ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼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 adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Ronapreve 300 mg + 300 mg solution for injection/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).

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

Ronapreve is indicated for:

- Treatment of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.
- Treatment of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg and receiving supplemental oxygen, who have a negative SARS-CoV-2 antibody test result.
- Prevention of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg.

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.

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 patients who do not require supplemental oxygen is 600 mg of casirivimab and 600 mg of imdevimab administered as a single intravenous infusion or by subcutaneous injection (see Tables 1 and 3). See sections 4.4 and 5.1. For these patients only, casirivimab with imdevimab should be given within 7 days of the onset of symptoms of COVID-19.

The dosage in patients who require supplemental oxygen (including low flow and high flow oxygen devices, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)) is 4 000 mg of casirivimab and 4 000 mg of imdevimab administered as a single intravenous infusion (see Table 2 of Ronapreve SmPC 120 mg/mL + 120 mg/mL). See section 5.1.

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 3).

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 3). 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 and intravenous infusion instructions for 600 mg casirivimab and 600 mg imdevimab or 300 mg casirivimab and 300 mg imdevimab

Indication	**Size of prefilled 9 mg/mL (0.9%) sodium chloride or 50 mg/mL (5%) dextrose infusion bag**	**Ronapreve Dose**	**Total Volume for 1 Dose**	**Volume to be withdrawn from each respective vial and injected into a single prefilled 9 mg/mL (0.9%) sodium chloride or 50 mg/mL (5%) dextrose infusion bag of 50-250 mL for co-administration**	**Minimum Infusion Time**
Treatment (patients not on supplemental oxygen), Post-exposure prophylaxis (single dose), Pre-exposure prophylaxis (initial dose)	50 mL, 100 mL, 150 mL	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	20 minutes
	250 mL				30 minutes
Pre-exposure prophylaxis (repeat dose)	50 mL, 100 mL, 150 mL	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	20 minutes
	250 mL				30 minutes

Table 2: Recommended dilution and intravenous infusion instructions for 4 000 mg casirivimab and 4 000 mg imdevimab

Indication	Size of prefilled 9 mg/mL (0.9%) sodium chloride or 50 mg/mL (5%) dextrose infusion bag	Ronapreve Dose	Total Volume for 1 Dose	Volume to be withdrawn from each respective vial and injected into a single prefilled 9 mg/mL (0.9%) sodium chloride or 50 mg/mL (5%) dextrose infusion bag of 50-250 mL for co-administration	Minimum Infusion Time
Treatment (patients on supplemental oxygen)	250 mL*	4 000 mg casirivimab and 4 000 mg imdevimab	66.6 mL	33.3 mL total of casirivimab from the 300 mg single-use vials 33.3 mL total of imdevimab from the 300 mg single-use vials *Also refer to Ronapreve SmPC 120 mg/mL + 120 mg/mL*	60 minutes

*Withdraw and discard 66.6 mL of 9 mg/mL (0.9%) sodium chloride or 50 mg/mL (5%) dextrose from the infusion bag prior to adding casirivimab and imdevimab

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 3: Preparation of 600 mg casirivimab and 600 mg imdevimab or 300 mg casirivimab and 300 mg 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 (patients not on supplemental oxygen), 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
Indication	**Ronapreve Dose**	**Total Volume for 1 Dose**	**Volume to be withdrawn from each respective vial to prepare 2 syringes**
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

4.3 Contraindications

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

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.

Cases of convulsive syncope have been observed following intravenous and subcutaneous administration (see section 4.8). Convulsive syncope should be differentiated from seizures and managed as clinically indicated.

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, pruritus, tachypnoea 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.

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, 8 596 subjects (6 173 via intravenous administration and 2 423 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 4: Tabulated list of adverse reactions identified from clinical trials and post-marketing:

System organ class	Adverse reaction	Frequency category
Intravenous administration		
Immune system disorders	Anaphylaxis	Rare
	Hypersensitivity	Rare
Nervous system disorders	Dizziness* Convulsive syncope	Uncommon Unknown
Vascular disorders	Flushing*	Uncommon
Respiratory, thoracic and mediastinal disorders	Tachypnoea*	Uncommon
Gastrointestinal disorders	Nausea*	Uncommon
Skin and subcutaneous tissue disorders	Pruritus*	Uncommon
	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, urticaria, and convulsive syncope
* In some cases, symptoms of IRRs and ISRs have been reported as individual ADRs

Paediatric population

Intravenous administration
In the RECOVERY study, 4 adolescents ≥ 12 and < 18 years old received treatment with casirivimab and imdevimab. The safety profile observed in this limited population was similar to that in adult patients.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Doses up to 4 000 mg each of casirivimab and imdevimab have been administered in clinical trials. No data are available beyond this 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

Pharmacotherapeutic group: Immune sera and immunoglobulins, antiviral monoclonal antibodies.
ATC code: J06BD07

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 EC_{50} 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 5.

