PACK INSERT FOR MALAYSIA

RONAPREVE®

SOLUTION FOR INJECTION / INFUSION

Casirivimab and Imdevimab

DISCLAIMER: THIS PRODUCT IS APPROVED UNDER MALAYSIAN CONDITIONAL REGISTRATION FOR PHARMACEUTICAL PRODUCTS DURING DISASTER GUIDELINE. THE ADMINISTRATION OF THE PRODUCT IS PURELY BASED ON INDIVIDUAL'S PREFERENCE.

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions.

This product information will be updated on a regular basis as further data and safety reports become available.

1. NAME OF THE MEDICINAL PRODUCT

Ronapreve solution for injection or infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Co-packaged 300 mg single-use vials

Each casirivimab vial contains 300 mg of casirivimab per 2.5 mL (120 mg/mL).

Each imdevimab vial contains 300 mg imdevimab per 2.5 mL (120 mg/mL).

Co-packaged 1 332 mg multidose vials

Each casirivimab multidose vial contains 1 332 mg of casirivimab per 11.1 mL (120 mg/mL).

Each imdevimab multidose vial contains 1 332 mg imdevimab per 11.1 mL (120 mg/mL).

Casirivimab and imdevimab are two IgG1 recombinant human monoclonal antibodies produced by recombinant DNA technology in Chinese hamster ovary cells.

Excipient(s) with known effect

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion.

Clear to slightly opalescent and colourless to pale yellow solution with a pH of 6.0.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment

Ronapreve is indicated for the treatment of COVID-19 in adults and adolescents aged 12 years and older and weighing at least 40 kg who do not require supplemental oxygen for COVID-19 and who are at increased risk of progressing to severe COVID-19.

Prevention

Ronapreve is indicated for the prevention of COVID-19 in adults and adolescents aged 12 years and older and weighing at least 40 kg who have been exposed or at high risk of exposure to SARS-CoV-2 AND who either

• have a medical condition making them unlikely to respond to or be protected by vaccination, or

• are not vaccinated against COVID-19.

Ronapreve is not intended to be used as a substitute for vaccination against COVID-19.

The use of Ronapreve should take into account information on the activity of Ronapreve against viral variants of concern. See sections 4.4 and 5.1.

The decision has been made on the basis of interim efficacy and safety data. Continued approval depends on the evidence of longer term efficacy and safety from ongoing clinical trials and post-market assessment.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Administration should be under conditions where management of severe hypersensitivity reactions, such as anaphylaxis, is possible. Individuals should be monitored after administration according to local medical practice.

Posology

Treatment

The dosage in adult patients and in adolescent patients 12 years of age and older weighing at least 40 kg is 600 mg of casirivimab and 600 mg of imdevimab administered as a single intravenous infusion or by subcutaneous injection (see Table 1). See sections 4.4 and 5.1.

Casirivimab with imdevimab should be given within 7 days of the onset of symptoms of COVID-19.

Prevention

Post-exposure prophylaxis

The dosage in adult patients and in adolescent patients 12 years of age and older weighing at least 40 kg is 600 mg of casirivimab and 600 mg of imdevimab administered as a single intravenous infusion or by subcutaneous injection (see Tables 1 and 2).

Casirivimab with imdevimab should be given as soon as possible after contact with a case of COVID-19.

Pre-exposure prophylaxis

The initial dose in adult patients and in adolescent patients 12 years of age and older weighing at least 40 kg is 600 mg of casirivimab and 600 mg of imdevimab administered as a single intravenous infusion or by subcutaneous injection (see Tables 1 and 2). Subsequent doses of 300 mg of casirivimab and 300 mg of imdevimab administered as a single intravenous infusion or by subcutaneous injection may be given every 4 weeks until prophylaxis is no longer required. There are no data on repeat dosing beyond 24 weeks (6 doses).

Missed dose

In case of repeated dosing for pre-exposure prophylaxis, if a dose of Ronapreve is missed it should be administered as soon as possible. Thereafter, the schedule of administration should be adjusted to maintain the appropriate interval between doses.

Special populations

Elderly

No dosage adjustment is required (see section 5.2).

Renal impairment

No dosage adjustment is required (see section 5.2).

Hepatic impairment

No dosage adjustment is required (see section 5.2).

Paediatric population

The safety and efficacy of casirivimab and imdevimab in children < 12 years of age has not yet been established. No data are available.

Method of administration

Ronapreve is for intravenous or subcutaneous use only.

