Report on the Deliberation Results

November 4, 2021
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Ronapreve for Intravenous Infusion Set 300, Ronapreve for Intravenous Infusion Set 1332
Non-proprietary Name	Casirivimab (Genetical Recombination) (JAN) and Imdevimab (Genetical Recombination) (JAN)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	October 11, 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 November 4, 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 presented below, and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period for the present application is the remainder of the re-examination period for the initial approval (until July 18, 2029).

Approval Conditions

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Report on Special Approval for Emergency

October 27, 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	(a) Ronapreve for Intravenous Infusion Set 300, (b) Ronapreve for Intravenous Infusion Set 1332
Non-proprietary name	Casirivimab (Genetical Recombination) and Imdevimab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	October 11, 2021
Dosage Form/Strength	(a) Injection: Each casirivimab 2.5 mL vial contains 300 mg of Casirivimab (Genetical Recombination) and each imdevimab 2.5 mL vial contains 300 mg of Imdevimab (Genetical Recombination). (b) Injection: Each casirivimab 11.1 mL vial contains 1,332 mg of Casirivimab (Genetical Recombination) and each imdevimab 11.1 mL vial contains 1,332 mg of Imdevimab (Genetical Recombination)
Application Classification	Prescription drug, (3) Drug with a new route of administration, (4) Drug with a new indication
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 1008-5, dated October 8, 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 in the suppression of development of disease caused by SARS-CoV-2 infection (COVID-19), and that the product has acceptable safety in view of its benefits (see Attachment).

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

Indication

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

(Underline donates additions.)

Dosage and Administration

The usual dosage in adults and pediatric patients (≥12 years of age weighing ≥40 kg) is 600 mg of Casirivimab (Genetical Recombination) and 600 mg of Imdevimab (Genetical Recombination) administered together as a single intravenous infusion or as a single subcutaneous injection.

(Underline donates additions.)

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
   The applicant is required to conduct a use-results survey on the product, and report the results.
   (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.

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

Attachment

Report on Special Approval for Emergency

October 27, 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	(a) Ronapreve for Intravenous Infusion Set 300, (b) Ronapreve for Intravenous Infusion Set 1332
Non-proprietary Name	Casirivimab (Genetical Recombination) and Imdevimab (Genetical Recombination)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	October 11, 2021
Dosage Form/Strength	(a) Injection: Each casirivimab 2.5 mL vial contains 300 mg of Casirivimab (Genetical Recombination) and each imdevimab 2.5 mL vial contains 300 mg of Imdevimab (Genetical Recombination). (b) Injection: Each casirivimab 11.1 mL vial contains 1,332 mg of Casirivimab (Genetical Recombination) and each imdevimab 11.1 mL vial contains 1,332 mg of Imdevimab (Genetical Recombination).

Proposed Indication

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

(Underline donates additions.)

Proposed Dosage and Administration

The usual dosage in adults and pediatric patients (≥12 years of age weighing ≥40 kg) is 600 mg of Casirivimab (Genetical Recombination) and 600 mg of Imdevimab (Genetical Recombination) administered together as a single intravenous infusion or as a single subcutaneous injection.

(Underline donates additions.)

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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 October 12, 2021, a total of 1,711,391 people have been infected (positive for polymerase chain reaction [PCR] test); among them, 9,654 (including 444 with severe disease) are in hospital, 1,682,452 were discharged or released from medical treatment, and 17,959 died.[5)]

Casirivimab (genetical recombination; hereinafter referred to as "casirivimab") and imdevimab (genetical recombination; hereinafter referred to as "imdevimab") were both discovered by Regeneron Pharmaceuticals Inc. in the United States. They are recombinant monoclonal immunoglobulin G (IgG)1 antibodies against the receptor binding domain (RBD) of SARS-CoV-2 S-protein. They bind to non-overlapping epitopes of S-protein RBD and inhibit the binding of RBD to ACE2, thereby preventing the entry of SARS-CoV-2 into host cells.

In Japan, the applicant submitted an application for the Special Approval for Emergency of Ronapreve for Intravenous Infusion Set 300 and Ronapreve for Intravenous Infusion Set 1332 (hereinafter referred to as Ronapreve), and the product was approved on July 19, 2021 for "treatment of disease caused by SARS-CoV-2 infection (COVID-19)."

In response to the Emergency Use Authorization issued by the U.S. Food and Drug Administration (FDA) and based on the results from Study COV-2069 (a foreign phase III study that enrolled asymptomatic household contacts with exposure to an individual with a diagnosis of SARS-CoV-2 infection [index case]), the applicant submitted an application for Special Approval for Emergency of "Ronapreve for suppression of development of COVID-19 and subcutaneous administration" on the understanding that Ronapreve 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 results of review conducted based on the data submitted by the applicant, in

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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 October 13, 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, 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 October 13, 2021)

accordance with the “Handling of drugs intended to be submitted for Special Approval for Emergency (Request)” (PSEHB/PED Notification 1008-5, dated October 8, 2021).

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

No new data were submitted under this section in the present application.

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

Results of primary pharmacodynamics studies were submitted as the nonclinical pharmacological data of casirivimab and imdevimab.

3.1 Primary pharmacodynamics

3.1.1 *In vivo* antiviral activity (administration before viral exposure)

Casirivimab and imdevimab were administered together to hamsters and monkeys, followed by exposure to SARS-CoV-2. Table 1 shows the results of antiviral activity of the drugs.

Table 1. *In vivo* antiviral activity (administration before viral exposure)

Animal species (number of animals per group)	Dosage regimen, viral exposure method	Summary of main results	Submission data CTD
Syrian hamsters (males and females [5 animals in total])	Casirivimab and imdevimab in combination (0.25/0.25, 2.5/2.5, 25/25 mg/kg[a]), 2 types of IgG4$^{P\text{-}GG}$ antibodies in combination[b] (0.25/0.25, 2.5/2.5, 25/25 mg/kg[a]), vehicle, or control antibody (IgG1 or IgG4 50 mg/kg) was administered intraperitoneally and, 2 days later, SARS-CoV-2 (strain USA-WA1/2020, 2.3×10^4 PFU/animal) was inoculated intranasally.	Body weight (7 days after SARS-CoV-2 inoculation): Weight decrease was suppressed in the casirivimab + imdevimab group (at any dose), compared with the vehicle group and the control antibody group. Viral RNA load (test specimen[c]: oral swabs and pulmonary tissue): There was no difference in viral RNA load in oral swabs between the casirivimab + imdevimab group (at any dose) and the vehicle or control antibody group. Viral RNA load in the pulmonary tissue in the casirivimab + imdevimab group was lower at any dose than in the vehicle or control antibody group, and tended to decrease in a dose-dependent manner. No clear difference was observed between the casirivimab + imdevimab group and the IgG4$^{P\text{-}GG}$ antibody group, in either of the test specimens. Histopathological examination of the lung (date of necropsy: 7 days after viral exposure): The casirivimab + imdevimab group (at any dose) had a smaller proportion of the area showing pneumonia, with a tendency of less severe inflammation, than the vehicle or control antibody group. No clear difference was observed between the casirivimab + imdevimab group and the IgG4$^{P\text{-}GG}$ antibody group.	4.2.1.1-1 to 3
Rhesus monkeys (males and females [2-4 animals in total])	Casirivimab and imdevimab in combination (0 [vehicle], 0.15/0.15, 25/25 mg/kg[a]) were administered intravenously and, 3 days later, SARS-CoV-2 (strain USA-WA1/2020, 5.25×10^5 PFU/animal for each route of administration) was inoculated intratracheally and intranasally.	Viral RNA load (test specimen[d]: oral swabs and nasal swabs): Viral RNA load tended to rapidly decrease to a low level in the casirivimab + imdevimab group (25/25 mg/kg[a]), compared with the vehicle group. Histopathological examination of the lung (date of necropsy: 8 days after viral exposure): The casirivimab + imdevimab group (25/25 mg/kg[a]) had fewer pulmonary lobes with pneumonic lesions and a tendency of less severe inflammation, than the vehicle group.	4.2.1.1-5 to 6
Rhesus monkeys (males and females [6 animals in total])	Casirivimab and imdevimab in combination (0 [vehicle], 25/25 mg/kg[a]) or 2 types of IgG4$^{P\text{-}GG}$ antibodies[b] in combination (0 [vehicle], 25/25 mg/kg[a]) were administered intravenously and, 3 days later, SARS-CoV-2 (strain USA-WA1/2020, 5.05×10^4 PFU/animal) was inoculated intratracheally and intranasally.	Viral RNA load (test specimen[e]: nasal swabs and bronchoalveolar lavage fluid): Viral RNA load tended to rapidly decrease to a low level in the casirivimab + imdevimab group, compared with the vehicle group. Histopathological examination of the lung (date of necropsy: 5 days after viral exposure): The casirivimab + imdevimab group had slightly less severe inflammation and slightly fewer pulmonary lobes with pneumonic lesions than the vehicle group. No clear difference was observed between the casirivimab + imdevimab group and the IgG4$^{P\text{-}GG}$ antibody group.	4.2.1.1-9 to 10

a) Dose of each antibody
b) These antibodies have the identical Fab region as that of casirivimab or imdevimab but without binding affinity to Fcγ receptor, and therefore have no Fcγ receptor-dependent effector function.
c) Oral swabs were collected before viral exposure and 2, 4, and 7 days after exposure.
Pulmonary tissue specimens were collected 7 days after vial exposure.
d) Samples were collected before viral exposure and 1, 2, 4, 6, 7 and 8 days after exposure.
e) Nasal swabs were collected before viral exposure and 1, 2, 3, 4, and 5 days after exposure.
Bronchoalveolar lavage fluid was collected 1, 3, and 5 days after viral exposure.

3.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that casirivimab and imdevimab (administered before viral exposure) are expected to have antiviral activity against SARS-CoV-2 from a pharmacological point of view.

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

No new data were submitted under this section in the present application.

5. Toxicity and Outline of the Review Conducted by PMDA

No new data were submitted under this section in the present application. Systemic toxicity and local tolerance in subcutaneous administration were evaluated in a repeated dose toxicity study in cynomolgus monkeys (Report on Special Approval for Emergency of Ronapreve for Intravenous Infusion Set 300 and 1332 [dated July 14, 2021]). No particular safety concerns were suggested.

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

Casirivimab and imdevimab concentrations (lower limit of quantitation: 0.156 μg/mL)[6)] and anti-drug antibodies (ADA) in human serum were measured by electrochemiluminescence.

6.2 Clinical pharmacology

The applicant submitted the results of a foreign phase II study (Study R10933-10987-COV-20145 [Study COV-20145]) in patients with COVID-19 and a foreign phase III study (Study COV-2069 [Study R10933-10987-COV-2069]) in asymptomatic household contacts with exposure to an individual with a diagnosis of SARS-CoV-2 infection (index case).

Pharmacokinetics (PK) parameters are expressed in means unless specified otherwise.

6.2.1 Foreign phase II study (CTD 5.3.5.1-2: Study COV-20145 [ongoing since December 2020; data cut-off on March 2021])

A single dose of casirivimab and imdevimab in combination was administered intravenously (150, 300, 600, or 1,200 mg each) over 60 (±15) minutes, or subcutaneously (300 or 600 mg each), to ≥18-year-old patients with COVID-19 (685 subjects evaluated for PK). Table 2 shows PK parameters.

6) Measured using a method that can determine the concentrations of casirivimab and imdevimab regardless of binding to virus.