Table 5: Pseudotyped virus-like particle neutralisation data for full sequence or key SARS-CoV-2 S-protein variant substitutions from variants of concern/interest* 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 (Colombia origin/Mu)	R346K, E484K, N501Y	no change[e]	23-fold	no change[e]
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: ≤ 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 concern/interest 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 6 for a comprehensive list of authentic SARS-CoV-2 Variants of Concern/Interest assessed for susceptibility to casirivimab and imdevimab alone and together.

Table 6: 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: ≤ 5-fold reduction in susceptibility.

Clinical efficacy

Treatment of COVID-19

COV-2067

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 and were at increased risk of progression to severe disease.

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 ≥ 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 ≥ 1 COVID-19-related hospitalisation or all-cause death through Day 29.

Table 7: 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 with ≥1 COVID-19-related hospitalisation 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 randomisation, 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).

RECOVERY

RECOVERY is an ongoing multi-centre, randomised, controlled, open-label platform study, evaluating the efficacy and safety of potential treatments in hospitalised subjects with COVID-19. RECOVERY enrolled hospitalised subjects on no oxygen, low or high flow oxygen therapy, non-invasive or invasive ventilation and ECMO. In this trial, 9 785 subjects in the United Kingdom (UK) were randomised to a single IV infusion of 4 000 mg of casirivimab and 4 000 mg of imdevimab plus usual care (n=4 839) or usual standard of care alone (n=4 946; herein after referred to as usual care alone). Subjects could receive between 0 and 4 treatments on top of usual standard of care.

Subjects had clinically suspected or laboratory-confirmed SARS-CoV-2 infection and were enrolled regardless of the respiratory support required. Baseline serology test results were used to define analysis populations.

At baseline, the mean age was 62 years (with 30% of subjects aged 70 years or older, 11 adolescents ≥ 12 and < 18 years old were included) and 63% of the subjects were male. Baseline demographics and disease characteristics were well balanced across the casirivimab and imdevimab, and usual care alone, treatment groups. Subjects were enrolled in the study when the B.1.1.7 (alpha) variant was the dominant variant in the UK. Respiratory support received by subjects included 7% on no supplemental oxygen, 61% on simple oxygen, 26% on non-invasive ventilation, and 6% on invasive ventilation (including 17 subjects on ECMO). In subjects who were seronegative at baseline, 10% were on no supplemental oxygen at baseline, 66% were on simple oxygen, 21% were on non-invasive ventilation, and 2% were on invasive ventilation (including one subject on ECMO). Approximately 94% of all randomised subjects received corticosteroids as part of background standard care.

The primary endpoint was 28-day all-cause mortality in all randomised subjects who were seronegative at baseline. The results are shown in Table 8.

Table 8: Summary of primary endpoint results from study RECOVERY

	4 000 mg of casirivimab and 4 000 mg of imdevimab (intravenously) plus usual care	Usual care alone
	n=1 633	n=1 520
28-Day all-cause mortality in seronegative subjects		
Number of subjects with all-cause mortality (%)	396 (24%)	452 (30%)
Rate Ratio (95% CI)	0.79 (0.69, – 0.91) (p=0.0009)	

In seropositive subjects, the 28-day all-cause mortality was 16% (410/2 636) in the casirivimab+imdevimab arm and 15% (384/2 636) in the usual care alone arm (rate ratio 1.09 [95% CI: 0.94, 1.25]).

In seronegative subjects aged ≥80 years, 28-day all-cause mortality was 54.5% (126/231) and 57.5% (134/233) in the casirivimab+imdevimab and usual care alone arms, respectively (rate ratio 0.97 [95% CI: 0.76, 1.25]). Statistical testing of the secondary endpoint was performed outside of the hierarchy and is, therefore, considered descriptive.

The secondary endpoint of discharge alive from hospital within 28 days was more common in the all-randomised seronegative population treated with casirivimab and imdevimab compared with usual care alone (64% vs. 58%; rate ratio 1.19 [95% CI: 1.09, 1.31]), with a 4-day shorter median duration of hospital stay (13 days vs. 17 days).

Among the all-randomised seronegative population not on invasive mechanical ventilation at baseline, treatment with casirivimab and imdevimab was associated with a lower risk of progressing to the composite endpoint of invasive mechanical ventilation or death (31% vs. 37%; risk ratio 0.83 [95% CI: 0.75, 0.92]).