Intravenous Infusion

For detailed instructions on the preparation and administration of Ronapreve, see section 6.6.

Table 1: Recommended dilution instructions for Ronapreve (casirivimab and imdevimab) for intravenous infusion

Indication	**Ronapreve Dose**	**Total Volume for 1 Dose**	**Volume to be withdrawn from each respective vial and injected into a single prefilled 0.9% sodium chloride or 5% dextrose infusion bag of 50-250 mL for co-administration**
Treatment, Post-exposure prophylaxis (single dose), Pre-exposure prophylaxis (initial dose)	600 mg casirivimab and 600 mg imdevimab	10 mL	2.5 mL from two 300 mg single-use vials of casirivimab 2.5 mL from two 300 mg single-use vials of imdevimab
			5 mL from one 1 332 mg multidose vial of casirivimab 5 mL from one 1 332 mg multidose vial of imdevimab
Pre-exposure prophylaxis (repeat dose)	300 mg casirivimab and 300 mg imdevimab	5 mL	2.5 mL from one 300 mg single-use vial of casirivimab 2.5 mL from one 300 mg single-use vial of imdevimab
			2.5 mL from one 1 332 mg multidose vial of casirivimab 2.5 mL from one 1 332 mg multidose vial of imdevimab

The infusion should be administered over 20-30 minutes. The rate of infusion may be slowed, interrupted or discontinued if the patient develops any signs of infusion-associated events or other adverse reactions (see section 4.4).

Subcutaneous injection

For detailed instructions on the preparation and administration of Ronapreve, see section 6.6.

Subcutaneous injections of casirivimab and imdevimab should be made consecutively at separate body sites (into upper thighs, upper outer arms or abdomen, avoiding 5 cm around the navel and the waistline).

Table 2: Preparation of Ronapreve (casirivimab and imdevimab) for subcutaneous injection

Indication	**Ronapreve Dose**	**Total Volume for 1 Dose**	**Volume to be withdrawn from each respective vial to prepare 4 syringes**
Treatment, Post-exposure prophylaxis (single dose), Pre-exposure prophylaxis (initial dose)	600 mg casirivimab and 600 mg imdevimab	10 mL	2.5 mL from two 300 mg single-use vials of casirivimab 2.5 mL from two 300 mg single-use vials of imdevimab
			2.5 mL (2x) from one 1 332 mg multidose vial of casirivimab 2.5 mL (2x) from one 1 332 mg multidose vial of imdevimab
Pre-exposure prophylaxis (repeat dose)	300 mg casirivimab and 300 mg imdevimab	5 mL	2.5 mL from one 300 mg single-use vial of casirivimab 2.5 mL from one 300 mg single-use vial of imdevimab
			2.5 mL from one 1 332 mg multidose vial of casirivimab 2.5 mL from one 1 332 mg multidose vial of imdevimab

4.3 CONTRAINDICATIONS

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

Subsequent doses of Ronapreve should not be given to those who have experienced severe allergic reactions (e.g. anaphylaxis, generalized urticarial) to the first dose.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Traceability

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

Activity against SARS-CoV-2 variants

Decisions regarding the use of Ronapreve for treatment or prophylaxis should take into consideration what is known about the characteristics of the circulating SARS-CoV-2 viruses including regional or geographical differences and available information on Ronapreve susceptibility patterns. See section 5.1.

When molecular testing or sequencing data is available, it should be considered when selecting antiviral therapy to rule out SARS-CoV-2 variants that are shown to have reduced susceptibility to Ronapreve.

Subcutaneous administration for treatment of COVID-19

The clinical efficacy of Ronapreve when administered by the subcutaneous route for treatment of COVID-19 has not been evaluated in clinical trials (see section 5.1). The pharmacokinetics of casirivimab and imdevimab in the first 48 hours after subcutaneous administration of 600 mg of each monoclonal antibody indicate lower serum exposures compared to intravenous administration of the same dose. It is unknown whether differences in initial systemic exposure result in differences in clinical efficacy. It is recommended that the subcutaneous route of administration is used only if intravenous administration is not feasible and would lead to a delay in treatment.

Hypersensitivity Reactions including Anaphylaxis

Hypersensitivity reactions, including anaphylaxis, have been reported with administration of casirivimab and imdevimab (see section 4.8). If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related reactions

Infusion-related reactions (IRRs) have been observed with intravenous administration of casirivimab and imdevimab.