Table 2. PK parameters following a single dose of casirivimab and imdevimab in combination in non-Japanese patients with COVID-19

Route of administration	Dose (casirivimab/imdevimab) (mg)	Analyte	N	$C_{1\ h}$ (μg/mL)	$C_{2\ day}$ (μg/mL)	$C_{4\ day}$ (μg/mL)	$C_{6\ day}$ (μg/mL)	C_{max} (μg/mL)	t_{max} (days)	$AUC_{0\text{-}6\ day}$ (day·μg/mL)
i.v.	150/150	Casirivimab	114	56.2±50.4 a)	33.3±17.5 c)	27.3±16.8 k)	24.4±15.1 g)	58.4±48.4	0.0747 [0.0306, 6.07]	187± 83.4
		Imdevimab	114	55.1±52.0 a)	33.6±18.1 c)	26.4±15.5 k)	23.3±14.4 g)	57.3±50.1	0.0747 [0.0306, 6.07]	183± 83.8
	300/300	Casirivimab	113	100±56.3 c)	53.8±16.4 i)	45.1±13.8 n)	39.8±11.8 f)	99.8±53.5	0.0694 [0, 6.10]	321± 111 a)
		Imdevimab	113	101±58.9 c)	55.4±17.0 i)	45.8±13.5 n)	37.5±11.5 f)	100±56.2	0.0694 [0, 6.09]	322± 112 a)
	600/600	Casirivimab	115	169±69.2 d)	114±31.3 j)	89.7±24.7 l)	86.5±23.0 e)	174±59.0	0.0715 [0, 6.74]	660± 211 d)
		Imdevimab	115	171±69.6 d)	117±30.8 k)	90.5±23.7 l)	81.2±20.9 e)	177±58.4	0.0701 [0, 5.98]	661± 210 d)
	1200/1200	Casirivimab	115	360±229 e)	234±60.5 l)	189±57.7 i)	166±46.3 e)	363±214	0.0778 [0, 6.20]	1,299± 417 d)
		Imdevimab	115	375±242 e)	234±59.5 l)	180±53.6 o)	151±41.9 e)	377±228	0.0743 [0, 6.20]	1,275± 411 d)
s.c.	300/300	Casirivimab	114	11.9±63.8 f)	24.3±20.7 h)	29.2±21.0 p)	28.3±8.94 q)	41.2±61.7	5.76 [0, 7.93]	142± 87.1 b)
		Imdevimab	114	11.7±62.4 c)	23.3±18.6 h)	27.7±16.3 p)	27.0±7.96 q)	39.3±59.4	5.76 [0, 7.16]	135± 80.8 a)
	600/600	Casirivimab	114	5.56±24.0 g)	42.1±19.2 m)	50.9±20.7 o)	55.0±18.9 q)	60.7±23.9	5.80 [0.0431, 9.99]	236± 105
		Imdevimab	114	6.13±26.3 g)	42.4±20.9 m)	48.7±19.3 o)	53.1±17.0 q)	58.4±25.0	5.81 [0.0431, 9.99]	231± 107

Mean ± SD, t_{max} is expressed in median [range].
a) N = 112, b) N = 111, c) N = 107, d) N = 114, e) N = 109, f) N = 106, g) N = 104, h) N = 103, i) N = 96, j) N = 102, k) N = 101, l) N = 105, m) N = 95, n) N = 98, o) N = 97, p) N = 99, q) N = 108

Figure 1 shows changes over time in serum concentrations of casirivimab and imdevimab.

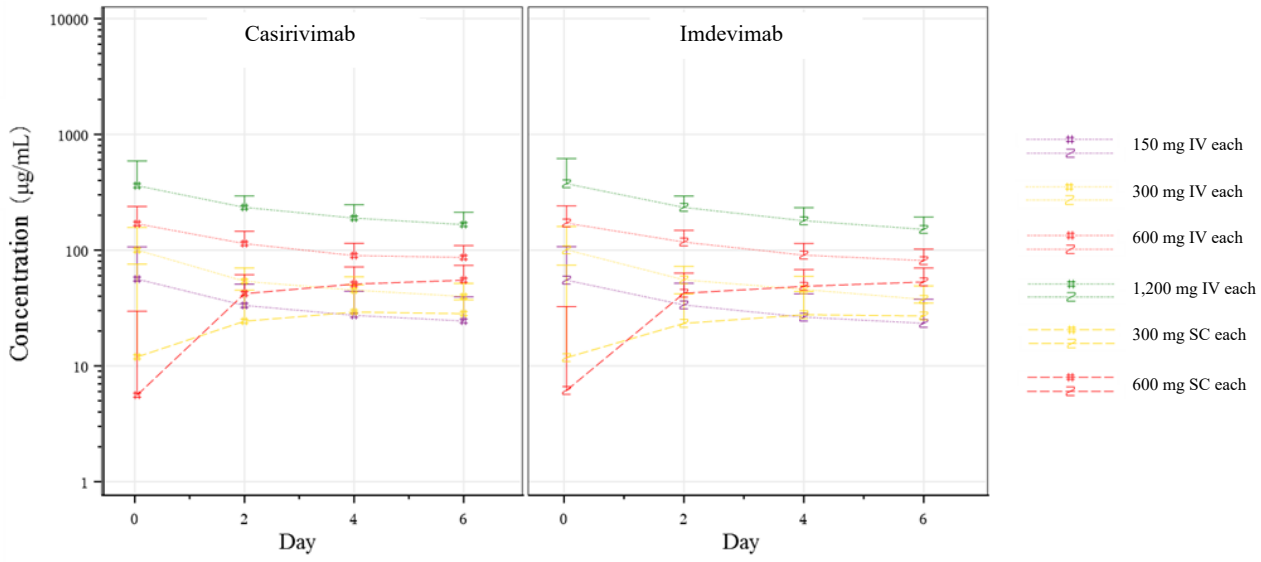

Figure 1. Changes over time in serum concentrations of casirivimab and imdevimab

Mean ± SD

6.2.2 Foreign phase III study (CTD 5.3.5.1-1: Study COV-2069, [ongoing since July 2020; data cut-off on March 2021])

A single dose of casirivimab and imdevimab in combination (600 mg each) was administered subcutaneously to ≥12-year-old asymptomatic household contacts with exposure to an individual infected with SARS-CoV-2 (16 subjects evaluated for PK). Table 3 shows PK parameters obtained from ≥18-year-old subjects. PK parameter values did not significantly differ between subjects with and without SARS-CoV-2 infection at baseline (RT-PCR). As for ADA, anti-casirivimab antibody was detected in 1.8% (17 of 960) of subjects and anti-imdevimab antibody in 2.5% (24 of 957) of subjects. Serum drug concentration in ADA-positive subjects was within the range of the concentration observed in ADA-negative subjects, suggesting that ADA has no significant effect on PK of either casirivimab or imdevimab.

Table 3. PK parameters following a single subcutaneous dose of casirivimab and imdevimab in combination in household contacts of SARS-CoV-2-infected individuals

SARS-CoV-2 at baseline (RT-PCR)	N	C_{max} (μg/mL)	t_{max} (days)	$t_{1/2}$ (days)	$AUC_{0\text{-}28\ day}$ (day•μg/mL)	AUC_{inf} (day•μg/mL)	$C_{1\ day}$ (μg/mL)	$C_{28\ day}$ (μg/mL)
Analyte: Casirivimab								
All	16	54.3±22.0	6.87 [2.82, 85.7]	31.8±8.33 a)	1,066±375	2,579±1,348 a)	22.5±11.0 g)	30.7±11.9 h)
Negative	12	56.6±24.4	6.88 [2.82, 85.7]	32.4±9.46 b)	1,095±418	2,769±1,547 b)	22.2±10.1 c)	30.4±11.9 d)
Positive	4	47.5±12.9	6.28 [2.92, 7.74]	30.2±5.27	980±216	2,103±515	23.3±15.0	33.5±12.3 f)
Analyte: Imdevimab								
All	16	53.6±22.0	5.73 [2.80, 13.8]	26.9±6.81 a)	996±369	1,988±1,138 a)	25.0±16.4 g)	24.8±9.58 i)
Negative	12	56.0±24.1	4.37 [2.80, 13.8]	27.0±7.56 b)	1,041±410	2,140±1,312 b)	25.8±17.6 c)	24.6±9.65 e)
Positive	4	46.1±13.8	6.28 [2.92, 7.74]	26.6±5.42	860±184	1,608±419	22.7±14.8	26.9±9.12 f)

Mean ± SD, t_{max} is expressed in median [range].
a) N = 14, b) N = 10, c) N = 11, d) N = 83, e) N = 84, f) N = 9, g) N = 15, h) N = 92, i) N = 93

6.R Outline of the review conducted by PMDA

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

Based on the results of the following investigations, the applicant explained that there was no clear difference in PK of casirivimab and imdevimab between the Japanese and non-Japanese populations following a single subcutaneous dose of casirivimab and imdevimab in combination.

- Since casirivimab and imdevimab are antibody products, their protein binding in blood is unlikely to affect PK, with a low probability of drug interactions or ethnic differences in their metabolism. No clear ethnic difference was observed in previous studies, although with a different route (intravenous) of administration (Report on Special Approval for Emergency of Ronapreve for Intravenous Infusion Set 300 and 1332 [dated July 14, 2021]).
- Table 4 shows PK parameters following a single subcutaneous administration of casirivimab and imdevimab in combination (600 mg each) to (a) Japanese adults without COVID-19 (Report on Special Approval for Emergency of Ronapreve for Intravenous Infusion Set 300 and 1332 [dated July 14, 2021]) and (b) non-Japanese household contacts of SARS-CoV-2-infected individuals [see Section 6.2.2]. The obtained parameters are similar in Japanese and non-Japanese subjects.

Table 4. PK parameters following a single subcutaneous dose of casirivimab and imdevimab (600 mg each) in combination in Japanese and non-Japanese subjects

	Population	Analyte	N	C_{max} (μg/mL)	t_{max} (days)	$t_{1/2}$ (days)	$AUC_{0\text{-}28\ day}$ (day•μg/mL)	$C_{28\ day}$ (μg/mL)
Japanese	Subjects without COVID-19	Casirivimab	6	64.0±13.9	7.08 [7.08, 7.10]	27.0±3.67 a)	1,360±285	37.4±6.81
		Imdevimab	6	62.1±16.0	7.08 [3.00, 7.09]	24.0±4.67	1,290±329	32.5±8.07
Non-Japanese	Household contacts of SARS-CoV-2-infected individuals	Casirivimab	16	54.3±22.0	6.87 [2.82, 85.7]	31.8±8.33 b)	1,066±375	30.7±11.9 c)
		Imdevimab	16	53.6±22.0	5.73 [2.80, 13.8]	26.9±6.81 b)	996±369	24.8±9.58 d)

Mean ± SD, t_{max} is expressed in median [range].
a) N = 5, b) N = 14, c) N = 92, d) N = 93

PMDA accepts the explanation of the applicant.

6.R.2 Rationale for dosage regimen

The dosage regimen in the foreign phase III study (Study COV-2069) was a single subcutaneous administration of casirivimab and imdevimab 600 mg each.

The applicant's rationale for the above dosage regimen:

(a) The results of the non-clinical pharmacokinetic studies suggested that changes over time in serum concentrations of casirivimab and imdevimab were similar between intravenous administration and subcutaneous administration, except for concentrations immediately after administration.

(b) Even if time to the target serum casirivimab and imdevimab concentrations after subcutaneous administration is longer than that after intravenous administration, the subcutaneous treatment was expected to have efficacy in the foreign phase III study (Study COV-2069) in asymptomatic household contacts with exposure to an individual with a diagnosis of SARS-CoV-2 infection (index case).

(c) In general, subcutaneous administration is a more convenient method than intravenous administration.

The appropriate target serum concentration of casirivimab and imdevimab was considered to be 20 μg/mL each, because it was expected to have sufficient neutralizing activity against SARS-CoV-2, as is the case in the foreign phase I/II/III study (Study COV-2067) in patients with COVID-19. (Report on Special Approval for Emergency of Ronapreve for Intravenous Infusion Set 300 and 1332 [dated July 14, 2021]). The dosage regimen in Study COV-2069 was defined as a single subcutaneous dose of casirivimab and imdevimab (600 mg each), because it was expected to achieve the target serum concentration (20 μg/mL each) in pediatric subjects aged ≥12 years and adults. Since body weight in ≥12-year-old pediatric subjects largely overlaps with the weight range of adult body weight, a similar level of exposure will be achieved in pediatric subjects as in adults.

In Study COV-2069, the mean serum concentration of casirivimab and imdevimab in ≥18-year-old subjects exceeded 20 μg/mL at 1 and 28 days after administration [see Section 6.2.2]. PK data in subjects aged 12 to <18 years in Study COV-2069 will be obtained in the fourth quarter of 2021.

PMDA's view:
The applicant's rationale for the dosage regimen used in the foreign phase III study (Study COV-2069) is acceptable from the clinical pharmacological point of view. Appropriateness of the proposed dosage and administration will be further discussed based on the efficacy and safety data from clinical studies [see Section 7.R.5].

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

The applicant submitted the results of clinical studies shown in Table 5 as the main efficacy and safety data.

