraph 3 of the Cabinet Order for Enforcement of Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 2 of the Pharmaceuticals and Medical Devices Act.
   (1) Matters related to Item 1
   Some of the data of clinical studies were not available for evaluation in the application review. The complete data should be submitted as soon as additional clinical data become available.
   (2) Matters related to Item 2
   When learning about diseases, disorders, or death suspected to be caused by the product, the applicant is required to report them promptly.
   (3) Matters related to Item 3
   The applicant is required to take necessary actions to ensure that healthcare professionals who use the product can understand, and appropriately explain to patients (or their legally acceptable representatives), that the product has been granted Special Approval for Emergency and the objectives of said approval.
   (4) Matters related to Item 4
   The applicant is required to report the quantity of the product sold or provided, as necessary.

2. The product is approved with the following conditions, based on the provisions of Article 79, Paragraph 1 of the Pharmaceuticals and Medical Devices Act:

(1) The applicant is required to develop and appropriately implement a risk management plan.
(2) The applicant is required to request that physicians administer the product only to patients considered eligible for treatment with the product who, or whose legally acceptable representatives, have been provided with the efficacy and safety information of the product in written form, and have provided written informed consent before the treatment.
(3) Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act, the grace period for data submission is 4 months after the approval. If newly submitted data, etc., necessitate a change in the approved product information, the change may be ordered in accordance with the provision in Article 74-2, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.

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

Appendix

List of Abbreviations

ACE2	Angiotensin-converting enzyme 2
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
ADE	Antibody-dependent enhancement
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the serum concentration-time curve
$AUC_{0\text{-}28\ day}$	Area under the serum concentration-time curve up to 28 days
AUC_{inf}	Area under the serum concentration-time curve up to infinity
AUC_{last}	Area under the serum concentration-time curve up to the time of last measurable drug concentration
AUC_{tau}	Area under the serum concentration-time curve over the dosing interval
BMI	Body mass index
C1q	Complement 1, q subcomponent
$C_{28\ day}$	Observed serum concentration 28 days after dosing
Cabinet Order for Enforcement of Pharmaceuticals and Medical Devices Act	Cabinet Order for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Cabinet Order No. 11, dated February 1, 1961)
CE-SDS	Capillary gel electrophoresis-sodium dodecyl sulfate
CHO	Chinese hamster ovary
cIEF	Capillary isoelectric focusing
CL	Total body clearance
C_{max}	Maximum serum concentration
COVID-19	Coronavirus disease caused by SARS-CoV-2 infection
CQA	Critical quality attribute
DNA	Deoxyribonucleic acid
EC_{50}	Half maximal effective concentration
EC_{90}	90% effective concentration
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EOPCB	End of production cell bank
[redacted]	[redacted]
FcRn	Neonatal Fc receptor
FcγR	Fc gamma receptor
GISAID	Global initiative on sharing avian influenza data
HCP	Host cell protein
IDMC	Independent data monitoring committee
IFN	Interferon
IgG	Immunoglobulin G
IL	Interleukin
IP-10	Interferon inducible protein-10
ITT	Intent-to-treat
LDH	Lactate dehydrogenase
MCB	Master cell bank
MCP-1	Monocyte chemoattractant protein-1
Ministerial Ordinance for Enforcement of Pharmaceuticals and Medical Devices Act	Enforcement Ordinance for the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Ordinance of the Ministry of Health and Welfare No. 1 of February 1, 1961)

NK	Natural killer
NYHA	New York heart association
[redacted]	[redacted]
PCR	Polymerase chain reaction
Pharmaceuticals and Medical Devices Act	Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of August 10, 1960)
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
Q	Inter-compartmental clearance
QbD	Quality by design
RBD	Receptor binding domain
RT-PCR	Reverse transcription PCR
SARS-CoV	SARS-associated coronavirus
SE-HPLC	Size exclusion high performance liquid chromatography
Sotrovimab	Sotrovimab (Genetical Recombination)
SPR	Surface plasmon resonance
S-protein	Spike protein
$t_{1/2}$	Estimate of the terminal elimination half-life
$TCID_{50}$	50% tissue culture infectious dose
The product	Xevudy for Intravenous Infusion 500 mg
t_{max}	Time to maximum concentration
TNF	Tumor necrosis factor
US CDC	Centers for disease control and prevention
V1	Volume of distribution of the central compartment
V2	Volume of distribution of the peripheral compartment
VOC	Variants of concern
VOI	Variants of interest
V_{ss}	Volume of distribution at steady state
WCB	Working cell bank
WHO	World health organization