IRRs observed in clinical studies were mostly moderate in severity and were typically observed during or within 24 hours of infusion. The frequently reported signs and symptoms for these reactions included nausea, chills, dizziness (or syncope), rash, urticaria and flushing. However, infusion-related reactions may present as severe or life threatening events and may include other signs and symptoms.

If an IRR occurs, the infusion may be interrupted, slowed or stopped.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No formal drug-drug interaction studies have been performed. Casirivimab and imdevimab are monoclonal antibodies, which are not renally excreted or metabolised by cytochrome P450 enzymes; therefore, interactions with concomitant medicinal products that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

COVID-19 Vaccines

Casirivimab and imdevimab bind to epitopes on spike protein used as immunogen in all COVID-19 vaccines, therefore it is possible that Ronapreve may interfere with the development of effective immune responses to COVID-19 vaccines. Based on the serum half-lives of casirivimab and imdevimab and the risk of reinfection, it is recommended that vaccines against COVID-19 should not be administered for at least 90 days after a dose of Ronapreve.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

There are no or limited amount of data from the use of casirivimab and imdevimab in pregnant women. Animal studies have not been performed with respect to reproductive toxicity. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placenta. It is unknown whether the potential transfer of casirivimab and imdevimab provides any treatment benefit or risk to the developing foetus. However, as casirivimab and imdevimab directly target the spike protein of SARS-CoV-2 and in view of lack of cross reactivity with reproductive or foetal tissues in the tissue cross reactivity studies, negative effects on developing foetus are not expected. Ronapreve should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the foetus considering all associated health factors. If a woman becomes pregnant while taking this medicine, the individual should be informed that any potential risk to the foetus is unknown.

Breast-feeding

It is unknown whether casirivimab and imdevimab are excreted in human milk, but maternal IgG is known to be transferred to milk during the first days after birth. As casirivimab and imdevimab directly target the spike protein of SARS-CoV-2 and in view of low systemic absorption after oral ingestion of antibodies, administration of Ronapreve whilst breast-feeding can be considered when clinically indicated.

Fertility

No fertility studies have been performed.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 UNDESIRABLE EFFECTS

Summary of the safety profile

Overall, 7 116 subjects (4 666 via intravenous administration and 2 450 via subcutaneous administration) have been treated with casirivimab and imdevimab in clinical trials.

The most frequently reported adverse drug reactions are hypersensitivity reactions, which include infusion related reactions (IRRs) and injection site reactions (ISRs).

Tabulated summary of adverse reactions

The adverse reactions in Table 3 are listed below by system organ class and frequency. Frequencies are defined as Very common (≥ 1/10), (Common (≥ 1/100 to 1/10), Uncommon (≥ 1/1 000 to < 1/100), Rare (≥ 1/10 000 to 1/1 000), Very rare (< 1/10 000).

Table 3: Tabulated list of adverse reactions identified from Clinical Trials:

System Organ Class	Adverse Reaction	Frequency Category
Intravenous administration		
Immune system disorders	Anaphylaxis	Rare
Nervous system disorders	Dizziness*	Uncommon
Vascular disorders	Flushing*	Rare
Gastrointestinal disorders	Nausea*	Uncommon
Skin and subcutaneous tissue disorders	Rash*	Uncommon
	Urticaria*	Rare
General disorders and administration site conditions	Chills*	Uncommon
Injury, poisoning and procedural complications	Infusion related reactions	Uncommon
Subcutaneous administration		
Blood and lymphatic system disorders	Lymphadenopathy	Uncommon
Nervous system disorders	Dizziness	Uncommon
Skin and subcutaneous tissue disorders	Pruritus[1]*	Rare

General disorders and administration site conditions	Injection site reactions[1]	Common

[1] ISRs include erythema, pruritus, ecchymosis, oedema, pain, tenderness and urticaria
* In some cases, symptoms of IRRs and ISRs have been reported as individual ADRs

Paediatric Population

Intravenous administration

No data are available for paediatric patients <18 years old.

Subcutaneous administration

In study COV-2069, 66 adolescents ⩾ 12 and < 18 years old received treatment with casirivimab and imdevimab. The safety profile observed was similar to that in adult patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 OVERDOSE

Doses up to 4 000 mg each of casirivimab and imdevimab (approximately 7-times the recommended dose) have been administered in clinical trials. The safety profile for 8000 mg intravenous was not substantially different to that for the recommended dose.

There is no known specific antidote for casirivimab and imdevimab overdose. Treatment of overdose should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Casirivimab:

Pharmacotherapeutic group: Not yet assigned. ATC code: Not yet assigned.