Table 5. Summary of clinical studies

Data category	Region	Study identifier	Phase	Population	No. of subjects enrolled	Dosage regimen	Main evaluation items
Evaluation	Foreign	COV-20145	II	Patients with COVID-19	Intravenous administration (a) N = 116 (b) N =117 (c) N = 116 (d) N = 116 (e) N = 58 Subcutaneous administration (a) N = 117 (b) N = 116 (c) N = 59	<u>Intravenous administration</u> (a) 150 mg each: A single intravenous dose of casirivimab 150 mg and imdevimab 150 mg in combination. (b) 300 mg each: A single intravenous dose of casirivimab 300 mg and imdevimab 300 mg in combination. (c) 600 mg each: A single intravenous dose of casirivimab 600 mg and imdevimab 600 mg in combination. (d) 1,200 mg each: A single intravenous dose of casirivimab 1,200 mg and imdevimab 1,200 mg in combination. (e) Placebo: A single intravenous dose of placebo <u>Subcutaneous administration</u> (a) 300 mg each: A single subcutaneous dose of casirivimab 300 mg and imdevimab 300 mg in combination. (b) 600 mg each: A single subcutaneous dose of casirivimab 600 mg and imdevimab 600 mg in combination. (c) Placebo: A single subcutaneous dose of placebo	Antiviral activity Safety PK
Evaluation	Foreign	COV-2069	III	Asymptomatic household contacts with exposure to an individual with a diagnosis of SARS-CoV-2 infection (index case)	Cohort A: RT-PCR negative for SARS-CoV-2 at baseline (a) N = 1,313 (b) N = 1,308 Cohort B: RT-PCR positive for SARS-CoV-2 at baseline (a) N = 156 (b) N = 158 Unknown RT-PCR results (a) N = 38 (b) N = 56	(a) Casirivimab + imdevimab: A single subcutaneous dose of casirivimab 600 mg and imdevimab 600 mg in combination (b) Placebo: A single subcutaneous dose of placebo	Efficacy Safety PK

7.1 Foreign phase II study (CTD 5.3.5.1-2: Study COV-20145 [ongoing since December 2020; data cut-off on February 2021])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in ≥18-year-old patients with COVID-19 (target sample size 1,400 [200 in each casirivimab + imdevimab group, 100 in each placebo group]) at 47 study sites in the United States, to investigate the antiviral activity and safety following intravenous or subcutaneous administration of casirivimab and imdevimab in combination at each dose. Table 6 shows main inclusion and exclusion criteria.

Table 6. Main inclusion and exclusion criteria

Inclusion criteria	1. Has a SARS-CoV-2-positive diagnostic test (by antigen test, RT-PCR, etc., using a nasopharyngeal, nasal, oropharyngeal, or saliva sample collected ≤72 hours prior to randomization) 2. Meets (a) or (b) below: (a) Symptomatic patient who meets the following criteria: • Has symptoms developing ≤7 days before randomization that were considered by the investigator to be consistent with COVID-19 • Meets all of the following 8 criteria: Age ≤50; BMI <30 kg/m^2; does not have cardiovascular disease or hypertension; does not have chronic lung disease or asthma; does not have type 1 or type 2 diabetes mellitus; does not have chronic kidney disease, with or without dialysis; does not have chronic liver disease; is not pregnant. (b) Asymptomatic patient who meets the following criteria: Has had no symptoms consistent with COVID-19 (as determined by the investigator) occurring at any time <2 months prior to randomization 3. Maintains O_2 saturation ≥93% on room air
Exclusion criteria	1. Was hospitalized for COVID-19 prior to randomization, or is being hospitalized for any reason at randomization 2. Tested positive for SARS-CoV-2 antibody by serological testing 3. Tested positive for SARS-CoV-2 by antigen test, RT-PCR, etc., using a sample collected >72 hours before randomization 4. Is immunosuppressed based on the investigator's assessment (e.g., treatment of malignant tumors, bone marrow or tissue transplantation, immunodeficiency, poorly controlled HIV, AIDS, sickle cell anaemia, thalassaemia, long-term treatment with immunosuppressants) 5. Received a vaccine (approved or unapproved) against COVID-19 before or during randomization, or plans to be vaccinated ≤22 days after study treatment (CDC-recommended period, if any, should be observed.) [a)]

a) The period after the study drug administration was specified in Protocol Amendment 1 (December 23, 2020).

Casirivimab and imdevimab in combination (150, 300, 600, or 1,200 mg each) or placebo was administered intravenously as a single dose, or casirivimab and imdevimab in combination (300 or 600 mg each) or placebo was administered subcutaneously as a single dose.[7)]

In total, 815 subjects were randomized (intravenous administration: 116 in the 150 mg each group, 117 in the 300 mg each group, 116 in the 600 mg each group, 116 in the 1,200 mg each group, 58 in the placebo group) (subcutaneous administration: 117 in the 300 mg each group, 116 in the 600 mg each group, 59 in the placebo group). Of the 815 subjects, 803 who received the study drug were included in the safety analysis population (intravenous administration: 115 in the 150 mg each group, 114 in the 300 mg each group, 116 in the 600 mg each group, 115 in the 1,200 mg each group, 57 in the placebo group) (subcutaneous administration: 114 in the 300 mg each group, 114 in the 600 mg each group, 58 in the placebo group). Of the subjects in the safety analysis population, 712 were included in the modified full analysis set (mFAS) because they tested positive for SARS-CoV-2 by reverse transcription PCR (RT-PCR) using a nasopharyngeal swab at baseline (intravenous administration: 104 in the 150 mg each group, 93 in the 300 mg each group, 107 in the 600 mg each group, 104 in the 1,200 mg each group, 47 in the placebo group) (subcutaneous administration: 108 in the 300 mg each group, 98 in the 600 mg each group, 51 in the placebo group). Of those in the mFAS, 507 were included in the seronegative mFAS and in the population for antiviral activity analysis because they were seronegative at baseline (intravenous administration: 80 in the 150 mg each group, 68 in the 300 mg each group, 72 in the 600 mg each group, 62 in the 1,200 mg each group, 37 in the placebo group) (subcutaneous administration: 75 in the 300 mg each group, 73 in the 600 mg each group, 40 in the placebo group).

7) Casirivimab 2.5 mL (120 mg/mL) and imdevimab 2.5 mL (120 mg/mL), or placebo 2.5 mL, were administered subcutaneously to 4 different sites in the abdomen (other than umbilicus and hip) and upper thigh.

Table 7 shows the time-weighted average daily change[8)] in viral load (in nasopharyngeal swabs) in the seronegative mFAS, the primary efficacy endpoint, from baseline to 7 days after randomization. The extent of viral load decrease was larger in all dose groups than in the placebo group.

Table 7. Time-weighted average daily change in viral load[a)] (in nasopharyngeal swabs) from baseline to 7 days after randomization (seronegative mFAS)

	Intravenous administration				Subcutaneous administration		Placebo [d)]
	150 mg each	300 mg each	600 mg each	1,200 mg each	300 mg each	600 mg each	
Baseline viral load	7.22 ± 1.578 (n = 80)	7.43 ± 1.451 (n = 68)	7.15 ± 1.518 (n = 72)	7.25 ± 1.602 (n = 62)	7.40 ± 1.540 (n = 75)	7.18 ± 1.564 (n = 73)	7.02 ± 1.389 (n = 77)
Time-weighted average daily change in viral load[b)] (in nasopharyngeal swabs) from baseline to 7 days after randomization	−2.24 ± 1.170 (n = 76)	−2.40 ± 1.089 (n = 66)	−2.24 ± 1.117 (n = 67)	−2.40 ± 1.066 (n = 61)	−2.29 ± 1.089 (n = 71)	−2.23 ± 1.117 (n = 71)	−1.64 ± 1.114 (n = 74)
Difference from placebo [95% confidence interval][c)]	−0.60 [−0.88, −0.25]	−0.76 [−0.99, −0.34]	−0.60 [−0.89, −0.24]	−0.75 [−1.05, −0.38]	−0.64 [−0.88, −0.24]	−0.58 [−0.87, −0.24]	

Mean ± SD; viral load, Log_{10} copies/mL; lower limit of quantitation by RT-PCR, 2.85 Log_{10} copies/mL

a) Values below the lower limit of quantitation by RT-PCR test were handled as 0, but handled as half the lower quantitation limit if the sample was positive in the qualitative test.
b) Subjects without viral load data at baseline and those without viral load data after baseline were excluded from the analysis.
c) ANCOVA model with covariates of treatment group, baseline viral load, and interaction between treatment group and baseline viral load.
d) The placebo groups of intravenous and subcutaneous administration are combined.

Figure 2 shows changes over time in viral load (in nasopharyngeal swabs) from baseline to 7 days after randomization in the seronegative mFAS.

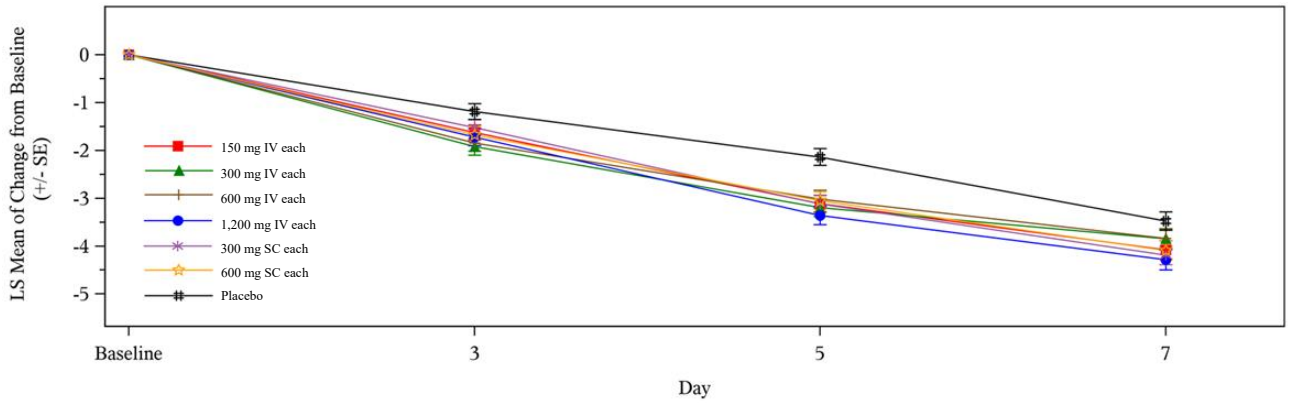

Figure 2. Changes over time in viral load (in nasopharyngeal swabs) (seronegative mFAS)

Least squares mean ± standard error (Log_{10} copies/mL)

Table 8 shows time-weighted average daily change in viral load (in nasopharyngeal swabs)[8)] from baseline to 5 days after randomization in the mFAS.

8) The area under the viral load-time curve (in nasopharyngeal swab samples) from baseline to the last day of observation, in each subject, was calculated by trapezoidal method and divided by the days of observation.

Table 8. Time-weighted average daily change in viral load[a)] (in nasopharyngeal swabs) from baseline to 5 days after randomization (mFAS)

	Intravenous administration				Subcutaneous administration		Placebo [d)]
	150 mg each	300 mg each	600 mg each	1,200 mg each	300 mg each	600 mg each	
Baseline viral load	6.88 ± 1.784 (n = 104)	6.94 ± 1.847 (n = 93)	6.56 ± 1.745 (n = 107)	6.43 ± 1.948 (n = 104)	6.86 ± 1.822 (n = 107)	6.73 ± 1.790 (n = 98)	6.81 ± 1.509 (n = 98)
Time-weighted average daily change in viral load[b)] (in nasopharyngeal swabs) from baseline to 5 days after randomization	−1.50 ± 1.161 (n = 99)	−1.75 ± 0.974 (n = 85)	−1.65 ± 1.014 (n = 100)	−1.53 ± 1.120 (n = 101)	−1.47 ± 1.021 (n = 100)	−1.56 ± 1.209 (n = 93)	−1.12 ± 1.038 (n = 94)
Difference from placebo [95% confidence interval][c)]	−0.38 [−0.64, −0.07]	−0.62 [−0.91, −0.31]	−0.53 [−0.85, −0.28]	−0.40 [−0.78, −0.21]	−0.34 [−0.60, −0.03]	−0.43 [−0.74, −0.16]	

Mean ± SD; viral load, Log_{10} copies/mL; lower limit of quantitation by RT-PCR, 2.85 Log_{10} copies/mL

a) Values below the lower limit of quantitation by RT-PCR test were handled as 0, but handled as half the lower quantitation limit if the sample was positive in the qualitative test.
b) Subjects without baseline viral load and those without viral load data after baseline were excluded from the analysis.
c) ANCOVA model with covariates of treatment group, baseline viral load, and interaction between treatment group and baseline viral load.
d) The placebo groups of intravenous and subcutaneous administration are combined.

Figure 3 shows changes over time in viral load (in nasopharyngeal swabs) from baseline to 7 days after randomization in the mFAS.