Imdevimab:

Pharmacotherapeutic group: Not yet assigned. ATC code: Not yet assigned.

Mechanism of Action

Casirivimab (IgG1κ) and imdevimab (IgG1λ) are two recombinant human monoclonal antibodies which are unmodified in the Fc regions. Casirivimab and imdevimab bind to non-overlapping epitopes of the spike protein receptor binding domain (RBD) of SARS-CoV-2. This prevents RBD binding to the human ACE2 receptor, so preventing virus entry into cells.

In-vitro antiviral activity

In a SARS-CoV-2 virus neutralisation assay in Vero E6 cells, casirivimab, imdevimab, and casirivimab and imdevimab together neutralised SARS-CoV-2 (USA-WA1/2020 isolate) with EC50 values of 37.4 pM (0.006 µg/mL), 42.1 pM (0.006 µg/mL), and 31.0 pM (0.005 µg/mL) respectively.

Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to casirivimab and imdevimab administered together.

The neutralising activity of casirivimab, imdevimab and casirivimab and imdevimab together was assessed against S protein variants, including known Variants of Concern/Interest, variants identified in in vitro escape studies, and variants from publicly available SARS-CoV-2 genome data obtained from the Global Initiative on Sharing All Influenza Data (GISAID). Casirivimab and imdevimab neutralising activity against the Variants of Concern/Interest are shown in Table 4.

Table 4: Pseudotyped virus-like particle neutralisation data for full sequence or key SARS-CoV-2 S-protein variant substitutions from variants of interest/concern* with casirivimab and imdevimab alone or together

Lineage with Spike Protein Substitutions	Key Substitutions Tested	Reduced Susceptibility to Casirivimab and Imdevimab Together	Reduced Susceptibility to Casirivimab Alone	Reduced Susceptibility to Imdevimab Alone
B.1.1.7 (UK origin/Alpha)	Full S protein[a]	no change[e]	no change[e]	no change[e]
B.1.351 (South Africa origin/Beta)	Full S protein[b]	no change[e]	45-fold	no change[e]
P.1 (Brazil origin/Gamma)	Full S protein[c]	no change[e]	418-fold	no change[e]
B.1.427/B.1.429 (California origin/Epsilon)	L452R	no change[e]	no change[e]	no change[e]
B.1.526 (New York origin/Iota)[f]	E484K	no change[e]	25-fold	no change[e]
B.1.617.1/B.1.617.3 (India origin/Kappa)	L452R+E484Q	no change[e]	7-fold	no change[e]
B.1.617.2 / AY.3 (India origin/Delta)	L452R+T478K	no change[e]	no change[e]	no change[e]
AY.1/AY.2[g] (India origin/Delta [+K417N])	K417N+L452R+ T478K[d]	no change[e]	9-fold	no change[e]
B.1.621/B.1.621.1	R346K, E484K,	no change[e]	23-fold	no change[e]

(Colombia origin/Mu)	N501Y			
C.37 (Peru origin/Lambda)	L452Q+F490S	no change[e]	no change[e]	no change[e]
B.1.1.529/BA.1 (Omicron)	Full S protein[h]	>1013-fold	>1732-fold	>754-fold

[a] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: del69-70, del145, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H.

[b] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: D80Y, D215Y, del241-243, K417N, E484K, N501Y, D614G, A701V.

[c] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I,
V1176F

[d] For AY.1: Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: (T19R, G142D, E156G, F157-, F158-, K417N, L452R, T478K, D614G, P681R, D950N).

[e] No change: $\leqslant$ 5-fold reduction in susceptibility.

[f] Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

[g] Commonly known as "Delta plus".

[h] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: A67V, del69-70, T95I, G142D/del143-145, del211/L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F.

*Variants of interest/concern as defined by the Centers for Disease Control and Prevention (CDC, 2021) {https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html}

See Table 5 for a comprehensive list of authentic SARS-CoV-2 Variants of Concern/Interest assessed for susceptibility to casirivimab and imdevimab alone and together.

Table 5: Neutralisation data for authentic SARS-CoV-2 variants of Concern/Interest with casirivimab and imdevimab alone or together

Lineage with Spike Protein Substitution	Reduced Susceptibility to Casirivimab and Imdevimab Together	Reduced Susceptibility to Casirivimab Alone	Reduced Susceptibility to Imdevimab Alone
B.1.1.7 (UK origin/alpha)	no change[a]	no change[a]	no change[a]
B.1.351 (South Africa origin/beta)	no change[a]	5-fold	no change[a]
P.1 (Brazil origin/Gamma)	no change[a]	371-fold	no change[a]
B.1.617.1 (India origin/Kappa)	no change[a]	6-fold	no change[a]
B.1.617.2 (India origin/Delta)	no change[a]	no change[a]	no change[a]

[a] No change: $\leqslant$ 5-fold reduction in susceptibility.