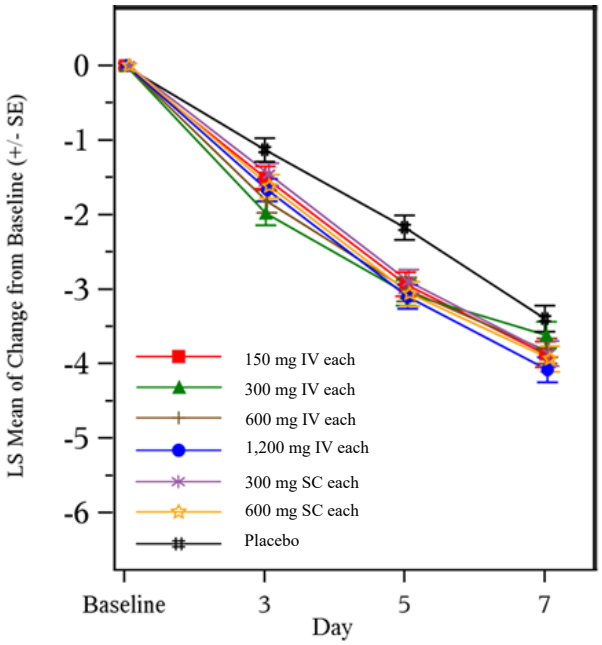

Figure 3. Changes over time in viral load (nasopharyngeal swabs) (mFAS)

Least squares mean ± standard error

The following safety events were collected[9)] (Table 9).

9) Data were analyzed at the data cut-off point (February 8, 2021; 7 days after randomization) when 803 randomized and treated subjects completed the observation. In the safety analysis population, 99.6% (515 of 517) of subjects receiving an intravenous dose and 99.7% (285 of 286) of subjects receiving a subcutaneous dose completed the observation on Day 7 after randomization, and 37.7% (195 of 517) of subjects receiving an intravenous dose and 37.1% (106 of 286) of subjects receiving a subcutaneous dose completed the observation on Day 29 after randomization. No subjects completed the observation on Day 60 or later after randomization

Table 9. Safety events collected

Original Protocol (November 23, 2020)	• Grade ≥2 hypersensitivity, Grade ≥2 infusion reaction, and Grade ≥2 injection site reaction occurring within 29 days after randomization • Serious adverse events occurring within 29 days after randomization • Serious adverse events occurring between 30 and 60 days after randomization
Protocol Amendment 1 (December 23, 2020)	• Adverse events occurring within 29 days after randomization • Grade ≥2 infusion reaction and Grade ≥3 injection site reaction occurring within 4 days after randomization Grade ≥2 hypersensitivity occurring within 29 days after randomization; and adverse events occurring within 169 days after randomization that led to hospitalization or emergency room (ER) visit • Grade 3 or 4 adverse events occurring between 30 and 169 days after randomization • Serious adverse events occurring within 169 days after randomization

Grading based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), v5.0.
The number of subjects randomized on or before December 22, 2020 is as follows:
Intravenous administration: 8 each in the 150 mg each group, 300 mg each group, 600 mg each group, and 1,200 mg each group
Subcutaneous administration: 4 in the placebo group; and 8 each in the 300 mg each group and 600 mg each group, and 4 in the placebo group.

Adverse events and adverse reactions[10] observed:
Intravenous administration: 8.7% (10 of 115) of subjects (adverse events) and in no subject (adverse reactions) in the 150 mg each group, 14.0% (16 of 114) and 0.9% (1 of 114) in the 300 mg each group, 19.0% (22 of 116) and 0.9% (1 of 116) in the 600 mg each group, 7.8% (9 of 115) and 0.9% (1 of 115) in the 1,200 mg each group, and 17.5% (10 of 57) and none in the placebo group.
Subcutaneous administration: 4.4% (5 of 114) and none in the 300 mg each group, 10.5% (12 of 114) and 0.9% (1 of 114) in the 600 mg each group, and 10.3% (6 of 58) and 1.7% (1 of 58) in the placebo group.

The adverse event reported in ≥2 subjects in any group was COVID-19, which was observed in the following subjects:
Intravenous administration: 4.3% (5 of 115) of subjects in the 150 mg each group, 10.5% (12 of 114) in the 300 mg each group, 14.7% (17 of 116) in the 600 mg each group, 4.3% (5 of 115) in the 1,200 mg each group, and 14.0% (8 of 57) in the placebo group.
Subcutaneous administration: 3.5% (4 of 114) of subjects in the 300 mg each group, 6.1% (7 of 114) in the 600 mg each group, and 8.6% (5 of 58) in the placebo group.
Causal relationship to the study drug was ruled out in all of the subjects, except for 2 subjects (1 in the 300 mg each group [intravenous] and 1 in the 600 mg each group [intravenous]; no information regarding causality was obtained by the cutoff date in the 2 subjects).

There was no adverse event leading to death.

Serious adverse events were observed in 1 subject in the 600 mg each group [intravenous] (abortion spontaneous) and in 1 subject in the 1,200 mg each group [intravenous] (abortion spontaneous). Their causal relationship to the study drug was ruled out.

An adverse event (infusion related reaction) led to treatment discontinuation in 1 subject in the 1,200 mg each group [intravenous]. Its causal relationship to the study drug could not be ruled out, and the outcome was “recovered.”

[10] Adverse events assessed as related to the study drug by the investigator, etc.

7.2 Foreign phase III study (Cohorts A and B[11]) (CTD 5.3.5.1-1: Study COV-2069 [ongoing since July 2021; data cut-off on March 2021][12])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to investigate the efficacy and safety of casirivimab and imdevimab in combination in ≥12-year-old asymptomatic household contacts with exposure to an individual with a diagnosis of SARS-CoV-2 infection (index case) (target sample size 3,500[13] [3,150 in Cohort A, 350 in Cohort B]) at 137 study sites in 3 countries (Moldova, Romania, United States).

According to the results of RT-PCR test for SARS-CoV-2 (nasopharyngeal swab) at baseline, subjects were divided into Cohort A (RT-PCR negative) and Cohort B (RT-PCR positive). Table 10 shows main inclusion and exclusion criteria.

Table 10. Main inclusion and exclusion criteria

Inclusion criteria	1. Asymptomatic household contact with exposure to an individual with a diagnosis of SARS-CoV-2 infection (index case). To be included in the study, subjects must be randomized within 96 hours of collection of the index cases' positive SARS-COV-2 diagnostic test sample. 2. Subject anticipates living in the same household with the index case until 29 days after randomization. 3. Is judged by the investigator to be in good health based on medical history and physical examination at screening/baseline, including subjects who are healthy or have a chronic, stable medical condition
Exclusion criteria	1. History of prior positive SARS-CoV-2 RT-PCR test or positive SARS-CoV-2 serology test at any time before the screening 2. Subject has lived with individuals who have had previous SARS-CoV-2 infection or currently lives with individuals who have SARS-CoV-2 infection, with the exception of the index case(s), the first individual(s) known to be infected in the household 3. Active respiratory or non-respiratory symptoms consistent with COVID-19 4. History of respiratory illness with sign/symptoms of COVID-19 within the prior 6 months to screening 5. Nursing home resident 6. Received a vaccine (approved or unapproved) against COVID-19.

Casirivimab and imdevimab in combination (600 mg each) or placebo was administered subcutaneously as a single dose. Casirivimab (120 mg/mL) and imdevimab (120 mg/mL) were not mixed before administration, but injected subcutaneously separately in 2.5 mL portions, each to 2 sites (4 sites in total).[14]

In total, 3,029 subjects were randomized (2,621 in Cohort A [1,313 in the casirivimab + imdevimab group, 1,308 in the placebo group], 314 in Cohort B [156 in the casirivimab + imdevimab group, 158 in the placebo group], 94 with unknown RT-PCR results [38 in the casirivimab + imdevimab group, 56 in the placebo group]). Of the 3,029 subjects, 3,002 were included in the safety analysis population (2,617 in Cohort A [1,311 in the casirivimab + imdevimab group, 1,306 in the placebo group], 311 in Cohort B [155 in the casirivimab + imdevimab group, 156 in the placebo group], 74 with unknown RT-PCR results [27 in the casirivimab + imdevimab group, 47 in the placebo group]). Of the 3,029 randomized subjects, 1,709 were included in the seronegative mFAS and the efficacy analysis population (1,505 in Cohort A [753 in the casirivimab + imdevimab group, 752 in the placebo group],

[11] Cohorts of <12-year-old subjects (Cohort A1: RT-PCR-negative; Cohort A2: RT-PCR-positive) were also included, but data from the cohorts were not submitted because no subjects were randomly assigned to the cohorts until data cut-off.
[12] Data were locked when data were collected from all subjects in Cohorts A and B up to 29 days after randomization.
[13] Subjects were assigned to the casirivimab + imdevimab group and the placebo group at a 1:1 ratio. For the rationale of the target sample size, see Section 10.2.
[14] Administration to different sites of the abdomen (other than umbilicus and hip) and upper thigh was recommended. Use of local anesthetics was prohibited to avoid the interference with the evaluation of adverse events.

204 in Cohort B [100 in the casirivimab + imdevimab group, 104 in the placebo group]), and the remaining subjects were excluded (554 enrolled in Cohort A between the start of study and October 16, 2020,[15] 94 with unknown RT-PCR results, 3 found to have symptoms of COVID-19 at baseline, and 669 with positive or unknown baseline serostatus).

Within 29 days after randomization, treatment was discontinued in 6 subjects in the casirivimab + imdevimab group (lost to follow-up in 2, withdrawal of consent in 4) and 2 in the placebo group (lost to follow-up and withdrawal of consent in 1 each) in Cohort A; 1 in the placebo group (withdrawal of consent) in Cohort B; and 1 in the casirivimab + imdevimab group (withdrawal of consent) and 1 in the placebo group (withdrawal of consent), both with unknown RT-PCR results.

In all cohorts, the primary efficacy endpoint was "the percentage of subjects (events) in the seronegative mFAS who showed symptoms of COVID-19 (Broad-term)[16] within 29 days after randomization and within 14 days[17] from the day of the first RT-PCR[18]-positive test sample collected." Table 11 shows the results in Cohorts A and B. In both cohorts, statistically significant difference was observed in the results of the primary endpoint between the casirivimab + imdevimab group and the placebo group. Figures 4 and 5 show Kaplan-Meier curves of changes over time in the percentage of cumulative occurrences of primary endpoint events. In the seronegative mFAS, the following percentages of subjects were living with index cases who had symptoms (pyrexia, cough, shortness of breath, chills, gastrointestinal disorder, loss of smell or ageusia) at baseline: 76.6% (577 of 753) in the casirivimab + imdevimab group and 76.1% (572 of 752) in the placebo group in Cohort A; and 83.0% (83 of 100) in the casirivimab + imdevimab group and 85.6% (89 of 104) in the placebo group in Cohort B.

Table 11. Primary endpoint (Cohort A and Cohort B) (seronegative mFAS)

		Casirivimab + imdevimab	Placebo
Cohort A (baseline RT-PCR negative)	Incidence of events	1.5% (11 of 753 subjects)	7.8% (59 of 752 subjects)
	Risk reduction rate [95% CI] a)	81.4% [65.3%, 90.1%]	
	Odds ratio [95% CI] b)	0.17 [0.090, 0.332]	
	p value b)	<0.0001	
Cohort B (baseline RT-PCR positive)	Incidence of events	29.0% (29 of 100 subjects)	42.3% (44 of 104 subjects)
	Risk reduction rate [95% CI] a)	31.5% [0.3%, 53.4%]	
	Odds ratio [95% CI] b)	0.54 [0.298, 0.966]	
	p value b)	0.0380	

a) (1− [percentage of subjects with events in the casirivimab + imdevimab group / percentage of subjects with events in the placebo group]) ×100

b) Two-sided significance level of 5%. Logistic regression model with covariates of treatment group, age (≥12 and <50, ≥50), and region (United States, other countries). Multiple imputation method was applied to subjects who discontinued the study without events.

15) A descriptive analysis was conducted using data from subjects in Cohort A who tested seronegative between the start of study and 29 days after randomization (efficacy evaluation period) and were randomized before approximately 30 RT-PCR-positive events occurred. These subjects were excluded from the efficacy analysis population but were included in the safety analysis population.

16) Any of the following symptoms:
Pyrexia of ≥38°C, feeling hot, sore throat, cough, shortness of breath/dyspnoea, chilliness, nausea, vomiting, diarrhoea, headache, ocular hyperaemia or runny eye, body aches such as myalgia and arthralgia, ageusia or smell loss, fatigability, anorexia or hypophagia, confusion, dizziness, chest pressure sensation or chest distress, chest pain, abdominal pain, rash, sneezing, runny nose, sputum, other. The following subjects in Cohort A had only "other" symptoms in the broad-term: nasal congestion in 3 and mild nasal congestion in 1 in the placebo group; pressure sensation of ethmoid sinus in 1 in the casirivimab + imdevimab group. In Cohort B, there were no subjects who had only "other" symptoms in the broad-term.