Clinical efficacy

Treatment of COVID-19

COV-2067 was a randomised, double-blinded, placebo-controlled clinical trial evaluating casirivimab and imdevimab for the treatment of subjects with COVID-19 (symptomatic with SARS-CoV-2 detected by quantitative reverse transcription polymerase chain reaction [RT-qPCR]) who did not require supplemental oxygen.

In Phase 3 Cohort 1 of this trial, subjects not previously vaccinated against SARS-CoV-2 were randomised within 7 days of symptom onset to a single intravenous infusion of 600 mg of casirivimab and 600 mg of imdevimab (n = 1 347), 1 200 mg of casirivimab and 1 200 mg of imdevimab (n = 2 036) or placebo (n = 2 009).

Subjects in Phase 3 Cohort 1 had at least one protocol-listed risk factor for developing severe COVID-19 (these included age > 50 years, obesity defined as BMI $\geqslant$ 30 kg/m^2, cardiovascular disease including hypertension, chronic lung disease including asthma, type 1 and 2 diabetes mellitus, chronic kidney disease including those on dialysis, chronic liver disease, pregnancy and immunosuppressed). The median age was 50 years (with 13.1% of subjects aged 65 years or older) and 51.4% of the subjects were female. Baseline demographics and disease characteristics were well balanced across the casirivimab and imdevimab and placebo treatment groups.

The primary endpoint was the proportion of subjects with $\geqslant$ 1 COVID-19-related hospitalisation or all-cause death through Day 29.

Table 6: Summary of primary endpoint phase 3 results from study COV-2067

	1,200 mg IV	**Placebo**	**2,400 mg IV**	**Placebo**
	n = 1 192	n = 1 193	n = 1 812	n = 1 790
Patients in the mFAS ≥1 COVID-19-related hospitalization or death through day 29				
Risk reduction	72.5% (p < 0.0001)		70.9% (p < 0.0001)	
Number of patients with events	11 (0.9%)	40 (3.4%)	23 (1.3%)	78 (4.4%)

mFAS: modified full analysis set included those subjects with a positive SARS-CoV-2 RT-qPCR result from nasopharyngeal (NP) swab at randomization, and with at least one risk factor for severe COVID-19.

The median time to symptom resolution, as recorded in a trial-specific daily symptom diary, was reduced from 13 days with placebo to 10 days with both doses of casirivimab and imdevimab (p<0.0001).

Prevention of COVID-19

COV-2069 was a randomised, double-blind, placebo-controlled clinical trial that compared 600 mg casirivimab and 600 mg imdevimab given subcutaneously to placebo for prevention of

COVID-19 in asymptomatic household contacts of symptomatic individuals infected with SARS-CoV-2 (index cases). Subjects had not been previously vaccinated against SARS-CoV-2.

Subjects were randomised 1:1 to casirivimab and imdevimab or placebo within 96 hours of collection of the first index case sample that gave a positive result (RT-qPCR) for SARS-CoV-2.

Randomised subjects with a negative SARS-CoV-2 RT-qPCR test result at baseline were assigned to Cohort A and those with a positive SARS-CoV-2 RT-qPCR test result were assigned to Cohort B.

Cohort A

The primary analysis population included subjects who were SARS-CoV-2 RT-qPCR negative and seronegative at baseline. Subjects who were seropositive or who had undetermined/missing baseline serology were excluded from the primary efficacy analysis.

For the primary analysis population at baseline, the median age was 44 years (with 9% of subjects ages 65 years or older) and 54% of the subjects were female. The baseline demographics and disease characteristics were well balanced across the casirivimab and imdevimab and placebo treatment groups.

The primary endpoint was the proportion of subjects who developed symptomatic RT-qPCR-confirmed COVID-19 through Day 29. There was a statistically significant 81% risk reduction in the development of COVID-19 with casirivimab and imdevimab treatment versus placebo. In a sensitivity analysis that included all RT-qPCR negative subjects at baseline, regardless of baseline serological status, there was a statistically significant 82% risk reduction in development of COVID-19 with casirivimab and imdevimab treatment compared to placebo.