17) Cohort B includes subjects with a positive RT-PCR result at baseline.

18) Nasopharyngeal swab samples for RT-PCR test were collected at baseline (before study drug administration) and on Day 8 (±1), 15 (±3), 22 (±3), and 29 (±3) after randomization.

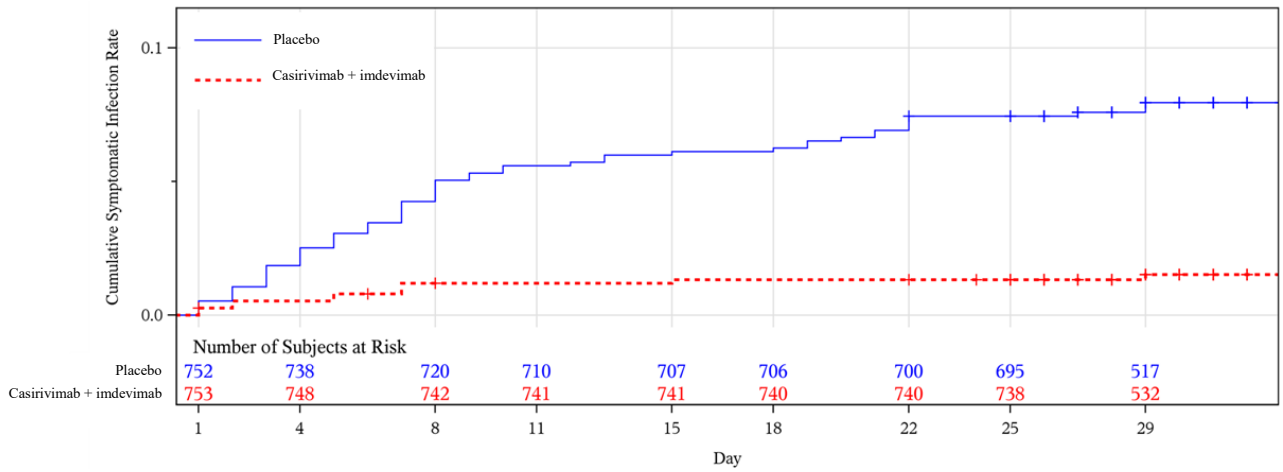

Figure 4. Cumulative incidence of primary endpoint events in Cohort A (seronegative mFAS)

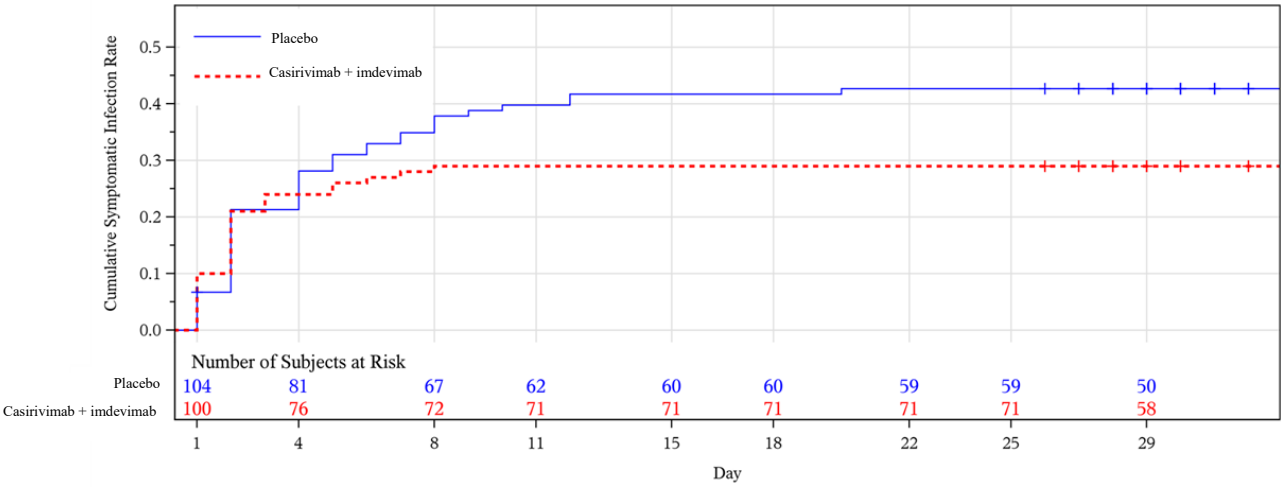

Figure 5. Cumulative incidence of primary endpoint events in Cohort B (seronegative mFAS)

In subjects with unknown RT-PCR results (seronegative mFAS), the incidence of primary endpoint events was 6.7% (1 of 15 subjects) in the casirivimab + imdevimab group and 15.2% (5 of 33) in the placebo group.

Table 12 shows the percentage of asymptomatic subjects, regardless of baseline serostatus, who showed symptoms of COVID-19 (Broad-term)[16] within 29 days after randomization and within 14 days from the day of the first RT-PCR-positive test sample collected.

Table 12. Primary endpoint (regardless of baseline serostatus)

		Casirivimab + imdevimab	Placebo
Cohort A (baseline RT-PCR negative)	Incidence of events	1.1% (12 of 1,046 subjects)	6.5% (66 of 1,021 subjects)
	Risk reduction rate [95% CI] [a)]	82.3% [67.7%, 90.3%]	
	Odds ratio [95% CI] [b)]	0.17 [0.090, 0.312]	
Cohort B (baseline RT-PCR positive)	Incidence of events	21.9% (34 of 155 subjects)	34.0% (53 of 156 subjects)
	Risk reduction rate [95% CI] [a)]	35.4% [7.0%, 55.5%]	
	Odds ratio [95% CI] [b)]	0.54 [0.325, 0.894]	
Cohorts A and B combined	Incidence of events	3.8% (46 of 1,201 subjects)	10.1% (119 of 1,177 subjects)
	Risk reduction rate [95% CI] [a)]	62.1% [47.4%, 72.8%]	
	Odds ratio [95% CI] [b)]	0.35 [-]	

-: Not submitted.

a) (1− [percentage of subjects with events in the casirivimab + imdevimab group/percentage of subjects with events in the placebo group]) ×100

b) Logistic regression model with covariates of treatment group, age (≥12 and <50, ≥50), and region (United States, other countries). Multiple imputation method was applied to subjects who discontinued the study without events.

Table 13 shows subgroup analysis results of Cohorts A and B.

Table 13. Subgroup analysis of the primary endpoint (seronegative mFAS)

		Casirivimab + imdevimab	Placebo
Cohort A (baseline RT-PCR negative)			
All subjects	Incidence of events	1.5% (11 of 753 subjects)	7.8% (59 of 752 subjects)
	Risk reduction rate [95% CI] [a)]	81.4% [65.3%, 90.1%]	
	Odds ratio [95% CI] [b)]	0.17 [0.090, 0.332]	
	p value [b)]	<0.0001	
12 to <18 years old	Incidence of events	0% (0 of 34 subjects)	11.8% (4 of 34 subjects)
	Risk reduction rate [95% CI] [a)]	100% [8.0%, 100%]	
	Odds ratio [95% CI] [b)]	0.17 [0.000, 1.066]	
18 to <50 years old	Incidence of events	1.2% (5 of 424 subjects)	6.6% (29 of 438 subjects)
	Risk reduction rate [95% CI] [a)]	82.2% [56.0%, 92.8%]	
	Odds ratio [95% CI] [b)]	0.17 [0.050, 0.446]	
≥50 years old	Incidence of events	2.0% (6 of 295 subjects)	9.3% (26 of 280 subjects)
	Risk reduction rate [95% CI] [a)]	78.1% [49.1%, 90.6%]	
	Odds ratio [95% CI] [b)]	0.20 [0.067, 0.516]	
Have risk factors for severe COVID-19 [c)]	Incidence of events	2.5% (6 of 238 subjects)	9.0% (20 of 221 subjects)
	Risk reduction rate [95% CI] [a)]	72.1% [34.0%, 88.3%]	
	Odds ratio [95% CI] [b)]	0.26 [0.084, 0.690]	
Cohort B (baseline RT-PCR positive)			
All subjects	Incidence of events	29.0% (29 of 100 subjects)	42.3 (44 of 104 subjects)
	Risk reduction rate [95% CI] [a)]	31.5% [0.3%, 53.4%]	
	Odds ratio [95% CI] [b)]	0.54 [0.298, 0.966]	
	p value [b)]	0.0380	
12 to <18 years old	Incidence of events	13.3% (2 of 15 subjects)	45.5% (5 of 11 subjects)
	Risk reduction rate [95% CI] [a)]	70.7% [−10.8%, 92.8%]	
	Odds ratio [95% CI] [b)]	0.20 [0.015, 1.642]	
18 to <50 years old	Incidence of events	38.2% (21 of 55 subjects)	41.8% (23 of 55 subjects)
	Risk reduction rate [95% CI] [a)]	8.7% [−44.5%, 42.6%]	
	Odds ratio [95% CI] [b)]	0.86 [0.373, 1.976]	
≥50 years old	Incidence of events	20.0% (6 of 30 subjects)	42.1% (16 of 38 subjects)
	Risk reduction rate [95% CI] [a)]	52.5% [−1.4%, 79.1%]	
	Odds ratio [95% CI] [b)]	0.35 [0.094, 1.152]	
Have risk factors for severe COVID-19 [c)]	Incidence of events	25.8% (8 of 31 subjects)	44.1% (15 of 34 subjects)
	Risk reduction rate [95% CI] [a)]	41.5% [−15.4%, 71.6%]	
	Odds ratio [95% CI] [b)]	0.45 [0.133, 1.412]	

a) (1− [percentage of subjects with events in the casirivimab + imdevimab group/percentage of subjects with events in the placebo group]) ×100

b) Logistic regression model with covariates of treatment group, age (≥12 and <50, ≥50), and region (United States, other countries). Multiple imputation method was applied to subjects who discontinued the study without events.

c) Subjects with any of the following conditions at baseline: age ≥65, BMI ≥35 kg/m^2; chronic kidney disease; diabetes mellitus; immunosuppressive disease; receiving immunosuppressive therapy; or age ≥55 with cardiovascular disease, hypertension, or chronic respiratory illness such as chronic obstructive pulmonary disease.

Table 14 shows the percentage of subjects who showed symptoms of COVID-19 within 29 days after randomization and within 14 days[19] from the day of the first RT-PCR-positive test sample collected, classified by symptoms.

Table 14. Percentage of subjects who showed symptoms of COVID-19 within 29 days after randomization and within 14 days from the day of the first RT-PCR-positive test sample collected (seronegative mFAS, classified by the definition of symptom)

		Casirivimab + imdevimab	Placebo
Cohort A (RT−PCR negative at baseline)			
Symptoms defined by CDC [a]	Incidence of events	0.8% (6 of 753 subjects)	6.1% (46 of 752 subjects)
	Risk reduction rate [95% CI] [c]	87.0% [70.4%, 94.3%]	
	Odds ratio [95% CI] [d]	0.12 [0.051. 0.286]	
Symptoms in strict term [b]	Incidence of events	0.3% (2 of 753 subjects)	2.9% (22 of 752 subjects)
	Risk reduction rate [95% CI] [c]	90.9% [65.4%, 97.6%]	
	Odds ratio [95% CI] [d]	0.09 [0.020, 0.370]	
Cohort B (RT−PCR positive at baseline)			
Symptoms defined by CDC [a]	Incidence of events	27.0% (27 of 100 subjects)	39.4% (41 of 104 subjects)
	Risk reduction rate [95% CI] [c]	31.5% [−1.7%, 54.4%]	
	Odds ratio [95% CI] [d]	0.54 [0.299, 0.989]	
Symptoms in strict term	Incidence of events	10.0% (10 of 100 subjects)	19.2% (20 of 104 subjects)
	Risk reduction rate [95% CI] [c]	48.0% [−3.6%, 74.2%]	
	Odds ratio [95% CI] [d]	0.47 [0.207, 1.070]	

a) Symptoms that correspond to any of (i) to (iii) below:
(i) Have ≥2 of the following symptoms (pyrexia or feeling hot, chills, myalgia, headache, pharyngeal pain, nausea, vomiting, diarrhoea, fatigue, nasal congestion, runny nose)
(ii) Have at least 1 of the following symptoms (cough, shortness of breath, dyspnoea, new dysosmia, new taste disorder)
(iii) Severe respiratory disorder accompanied by clinically or imaging confirmed pneumonia or acute respiratory distress syndrome

b) Symptoms that correspond to any of (i) to (iii) below:
(i) Pyrexia of ≥38°C and at least 1 of the following respiratory symptoms: pharyngeal pain, cough, or shortness of breath.
(ii) Two of the following respiratory symptoms: pharyngeal pain, cough, or shortness of breath.
(iii) One of respiratory symptoms (pharyngeal pain, cough, or shortness of breath) and ≥2 of non-respiratory symptoms (chills, nausea, vomiting, diarrhoea, headache, conjunctivitis, myalgia, arthralgia, dysosmia or taste disorder, fatigability, and general malaise)

c) (1− [percentage of subjects with events in the casirivimab + imdevimab group/percentage of subjects with events in the placebo group]) ×100

d) Logistic regression model with covariates of treatment group, age (≥12 and <50, ≥50), and region (United States, other countries). Multiple imputation method was applied to subjects who discontinued the study without events.

The number of subjects (seronegative mFAS) with a medically attended visit(s)[20] for the treatment of COVID-19 within 29 days after randomization was 0 of 753 in the casirivimab + imdevimab group and 9 of 752 in the placebo group in Cohort A; and 0 of 100 in the casirivimab + imdevimab group and 6 of 104 in the placebo group in Cohort B.

As for safety, the percentages of adverse events and adverse reactions[21] are as follows:

Cohort A: 20.2% (265 of 1,311 subjects) (adverse events) and 4.3% (57 of 1,311) (adverse reactions) in the casirivimab + imdevimab group; and 29.0% (379 of 1,306) and 2.5% (32 of 1,306) in the placebo group.

Cohort B: 33.5% (52 of 155 subjects) (adverse events) and 4.5% (7 of 155) (adverse reactions) in the casirivimab + imdevimab group; and 48.1% (75 of 156) and 4.5% (7 of 156) in the placebo group.

19) Cohort B includes subjects with a positive RT-PCR result at baseline.
20) Hospitalization, emergency room (ER) visit, or urgent care center visit due to COVID-19
21) Adverse events considered by the investigator to be related to the study drug.

Subjects with unknown RT-PCR results: 11.1% (3 of 27 subjects) (adverse events) and 3.7% (1 of 27) (adverse reactions) in the casirivimab + imdevimab group; and 27.7% (13 of 47) and 2.1% (1 of 47) in the placebo group.

Table 15 shows adverse events and adverse reactions with an incidence of ≥2% in either group in Cohort A or B.

Table 15. Adverse events and adverse reactions with an incidence of ≥2% in either group in Cohort A or B (safety analysis population)

Event	Adverse events						Adverse reactions					
	Cohort A		Cohort B		Subjects with unknown RT-PCR results		Cohort A		Cohort B		Subjects with unknown RT-PCR results	
	Casirivimab + imdevimab (N = 1,311)	Placebo (N = 1,306)	Casirivimab + imdevimab (N = 155)	Placebo (N = 156)	Casirivimab + imdevimab (N = 27)	Placebo (N = 47)	Casirivimab + imdevimab (N = 1,311)	Placebo (N = 1,306)	Casirivimab + imdevimab (N = 155)	Placebo (N = 156)	Casirivimab + imdevimab (N = 27)	Placebo (N = 47)
All	265 (20.2)	379 (29.0)	52 (33.5)	75 (48.1)	3 (11.1)	13 (27.7)	57 (4.3)	32 (2.5)	7 (4.5)	7 (4.5)	1 (3.7)	1 (2.1)
COVID-19[a)]	15 (1.1)	112 (8.6)	34 (21.9)	49 (31.4)	1 (3.7)	7 (14.9)	0	2 (0.2)	0	2 (1.3)	0	1 (2.1)
Asymptomatic COVID-19[b)]	54 (4.1)	108 (8.3)	7 (4.5)	12 (7.7)	0	4 (8.5)	0	0	0	1 (0.6)	0	0
Injection site reaction	55 (4.2)	19 (1.5)	6 (3.9)	1 (0.6)	0	0	53 (4.0)	17 (1.3)	6 (3.9)	1 (0.6)	0	0
Headache	24 (1.8)	46 (3.5)	0	1 (0.6)	1 (3.7)	0	2 (0.2)	2 (0.2)	0	1 (0.6)	1 (3.7)	0

n (%), MedDRA ver. 23.1

a) Defined as symptoms (broad-term) of COVID-19 occurring within 14 days before or after positive RT-PCR test. In 2 subjects receiving placebo (1 in Cohort A and 1 with an unknown RT-PCR result), COVID-19 was reported as an adverse event during the efficacy evaluation period (29 days after randomization), but not classified as a primary endpoint event.

b) Defined as a RT-PCR-positive case without symptoms of COVID-19. In Cohort B, this term was defined as a RT-PCR-positive result (without symptoms of COVID-19) obtained after recovery from the baseline infection.

Adverse events leading to death were observed in 2 subjects (cardiac failure congestive and sudden death in 1 subject each) in the casirivimab + imdevimab group and in 2 subjects (cardiac arrest and gunshot wound in 1 subject each) in the placebo group, all in Cohort A. The causal relationship to the study drug was ruled out for all of them.

Serious adverse events:

Cohort A: 10 subjects in the casirivimab + imdevimab group (gastroenteritis, pneumonia, sepsis, soft tissue infection, acute myocardial infarction, cardiac failure congestive, abdominal pain upper, sudden death, cholecystitis acute, ankle fracture, foot fracture, tibia fracture, cervix carcinoma recurrent, and respiratory failure in 1 subject each [some subjects had more than 1 event])

15 subjects in the placebo group (COVID-19 in 4, COVID-19 pneumonia in 2, pneumonia, appendicitis, scrotal abscess, urinary tract infection, cardiac arrest, abdominal pain, gunshot wound, breast cancer, mania, suicidal ideation, and essential hypertension in 1 each [some subjects had more than 1 event])

Cohort B: 4 subjects in the placebo group (COVID-19 in 2, COVID-19 pneumonia and pancreatitis acute in 1 each).

The causal relationship to the study drug was ruled out for all of them.

There were no adverse events leading to treatment discontinuation.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

The applicant's explanation about the efficacy of casirivimab and imdevimab in combination in the suppression of development of COVID-19:

In the foreign phase III study (Study COV-2069), casirivimab and imdevimab in combination was administered to asymptomatic household contacts with exposure to an individual with a diagnosis of SARS-CoV-2 infection (index case). In this study, the primary endpoint was "the percentage of subjects in the seronegative mFAS who showed symptoms of COVID-19 (Broad-term)[22)] within 29 days after randomization and within 14 days[23)] from the day of the first RT-PCR[24)]-positive test sample collected."

The following points in the primary endpoint are considered to be appropriate:

(a) Approximately 70% of patients with COVID-19 present with pyrexia, cough, or shortness of bless, but COVID-19 has been reported to also cause other various symptoms. Broad-term was therefore used because it allows evaluation of all symptomatic subjects regardless of type or severity of symptoms.

(b) Symptoms that occurred within 14 days from the day of the first RT-PCR-positive test sample collected were handled as the symptoms of COVID-19, because COVID-19 symptoms have been reported to develop 2 to 14 days after the exposure to SARS-CoV-2.

Table 16 shows the results of the primary endpoint. In both cohorts, a statistically significant difference was observed between the casirivimab + imdevimab group and the placebo group. These results show the efficacy of the treatment in suppressing the development of COVID-19 in uninfected subjects who had been in close contact with a SARS-CoV-2-infected individual (Cohort A) and in asymptomatic subjects infected with SARS-CoV-2 (Cohort B).

Table 16. Primary endpoint (Cohorts A and B) (seronegative mFAS)

		Casirivimab + imdevimab	Placebo
Cohort A (RT-PCR negative at baseline)	Incidence of events	1.5% (11 of 753 subjects)	7.8% (59 of 752 subjects)
	Risk reduction rate [95% CI] [a)]	81.4% [65.3%, 90.1%]	
	Odds ratio [95% CI] [b)]	0.17 [0.090, 0.332]	
	p value [b)]	<0.0001	
Cohort B (RT-PCR positive at baseline)	Incidence of events	29.0% (29 of 100 subjects)	42.3% (44 of 104 subjects)
	Risk reduction rate [95% CI] [a)]	31.5% [0.3%, 53.4%]	
	Odds ratio [95% CI] [b)]	0.54 [0.298, 0.966]	
	p value [b)]	0.0380	

a) (1− [percentage of subjects with events in the casirivimab + imdevimab group/percentage of subjects with events in the placebo group]) ×100

b) Logistic regression model with covariates of treatment group, age (≥12 and <50, ≥50), and region (United States, other countries). Multiple imputation method was applied to subjects who discontinued the study without events.

22) Any of the following symptoms:
Pyrexia of ≥38°C, feeling hot, sore throat, cough, shortness of breath/dyspnoea, chilliness, nausea, vomiting, diarrhoea, headache, ocular hyperaemia or runny eye, body aches such as myalgia and arthralgia, ageusia or smell loss, fatigability, anorexia or hypophagia, confusion, dizziness, chest pressure sensation or chest distress, chest pain, abdominal pain, rash, sneezing, runny nose, sputum, other. The following subjects in Cohort A had only "other" symptoms in the broad-term: nasal congestion in 3 and mild nasal congestion in 1 in the placebo group; and pressure sensation of ethmoid sinus in 1 in the casirivimab + imdevimab group. In Cohort B, there were no subjects who had only "other" symptoms in the broad-term.

23) Cohort B includes subjects with a positive RT-PCR result at baseline.

24) Nasopharyngeal swab samples for RT-PCR test were collected at baseline (before study drug administration) and on Day 8, 15, 22, and 29 (±3) after randomization.

Although no clinical study was conducted in Japanese subjects living with SARS-CoV-2-infected individual(s), the treatment is expected to be effective in the Japanese population as well based on the results of Study COV-2069, for the following reasons:

(a) Symptoms of COVID-19 are similar between Japanese and non-Japanese patients.
(b) The incidence of SARS-CoV-2 infection and COVID-19 in close contacts are not considered to differ significantly between the Japanese and U.S. populations.[25)]
(c) Casirivimab and imdevimab are both antibodies against adventitious agents.
(d) No clear difference was observed in PK of casirivimab or imdevimab between the Japanese and non-Japanese populations [see Section 6.R.1].

During the period of the foreign phase III study (Study COV-2069), main SARS-CoV-2 strains detected in participating countries[26)] were the wild strain, strain B.1.1.7 (Alpha), and strain B.1.427/B.1.429 (epsilon). *In vitro* studies showed no decrease in the neutralization activity of casirivimab and imdevimab in combination against main variants including strain B.1.617.2 (Delta), the most prevalent SARS-CoV-2 strain in Japan currently (Report on Special Approval for Emergency of Ronapreve for Intravenous Infusion Set 300 and 1332 [dated July 14, 2021]).

PMDA's view:
Taking account of the population in the foreign phase III study (Study COV-2069), PMDA accepts the applicant's explanation that casirivimab and imdevimab in combination was shown to have efficacy in suppressing the development of COVID-19 in uninfected people who had been in close contact with a SARS-CoV-2-infected individual and asymptomatic people infected with SARS-CoV-2. Although no Japanese patients were enrolled in the foreign phase III study (Study COV-2069), there appears to be no significant difference between Japanese and non-Japanese people in COVID-19 symptoms and in the incidence of COVID-19 in close contacts. Also, no clear difference was observed in PK of casirivimab and imdevimab between the Japanese and non-Japanese populations [see Section 6.R.1]. In addition, casirivimab and imdevimab are antibodies against adventitious agents. Based on these findings, casirivimab and imdevimab are expected to be effective in Japanese people as well. Information on the efficacy of casirivimab and imdevimab against variants should be collected continuously and provided promptly to healthcare professionals.

7.R.2 Safety

The applicant's explanation about the safety profile of casirivimab and imdevimab in combination:
Table 17 shows the summary of safety data in the foreign phase III study (Study COV-2069). There were no tendencies of higher incidences of adverse events in the casirivimab + imdevimab group compared with those in the placebo group, and causal relationship to the study drug was ruled out for serious adverse events and for adverse events leading to death. These results suggest that the product has an acceptable safety profile.