Table 7: Primary analysis of study COV-2069, Cohort A

	casirivimab and imdevimab (single 1 200 mg dose)	**Placebo**
Primary Analysis Population: Seronegative at Baseline	n = 753	n = 752
Risk of COVID-19		
Through Day 29 (primary endpoint)		
Unadjusted risk reduction (Adjusted Odds ratio, p-Value)[1]	81% (0.17; p < 0.0001)	
Number of individuals with events	11 (1.5%)	59 (7.8%)

[1] The confidence interval (CI) with p-value is based on the odds ratio (casirivimab and imdevimab group vs placebo group) using logistic regression model with the fixed categorical effects of treatment group, age group (age in years:>=12 to<50 and >=50), and region (US vs ex-US).

Cohort B

The primary analysis population included asymptomatic subjects who were SARS-CoV-2 RT-qPCR positive and seronegative at baseline.

For the primary analysis population at baseline, the median age was 40 years (with 11% of subjects ages 65 years or older) and 55% of the subjects were female. The baseline demographics and disease characteristics were well balanced across the casirivimab and imdevimab and placebo treatment groups.

The primary efficacy endpoint was the proportion of subjects who developed RT-qPCR-confirmed COVID-19 through Day 29. There was a 31% risk reduction in the development of COVID-19 with casirivimab and imdevimab treatment vs. placebo. In a sensitivity analysis that included all RT-qPCR positive subjects at baseline, regardless of baseline serological status, there was a 35% risk reduction in RT-qPCR-confirmed COVID-19 with casirivimab and imdevimab treatment compared to placebo.

Table 8: Primary analysis study COV-2069, Cohort B

	casirivimab and imdevimab (single 1 200 mg dose)	**Placebo**
Primary Analysis Population: Seronegative at Baseline	n = 100	n = 104
Risk of COVID-19		
Overall risk reduction through Day 29 (primary endpoint)		
Unadjusted risk reduction (Adjusted Odds ratio, p-Value)[1]	31% (0.54; p = 0.0380)	
Number of individuals with events	29 (29%)	44 (42.3%)

[1] The confidence interval (CI) with p-value is based on the odds ratio (casirivimab and imdevimab group vs placebo group) using logistic regression model with the fixed categorical effects of treatment group, age group (age in years:>=12 to<50 and >=50), and region (US vs ex-US).

5.2 PHARMACOKINETIC PROPERTIES

Both casirivimab and imdevimab exhibited linear and dose-proportional PK across the intravenous (150 to 4 000 mg of each monoclonal antibody) and subcutaneous (300 and 600 mg of each monoclonal antibody) dose ranges evaluated in clinical studies.

Mean peak concentration (C_{max}), area under the curve from 0 to 28 days (AUC_{0-28}) and concentration at 28 days after dosing (C_{28}) for casirivimab and imdevimab were comparable after either a single 1 200 mg (600 mg of each monoclonal antibody) intravenous dose (182.7 mg/L, 1 754.9 mg.day/L, 37.9 mg/L, respectively for casirivimab, and 181.7 mg/L, 1 600.8 mg.day/L, 27.3 mg/L, respectively for imdevimab), or a single 1 200 mg (600 mg of each monoclonal antibody) subcutaneous dose (52.5 mg/L, 1 121.7 mg.day/L, 30.5 mg/L, respectively for casirivimab, and 49.2 mg/L, 1 016.9 mg.day/L, 25.9 mg/L, respectively for imdevimab).

For the pre-exposure prophylaxis of intravenous and subcutaneous regimens at monthly administration of 300 mg each for casirivimab and imdevimab following an initial (loading) dose of 600 mg each for casirivimab and imdevimab, the median predicted casirivimab and imdevimab trough serum concentrations at steady state are similar to observed mean day 29 concentrations in serum for a single subcutaneous dose of casirivimab and imdevimab 1 200 mg (600 mg of casirivimab and 600 mg of imdevimab).

Absorption

Casirivimab and imdevimab administered as a single intravenous dose of 600 mg for each monoclonal antibody results in peak serum concentrations at the end of infusion. The median (range) time to reach maximum serum concentration of casirivimab and imdevimab (Tmax) estimates following a single subcutaneous dose of 600 mg of each monoclonal antibody are 6.7 (range 3.4 - 13.6) days and 6.6 (range 3.4 - 13.6) days for casirivimab and imdevimab, respectively. After a single subcutaneous dose of 600 mg of each monoclonal antibody, casirivimab and imdevimab had an estimated bioavailability of 71.8% and 71.7%, respectively.