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25) United States: In close contacts, the incidence of SARS-CoV-2 infection was 0.45% to 38.2% and the incidence of COVID-19 was 12% to 46.5% (*Clin Infect Dis.* 2020;71:1953-59, etc.). In the placebo group of the foreign phase III study (Study COV-2069), the incidence of SARS-CoV-2 infection was 14.2% and the incidence of COVID-19 was 7.8% in asymptomatic, RT-PCR-negative, close contacts; and the incidence of COVID-19 in asymptomatic, RT-PCR-positive, close contacts was 42.3%.
Japan: The incidence of SARS-CoV-2 infection was 10.6% in close contacts and 14.2% in household contacts, and 19.8% had symptom at RT-PCR test (*National Institute of Infectious Diseases: Infectious Agents Surveillance Report* Vol. 42, No. 5, published in May 2021).

26) United States and Romania. No information available from Moldova.

Table 17. Safety summary in foreign phase III study (Study COV-2069) (safety analysis population)

	Cohort A (RT-PCR negative)		Cohort B (RT-PCR positive)		Subjects with unknown RT-PCR results	
	Casirivimab + imdevimab (N = 1,311)	Placebo (N = 1,306)	Casirivimab + imdevimab (N = 155)	Placebo (N = 156)	Casirivimab + imdevimab (N = 27)	Placebo (N = 47)
Adverse events	265 (20.2)	379 (29.0)	52 (33.5)	75 (48.1)	3 (11.1)	13 (27.7)
Adverse reactions	57 (4.3)	32 (2.5)	7 (4.5)	7 (4.5)	1 (3.7)	1 (2.1)
Serious adverse events	10 (0.8)	15 (1.1)	0	4 (2.6)	0	0
Adverse events leading to death	2 (0.2)	2 (0.2)	0	0	0	0
Adverse events leading to treatment discontinuation	0	0	0	0	0	0

n (%)

The foreign phase II study (Study COV-20145) reported no Grade[27] ≥2 infusion related reaction[28] or hypersensitivity or Grade ≥3 injection site reaction. The foreign phase III study (Study COV-2069) reported no Grade[27] ≥3 injection site reaction or hypersensitivity.

The percentages of adverse events and adverse reactions in subjects 12 to <18 years of age in the foreign phase III study (Study COV-2069) are as follows:

Cohort A: 17.8% (8 of 45 subjects) (adverse events) and 8.9% (4 of 45) (adverse reactions) in the casirivimab + imdevimab group; and 32.6% (14 of 43) and 2.3% (1 of 43) in the placebo group

Cohort B: 9.5% (2 of 21 subjects) (adverse events) and none (adverse reactions) in the casirivimab + imdevimab group; and 47.1% (8 of 17) and none in the placebo group

Subjects with unknown RT-PCR results: 0 of 2 subjects (adverse events) and none (adverse reactions) in the casirivimab + imdevimab group; and 50.0% (1 of 2) and none in the placebo group.

There were no serious adverse events or adverse events leading to death or treatment discontinuation in any group. Adverse events with a >2% higher incidence in 12 to <18-year-old subjects than in ≥18-year-old subjects in the casirivimab + imdevimab group were administration site reaction in Cohort A and vomiting in Cohort B.

Administration site reaction in Cohort A:

12 to <18-year-old subjects: 8.9% (4 of 45) in the casirivimab + imdevimab group, 2.3% (1 of 43) in the placebo group

≥18-year-old subjects: 4.0% (51 of 1,266) in the casirivimab + imdevimab group, 1.4% (18 of 1,263) in the placebo group

Vomiting in Cohort B:

12 to <18-year-old subjects: 4.8% (1 of 21) in the casirivimab + imdevimab group, 0 of 17 in the placebo group;

≥18-year-old subjects: 0 of 134 in the casirivimab + imdevimab group, 0 of 139 in the placebo group.

[27] Grading based on National cancer institute-common terminology criteria for adverse events (NCI-CTCAE) v5.0 (Division of Cancer Treatment and Diagnosis, 2020)

[28] Intravenous dose group

These results suggest that the product has an acceptable safety profile.

Japanese subjects were not included in the foreign phase III study (Study COV-2069). However, for the reasons listed below, the safety of casirivimab and imdevimab in combination in the Japanese population can be evaluated to a certain degree, and the therapy is expected to be safe in the Japanese population.

(a) Symptoms of COVID-19 are similar between Japanese and non-Japanese patients.
(b) Casirivimab and imdevimab are both antibodies against adventitious agents.
(c) No clear differences have been observed in PK between the Japanese and non-Japanese populations [see Section 6.R.1].
(d) No safety concerns were observed in the Japanese phase I study (Study JV43180), which evaluated casirivimab and imdevimab in combination in Japanese adults without COVID-19 (Report on Special Approval for Emergency of Ronapreve for Intravenous Infusion Set 300 and 1332 [dated July 14, 2021]).

Adverse events commonly reported in spontaneous reports (data cut off on September 29, 2021) after the approval of Ronapreve were pyrexia (154 events), infusion related reaction (35), oxygen saturation decreased (37), headache (33), rash (32), and nausea (27). The outcome was "recovered" or "recovering" in most cases except in those with insufficient information. Adverse events leading to death were reported in 5 patients (death, disease progression, COVID-19, cardio-respiratory arrest, and pancreatic carcinoma in 1 each) and, except for COVID-19, their causal relationship to Ronapreve was ruled out. There was an adverse event (haemorrhagic cerebral infarction) that resolved with sequelae. Its causal relationship to Ronapreve could not be ruled out, but the patient had concurrent diseases of hypertension, atrial fibrillation, and obesity. Spontaneous reports (data cut-off on September 29, 2021) after Emergency Use Authorization in the United States included 2,312 adverse events following intravenous administration (there were ≥50 events of pyrexia [133 events], chills [115], nausea [88], dyspnoea [86], oxygen saturation decreased [64]) and 355 adverse events following subcutaneous administration (there were ≥10 events of pyrexia [23], urticaria [12], nausea [11], and pruritus [10]). Thus, most of the reported events were related to COVID-19 or hypersensitivity, and no difference was observed in the safety profile between before and after the approval in Japan.

Based on the above, the applicant considers that subcutaneous administration of casirivimab and imdevimab has an acceptable safety profile. The package insert will include a precautionary statement regarding the risk of injection site reaction observed following subcutaneous administration.

PMDA's view:
The safety profile of subcutaneous administration of casirivimab and imdevimab in combination is acceptable. Although reaching a definite conclusion is difficult because of the limited experience with casirivimab and imdevimab in combination in Japanese subjects, PMDA has concluded that the safety profile in the Japanese population would not significantly differ from that in the non-Japanese population, for the following reasons:

(a) Casirivimab and imdevimab are antibodies against an adventitious agent.

(b) No clear differences were observed in PK between the Japanese and non-Japanese populations [see Section 6.R.1].
(c) No particular safety concerns were noted in the Japanese phase I study (Study JV431809), which evaluated casirivimab and imdevimab in combination in Japanese adults without COVID-19 (Report on Special Approval for Emergency of Ronapreve for Intravenous Infusion Set 300 and 1332 [dated July 14, 2021]).

Safety data in Japanese patients should be collected continuously after the market launch and provided appropriately to healthcare professionals.

7.R.3 Clinical positioning

The applicant's explanation about the clinical positioning of casirivimab and imdevimab in combination:

In Japan, Comirnaty intramuscular injection, COVID-19 Vaccine Moderna Intramuscular Injection, and Vaxzevria Intramuscular Injection are approved as vaccines indicated for the prevention of COVID-19. As with other infectious diseases, vaccination is most important for preventing COVID-19. However, vaccination may not be sufficiently effective under the following situations:

(a) In unvaccinated people
(b) The period between the completion of vaccination and the effectiveness is obtained
(c) In immunodeficient or immunocompromised people and those receiving immunosuppressive therapy
(d) Emergence of vaccine-resistant variants

Ronapreve provides a treatment option for these conditions.

In fully vaccinated people, however, Ronapreve may not have the same efficacy as demonstrated in the foreign phase III study (Study COV-2069). Whether to administer Ronapreve should be decided carefully for individual patients based on the history of vaccination, presence/absence of underlying comorbidities affecting vaccine effectiveness, etc.

The foreign phase III study (Study COV-2069) enrolled subjects regardless of risk factors for severe COVID-19, and demonstrated the efficacy of Ronapreve in the entire population. However, upon discussion with U.S. FDA on the Emergency Use Authorization in the United States, the target population in the Fact Sheet was limited to those with risk factors for severe COVID-19, because allowing the use of Ronapreve in close contacts of SARS-CoV-2-infected individuals may give the wrong perception that Ronapreve is an alternative to vaccination and may adversely affect the promotion of vaccination. In Japan as well, it is desirable to facilitate prompt administration of Ronapreve to those in high need, given the limited supply[29)] of Ronapreve at the current moment. Thus, in order to keep the consistency with the target population for the approved indication, the target population for the additional indication should be limited to those with risk factors for severe COVID-19.

[29)] "Distribution of Neutralizing Antibodies Against COVID-19 to Medical Institutions (Corrections to Questions and Answers)" (dated July 20, 2021 [final correction on October 1, 2021], COVID-19 Prevention Headquarters, Ministry of Health, Labour and Welfare) https://www.mhlw.go.jp/content/000836895.pdf (last accessed on October 21, 2021)]

PMDA's view:

Based on the discussions in Sections 7.R.1 and 7.R.2, PMDA considers that the administration of casirivimab and imdevimab in combination provides a novel treatment option for suppressing the development of COVID-19 in uninfected people who were in close contact with a SARS-CoV-2-infected individual and in asymptomatic people infected with SARS-CoV-2. However, Ronapreve is not an alternative to vaccination, for the following reasons:

(a) Vaccination is fundamental for preventing infectious diseases.
(b) In Japan, several vaccines are approved against COVID-19 and have shown relatively high preventive effects.
(c) It is unknown whether Ronapreve has the same efficacy in vaccine responders who have been fully vaccinated as in the population enrolled in the foreign phase III study (Study COV-2069).

Thus, Ronapreve provides an option for suppressing the development of COVID-19 in unvaccinated people and non-responders to a vaccine. Whether to administer Ronapreve should be decided carefully for individual patients based on the history of vaccination, presence/absence of underlying comorbidities affecting vaccine effectiveness, etc.

The applicant's proposal to limit the target population for suppression of development of COVID-19 to those with risk factors for severe COVID-19 is acceptable, for the following reasons:

(a) Most (approximately 80%) of the patients with COVID-19 recover within 1 week after the onset of symptoms.
(c) Some patients require supplemental oxygen or treatment in an intensive-care unit. Those with risk factors for severe COVID-19 tend to develop serious illness after hospitalization than those without the risk factors (Guidelines for Diagnosis and Treatment of COVID-19, ver. 5.3).
(d) In the placebo group of the foreign phase III study (Study COV-2069, seronegative mFAS), all of the subjects hospitalized for the treatment of COVID-19 had risk factors for severe COVID-19.

Information on the target population should be provided appropriately to healthcare professionals to avoid confusion in the clinical practice, such as by employing guidelines of relevant academic societies.

7.R.4 Indication

PMDA's view:

Based on the discussion presented in Sections 7.R.1 and 7.R.2, the additional indication of casirivimab and imdevimab should be "suppression of development of COVID-19."[30)]

[30)] The proposed indication was "Treatment and prevention of disease caused by SARS-CoV-2 infection (COVID-19)" but was later changed to "Treatment and suppression of development of disease caused by SARS-CoV-2 infection (COVID-19)" at the request of the applicant.

7.R.5 Dosage and administration

7.R.5.1 Dosage and administration for the suppression of development of COVID-19

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

Based on the evaluation of the results of nonclinical studies, etc., the dosage regimen of the foreign phase III study (Study COV-2069) was determined to be a single subcutaneous dose of casirivimab and imdevimab in combination (600 mg each) [see Section 6.R.2]. The study showed the efficacy and safety in the suppression of development of COVID-19 in ≥12-year-old people [see Sections 7.R.1 and 7.R.2]. No clinical study has been conducted to investigate the efficacy of a single intravenous administration for suppressing the development of COVID-19. However, the mean serum concentration of Ronapreve following a single intravenous administration exceeded the level achieved by a single subcutaneous administration, up to 6 days after administration [see Section 6.2.1] and at 28 days after administration (Report on Special Approval for Emergency of Ronapreve for Intravenous Infusion Set 300 and 1332 [dated July 14, 2021]) [see Section 6.2.2]. This suggests that a single intravenous dose of Ronapreve is also effective for suppressing the development of COVID-19. Further, it is important to ensure that either route of administration can be selected depending on the clinical situations. Therefore the dosage and administration should be "a single subcutaneous or intravenous administration of casirivimab and imdevimab (600 mg each) in combination." In the foreign phase III study (Study COV-2069), ≥12-year-old pediatric individuals were enrolled regardless of body weight. However, the intended patients in the present application are those ≥12 years old weighing ≥40 kg as was the case with the initial approval because of the limited information in pediatric individuals weighing <40 kg.