Distribution

The total volume of distribution estimated via population pharmacokinetic analysis is 7.161 L and 7.425 L for casirivimab and imdevimab, respectively.

Biotransformation

As human monoclonal IgG1 antibodies, casirivimab and imdevimab are expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Elimination

The mean (5th, 95th percentile) serum elimination half-lives after a 600 mg dose of each monoclonal antibody were 29.8 (16.4, 43.1) days and 26.2 (16.9, 35.6) days, respectively, for casirivimab and imdevimab.

Paediatric population

For adolescent patients with COVID-19 (12 years of age and older and weighing at least 40 kg in COV-2067) receiving a single 1200 mg IV dose, the mean ± SD concentration at the end of infusion and at 28 days after dosing was 172 ± 96.9 mg/L and 54.3 ± 17.7 mg/L for casirivimab and 183 ± 101 mg/L and 45.3 ± 13.1 mg/L for imdevimab.

For adolescents not infected with SARS-CoV-2 (12 years of age and older and weighing at least 40 kg in COV-2069) receiving a single 1200 mg SC dose, the mean ± SD concentration 28 days after dosing was 44.9 ± 14.7 mg/L for casirivimab and 36.5 ± 13.2 mg/L for imdevimab.

The pharmacokinetics of casirivimab and imdevimab in children < 12 years of age has not yet been established.

Elderly

In the population PK analysis, age (18 years to 96 years) was not identified as a significant covariate on PK of casirivimab and imdevimab.

Renal impairment

Casirivimab and imdevimab are not expected to undergo significant renal elimination due to their molecular weight (> 69 kDa).

Hepatic impairment

Casirivimab and imdevimab are not expected to undergo significant hepatic elimination.

5.3 PRECLINICAL SAFETY DATA

Carcinogenicity, genotoxicity, and reproductive toxicology studies have not been conducted with casirivimab and imdevimab. Antibodies such as casirivimab and imdevimab are not expected to display genotoxic or carcinogenic potential. In tissue cross-reactivity studies with casirivimab and imdevimab using human and monkey adult tissues and human foetal tissues, no binding was detected.

In a toxicology study in cynomolgus monkeys, non-adverse liver findings (minor transient increases in AST and ALT) were observed.

6. PHARMACOLOGICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

L-histidine
L-histidine monohydrochloride monohydrate
polysorbate 80
sucrose
Water for Injections

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

Unopened vial: 12 months

Co-packaged 300 mg single-use vials

After initial puncture: the medicinal product should be used immediately, any remaining product should be discarded.

Co-packaged 1 332 mg multidose vials

After initial puncture: If not used immediately, the product in the vial can be stored for 16 hours at room temperature up to 25 °C or for no more than 48 hours in a refrigerator (2 °C to 8 °C). Beyond these times and conditions, in-use storage is the responsibility of the user.

Diluted Solution for Intravenous Administration

Solution in vial requires dilution prior to administration. The prepared infusion solution is intended to be used immediately. The chemical and physical in-use stability data has been demonstrated for 20 hours at room temperature (up to 25 °C) and 72 hours at 2 °C to 8 °C. From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions. If refrigerated, allow the intravenous infusion bag to equilibrate to room temperature for approximately 30 minutes prior to administration.

Storage of Syringes for Subcutaneous Administration

The prepared syringes should be administered immediately. The chemical and physical in-use stability data has been demonstrated for 24 hours at room temperature (up to 25 °C) and 72 hours at 2 °C to 8 °C. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless preparation has taken place in controlled and validated aseptic conditions. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 10-15 minutes prior to administration.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2 °C - 8 °C).
Do not freeze.
Do not shake.
Keep the vials in the original carton in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 NATURE AND CONTENTS OF CONTAINER

Ronapreve is provided in 6 mL or 20 mL clear Type 1 glass vials.

Ronapreve 300 mg + 300 mg solution for injection/infusion, single-use vials

Each carton contains 1 vial of each antibody:

Pack of two 6 mL clear Type I glass vials with butyl rubber stopper containing one vial of 2.5 mL solution of 300 mg of casirivimab and one vial of 2.5 mL solution of 300 mg of imdevimab.

Ronapreve 1 332 mg + 1 332 mg solution for injection/infusion, multidose vials

Each carton contains 1 vial of each antibody:

Pack of two 20 mL clear Type I glass vials with butyl rubber stopper containing one vial of 11.1 mL solution of 1 332 mg of casirivimab and one vial of 11.1 mL solution of 1 332 mg of imdevimab.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Preparation of Ronapreve for Intravenous Infusion

Ronapreve should be prepared by a healthcare professional using aseptic technique:

1. Remove the casirivimab and imdevimab vials from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation.
   - Do not expose to direct heat.