PMDA's view:

Taking account of the explanation of the applicant and of the fact that there was no significant difference in the safety profile between subcutaneous and intravenous administration [see Sections 7.1 and 7.R.2], PMDA has concluded that the dosage and administration of "a single intravenous or subcutaneous administration of casirivimab 600 mg and imdevimab 600 mg in combination" is acceptable for the suppression of development of COVID-19 in adults and pediatric patients ≥12 years old weighing ≥40 kg

7.R.5.2 New route of administration (subcutaneous) for COVID-19

The applicant explained the reasons for proposing a new route of administration (subcutaneous) against COVID-19, in addition to the already approved intravenous administration. The dosage is the same in both administration routes (casirivimab 600 mg and imdevimab 600 mg in combination).

The applicant's explanation:

Although no clinical study has been conducted to investigate the efficacy of a single subcutaneous administration of Ronapreve against COVID-19, the treatment is expected to be effective, for the following reasons:

Following a single subcutaneous administration of casirivimab and imdevimab (600 mg each) in combination, the mean serum drug concentrations up to 6 days after administration remained lower than the levels achieved by intravenous administration at the same dose, and the concentrations immediately after administration were below the target level of 20 μg/mL [see

Section 6.2.1]. However, the mean serum drug concentrations exceeded the target level from 2 to 6 days after administration [see Section 6.2.1] and at 28 days after administration (Report on Special Approval for Emergency of Ronapreve for Intravenous Infusion Set 300 and 1332 [dated July 14, 2021]) [see Sections 6.2.1 and 6.2.2]. Further, changes in the viral load from baseline were similar regardless of the route of administration (see Section 7.1).

Subcutaneous administration is a convenient, timesaving, and less demanding clinical work, and vascular access creation may become difficult in patients with high body mass index (BMI). Therefore subcutaneous route should be made available as an option. Accordingly, it is appropriate to add subcutaneous administration for the treatment of COVID-19. However, the package insert will state that casirivimab and imdevimab in combination should be administered intravenously as a general rule.

PMDA's view:

Taking account of the applicant's explanation, the proposed dosage and administration for COVID-19 (a single subcutaneous administration of casirivimab 600 mg and imdevimab 600 mg in combination) is acceptable, because no significant difference was observed in the safety profile between subcutaneous and intravenous administration [see Sections 7.1 and 7.R.2], and because only limited treatment options are currently available for mild to moderate COVID-19.

However, intravenous administration should be used as a general rule, unless subcutaneous route is inevitable due to the patient's conditions, for the following reasons:

(a) No clinical studies have been conducted to investigate the efficacy of subcutaneous casirivimab and imdevimab in combination against COVID-19.
(b) The relationship between viral load and clinical efficacy is unknown.
(c) The target serum concentration is reached sooner after intravenous administration than after subcutaneous administration.

Thus, the package insert should state that casirivimab and imdevimab in combination should be administered intravenously as a general rule.

7.R.6 Post-marketing investigations and risk management plan (draft)

The applicant has no plan to conduct additional pharmacovigilance activities such as use-results survey after the market launch.

PMDA's view:

In order to confirm the safety profile in Japanese patients with COVID-19 after the market launch, the applicant should conduct a use-results survey, for the following reasons:

(a) There is no experience with casirivimab and imdevimab in combination in the Japanese population for the suppression of development of COVID-19.
(b) There are only limited experiences with subcutaneous administration of Ronapreve in the Japanese population.

The current version of risk management plan (draft) for Ronapreve should include the safety specification presented in Table 18, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 19 and 20.

Table 18. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Serious hypersensitivity reactions such as anaphylaxis, infusion reactions	None	None
Efficacy specification		
None		

Table 19. 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 (intravenous infusion and subcutaneous injection for the suppression of development of COVID-19; subcutaneous injection for treatment of COVID-19) • Use-results survey	None	• Disseminate data gathered during early post-marketing phase vigilance (intravenous infusion and subcutaneous injection for suppression of development of COVID-19; subcutaneous injection for treatment of COVID-19)

Table 20. Summary of use-results survey (draft)

Objective	Monitor the occurrence of hypersensitivity, infusion reactions, etc., after administration of Ronapreve.
Survey method	Central registry system or consecutive patients
Population	Ronapreve-treated patients who have risk factors for severe COVID-19
Observation period	7 days after Ronapreve administration
Planned sample size	770 patients
Main survey items	Patient characteristics, prior treatments, the status of Ronapreve therapy, concomitant drugs, adverse events

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

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

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

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

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the suppression of development of COVID-19 and acceptable safety in view of its benefits. The product is

clinically meaningful because it offers a new treatment option for suppression of development of COVID-19. 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.

Although the present application is classified as "Drug with new routes of administration" and "Drug with new indications," the re-examination period for the present application should be the remainder of re-examination period for the initial approval (until July 18, 2029) because it has more than 6 years left.

Indication

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

(Underline donates a change from the proposed indication.)

Dosage and Administration

The usual dosage in adults and pediatric patients (≥12 years of age weighing ≥40 kg) is 600 mg of Casirivimab (Genetical Recombination) and 600 mg of Imdevimab (Genetical Recombination) administered together as a single intravenous infusion or as a single subcutaneous injection.

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
   The applicant is required to conduct a use-results survey on the product, and report the results.
   (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.

3. The product is approved based on Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. The approval may be withdrawn in accordance with the provision in Article 75-3 of

the Act in a case where (1) the product does not conform to one or more Items of Article 14-3, Paragraph 1 of the Act or (2) the withdrawal is necessary to prevent the emergence or expansion of public health risks.

10. Other

10.1 Brand name

The current brand name is “Ronapreve for Intravenous Infusion Set 300, Ronapreve for Intravenous Infusion Set 1332.” The approval of the present application will make available a new route of administration (subcutaneous) in addition to the already approved intravenous infusion. After the approval of the present application, the applicant will submit a new application for replacement of license to change the brand name to “Ronapreve Injection Set 300, Ronapreve Injection Set 1332,” to ensure prompt delivery of the product under the new brand name after the approval of the present application.

10.2 Rationale for the target sample size in Study COV-2069

The rationale for the target sample size in Study COV-2069 is shown in the follow table:

Original Protocol (June 16, 2020)

Efficacy endpoints

Primary endpoints in Cohort A:

- Percentage of subjects who have symptoms of COVID-19 (strict-term) and a positive RT-PCR result within 29 days after randomization
- Percentage of subjects with a positive RT-PCR result within 29 days after randomization

Endpoint in Cohort B:

- Percentage of subjects who have symptoms of COVID-19 (strict-term)

Target sample size

Cohort A, 1,700; Cohort B, 300

Rationale for the target sample size

Assuming that the incidence of both primary endpoints in Cohort A to be 5% in the casirivimab + imdevimab group and 10% in the placebo group, the sample size required to ensure the statistical power of approximately 90% at 2-sided significance level of 2.5% was calculated to be 1,368 subjects in the 2 groups combined. Assuming the drop-out rate of 10% and the percentage of seropositive subjects enrolled in the entire study to be 10%, the target sample size in Cohort A was determined to be 1,700 subjects in the 2 groups combined. In order to enroll 1,700 subjects in Cohort A, 2,000 subjects had to be enrolled in the entire study, resulting in the target sample size of 300 subjects for Cohort B. Assuming the between-group ratio of the incidence to be 0.5, the sample size in Cohort B (300) ensures the statistical power of >95% at 2-sided significance level of 5%.

Protocol Amendment 4 (November 24, 2020)

Efficacy endpoints

Primary endpoint in Cohort A:

- Percentage of subjects with a positive RT-PCR result within 29 days after randomization

Endpoint in Cohort B:

- Percentage of subjects who have symptoms of COVID-19 (strict term)

Target sample size

Cohort A, 1,980; Cohort B, 220

Rationale for the target sample size

Assuming that the incidence of the primary endpoint in Cohort A to be 5% in the casirivimab + imdevimab group and 10% in the placebo group, the sample size required to ensure the statistical power of at least 90% at 2-sided significance level of 5% was calculated to be 1,248 subjects in the 2 groups combined. Assuming the drop-out rate of 10% and the percentage of seropositive subjects at baseline in the overall population to be 30%, the target sample size in Cohort A was determined to be 1,980 subjects in the 2 groups combined. In order to enroll 1,980 subjects in Cohort A, 2,200 subjects had to be enrolled in the entire study, resulting in the target sample size of 220 subjects for Cohort B. Assuming the between-group ratio of the incidence to be 0.5, the sample size in Cohort B (220) ensures the statistical power of >95% at 2-sided significance level of 5%.

Protocol Amendment 5 (January 19, 2021)

Efficacy endpoints

Primary endpoint in Cohort A:

- Percentage of subjects with a positive RT-PCR result within 29 days after randomization

Endpoint in Cohort B:

- Percentage of subjects who have symptoms of COVID-19 (strict term)

Target sample size

Cohort A, 3,150; Cohort B, 350

Rationale for the target sample size

An interim analysis not intended for early termination for futility or efficacy was conducted based on data from subjects in Cohort A who tested seronegative between the start of study and 29 days after randomization and were randomized before approximately 30 RT-PCR-positive events occurred. Using the interim analysis results, the number of subjects to be enrolled in the entire study was reconsidered based on the status of vaccination and SARS-CoV-2 infection. The data used in the interim analysis were to be excluded from the efficacy evaluation in the study. Based on the above, the overall target sample size was changed to 3,500 (3,150 in Cohort A, 350 in Cohort B) although there were no changes from Protocol Amendment 4 in the number of subjects needed and its assumption.

Protocol Amendment 5 (March 25, 2021)

Efficacy endpoint

Primary endpoint in Cohorts A and B:

Percentage of subjects who have symptoms of COVID-19 (broad-term) within 29 days after randomization and within 14 days from the day of the first RT-PCR-positive test sample collected

Target sample size

Cohort A, 3,150; Cohort B, 350

Rationale for the target sample size

Assuming that the incidence of the primary endpoint in Cohort A to be 5% in the casirivimab + imdevimab group and 10% in the placebo group, the sample size required to ensure the statistical power of at least 90% at 2-sided significance level of 5% was calculated to be 1,248 subjects in the 2 groups combined. Assuming the drop-out rate of 10% and the percentage of seropositive subjects at baseline in the overall population to be 30%, the target sample size in Cohort A was determined to be 1,980 subjects in the 2 groups combined. If 220 subjects were enrolled in Cohort B, 200 of them were expected to be seronegative. Assuming the between-group ratio of the incidence to be 0.5 (odds ratio 0.47), the target sample size of 200 in Cohort B ensures the statistical power of >90% at 2-sided significance level of 5%. The overall target sample size remained unchanged from Protocol Amendment 5 (3,500 subjects [3,150 in Cohort A and 350 in Cohort B]).

List of Abbreviations

ACE2	Angiotensin-converting enzyme 2
ADA	Anti-drug antibodies
AUC	Area under the serum concentration-time curve
$AUC_{0\text{-}t\ day}$	Area under the serum concentration-time curve up to t 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
BMI	Body mass index
$C_{1\ h}$	Observed serum concentration 1 hour after dosing
$C_{t\ day}$	Observed serum concentration t 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)
Casirivimab	Casirivimab (genetical recombination)
C_{max}	Maximum serum concentration
COVID-19	Coronavirus disease caused by SARS-CoV-2 infection
EC_{99}	99% effective concentration
FDA	Food and Drug Administration
IgG	Immunoglobulin G
Imdevimab	Imdevimab (Genetical Recombination)
IV	Intravenous
MedDRA	Medical dictionary for regulatory activities
mFAS	Modified full analysis set
PCR	Polymerase chain reaction
PFU	Plaque-forming units
Pharmaceuticals and Medical Devices Act	Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of August 10, 1960)
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
RBD	Receptor binding domain
RNA	Ribonucleic acid
Ronapreve for Intravenous Infusion Set 300 and 1332	Ronapreve for Intravenous Infusion Set 300, Ronapreve for Intravenous Infusion Set 1332
RT-PCR	Reverse transcription PCR
SARS-CoV	SARS-associated coronavirus
SC	Subcutaneous
S-protein	Spike protein
Study COV-20145	Study R10933-10987-COV-20145
Study COV-2069	Study R10933-10987-COV-2069
$t_{1/2}$	Estimate of the terminal elimination half-life
The product	Ronapreve for Intravenous Infusion Set 300, Ronapreve for Intravenous Infusion Set 1332
t_{max}	Time to maximum concentration
US CDC	Centers for disease control and prevention
WHO	World health organization