- Do not shake the vials.

2. Inspect casirivimab and imdevimab vials visually for particulate matter and discolouration prior to administration. Should either be observed, the vial must be discarded and replaced with a new vial.
   - The solution for each vial should be clear to slightly opalescent, colourless to pale yellow.
3. Obtain a prefilled intravenous infusion bag [made from polyvinyl chloride (PVC) or polyolefin (PO)] containing either 50 mL, 100 mL, 150 mL, or 250 mL of 0.9% Sodium Chloride Injection or 5% Dextrose Injection.
4. Using a sterile syringe and needle, withdraw the appropriate volume of casirivimab and imdevimab from each respective vial and inject into a prefilled infusion bag containing 0.9% sodium chloride injection or 5% dextrose injection (see section 4.2, Table 1).
5. Gently mix infusion bag by inversion. Do not shake.
6. Ronapreve is preservative-free and therefore, the diluted infusion solution should be administered immediately.

<u>Administration of Ronapreve by Intravenous Infusion</u>

- Gather the recommended materials for infusion:
  - Polyvinyl chloride (PVC), polyethylene (PE)-lined PVC, or polyurethane (PU) infusion set
  - In-line or add-on 0.2 µm to 5 µm polyethersulfone, polysulfone, or polyamide filter for intravenous administration.
- Attach the infusion set to the intravenous bag.
- Prime the infusion set.
- Administer the entire infusion solution in the bag via pump or gravity through an intravenous line containing a sterile, in-line or add-on 0.2 µm to 5 µm polyethersulfone, polysulfone, or polyamide filter for intravenous administration.
- The prepared infusion solution should not be administered simultaneously with any other medicinal product. The compatibility of casirivimab and imdevimab injection with intravenous solutions and medicinal products other than 0.9% Sodium Chloride Injection or 5% Dextrose Injection is not known.
- After infusion is complete, flush the tubing with 0.9% Sodium Chloride Injection or 5% Dextrose Injection to ensure delivery of the required dose.
- Individuals should be monitored post intravenous infusion according to local medical practice.

<u>Preparation of Ronapreve for Subcutaneous Injection</u>

Remove the casirivimab and imdevimab vial(s) from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation.
Do not expose to direct heat.
Do not shake the vials.

Inspect casirivimab and imdevimab vial(s) visually for particulate matter and discolouration prior to administration. Should either be observed, the vial must be discarded and replaced with a new vial. The solution for each vial should be clear to slightly opalescent, colourless to pale yellow.

1. Ronapreve should be prepared using the appropriate number of syringes (see section 4.2, Table 2). Obtain 3 mL or 5 mL polypropylene syringes with luer connection and 21-gauge transfer needles.

2. Using a sterile needle and syringe, withdraw the appropriate volume of casirivimab and imdevimab from each respective vial into each syringe (see section 4.2, Table 2) for a total of 4 syringes for the 1 200 mg combined total dose and a total of 2 syringes for the 600 mg combined total dose. Store any remaining product as directed in Section 6.3.
3. Replace the 21-gauge transfer needle with a 25-gauge or 27-gauge needle for subcutaneous injection.

Administration of Ronapreve by Subcutaneous Injection

- For the administration of Ronapreve 1 200 mg dose (600 mg of casirivimab and 600 mg of imdevimab), gather 4 syringes (see section 4.2, Table 2) and prepare for subcutaneous injections.
- For the administration of Ronapreve 600 mg dose (300 mg of casirivimab and 300 mg of imdevimab), gather 2 syringes (see section 4.2, Table 2) and prepare for subcutaneous injections.
- Due to the volume, administer the subcutaneous injections consecutively, at separate body sites (into upper thighs, upper outer arms, or abdomen, avoiding 5 cm around the navel and the waistline).

Disposal

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

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused.
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).

Medicine: keep out of reach of children

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Drug Product Manufacturing Sites:
Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland
by Genentech, 4625 NE Brookwood Pkwy Hillsboro, OR 97124 USA.

Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland
by Catalent Indiana, LLC, 1300 S. Patterson Drive Bloomington, IN 47403 USA.

Batch Release Site:
F. Hoffmann-La Roche Ltd Wurmisweg 4303 Kaiseraugst Switzerland.