COV-2066

COV-2066 was a randomised, double-blinded, placebo-controlled clinical trial evaluating casirivimab and imdevimab for the treatment of hospitalised subjects with COVID-19 on low flow oxygen devices (e.g. by face mask or nasal cannula) or no supplemental oxygen. In this phase 2/3 trial, 1 197 subjects had a positive SARS-CoV-2 RT-qPCR result at baseline and were randomised 1:1:1 to a single intravenous infusion of 1 200 mg of casirivimab and 1 200 mg of imdevimab (n=406), 4 000 mg of casirivimab and 4 000 mg of imdevimab (n=398), or placebo (n=393), with all subjects receiving casirivimab and imdevimab, or placebo in addition to the usual standard of care for COVID-19. The overall sample size was smaller than anticipated due to the early study termination following several months of low recruitment rates. Overall, similar effects were observed in patients on no supplemental oxygen or on low flow oxygen devices for casirivimab and imdevimab 2 400 mg, and casirivimab and imdevimab 8 000 mg doses, indicating an absence of a dose effect in this population. These dose groups were combined when compared to the placebo group for the efficacy analysis.

At baseline, the median age was 62 years (with 44% of subjects aged 65 years or older), and 54% of the subjects were male, 43% of the subjects were seronegative, 48% were seropositive and 9% had an unknown serostatus. Baseline respiratory support received by subjects included 44% on no supplemental oxygen and 56% on low flow oxygen devices. Prior to randomisation, approximately 33% of subjects received remdesivir and 50% received systemic corticosteroids as part of background usual care. Baseline demographics and disease characteristics were well balanced across the casirivimab and imdevimab and placebo treatment groups.

The primary virologic efficacy endpoint was time weighted average (TWA) daily change from baseline in viral load (log_{10} copies/mL) through day 7, measured by RT-qPCR in NP swab samples, in subjects who were seronegative and had a positive SARS-CoV-2 RT-qPCR result at baseline. Treatment with casirivimab and imdevimab for the combined doses group resulted in a statistically significant reduction in the LS mean viral load (log_{10} copies/mL) compared to placebo (-0.28 log_{10} copies/mL/day for casirivimab and imdevimab; p=0.0172).

The primary clinical endpoint was the proportion of subjects who died or went on mechanical ventilation in those with a positive SARS-CoV-2 RT-qPCR result.

Treatment with casirivimab and imdevimab for the combined doses group resulted in a reduced proportion of subjects with a high viral load who died or went on mechanical ventilation from day 6 to day 29, but the endpoint did not achieve statistical significance (relative risk reduction [RRR] 25.5% [95% CI: -16.2%, 52.2%]; p=0.2048).

Treatment with casirivimab and imdevimab for the combined doses group resulted in a 47.1% RRR (95% CI: 10.2%, 68.8%) in the proportion of seronegative subjects who died or went on mechanical ventilation from day 6 to day 29.

In a post hoc analysis of all randomized seronegative subjects aged ≥ 80 years, all-cause mortality from day 1 to day 29 was 18.1% (19/105 subjects) and 30.0% (18/60 subjects) in the casirivimab+imdevimab (combined doses) and placebo arms, respectively (risk ratio 0.60 [95% CI: 0.34, 1.06]).

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 9: 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 10: 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 intravenous regimen of 8 000 mg (4 000 mg of each monoclonal antibody) in patients who require oxygen supplementation, the 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 1 046 mg/L, 9280 mg.day/L, 165.2 mg/L, respectively for casirivimab, and 1 132 mg/L, 8789 mg.day/L, 136.2 mg/L, respectively for imdevimab, after a single intravenous dose.

For the pre-exposure prophylaxis 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 results in peak serum concentrations at the end of infusion. The median (range) time to reach maximum serum concentration of casirivimab and imdevimab (T_{max}) 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 was 7.072 L and 7.183 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 (5^{th}, 95^{th} 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. The mean (5^{th}, 95^{th} percentile) clearances were 0.188 (0.11, 0.30) and 0.227 (0.15, 0.35), respectively, for casirivimab and imdevimab.

For patients who require supplemental oxygen, the mean (5^{th}, 95^{th} percentile) serum elimination half-lives after a 4 000 mg dose of each monoclonal antibody were 21.9 (12.4, 36.9) days and 18.8 (11.7, 29.4) days, respectively, for casirivimab and imdevimab. The mean (5^{th}, 95^{th} percentile) clearances were 0.303 (0.156, 0.514) and 0.347 (0.188, 0.566), 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.

The pharmacokinetics of casirivimab and imdevimab in children < 18 years of age who require supplemental oxygen 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. PHARMACEUTICAL 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: 2 years

Co-packaged 300 mg single-use vials

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

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 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.

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 9 mg/mL (0.9%) sodium chloride injection or 50 mg/mL (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 9 mg/mL (0.9%) sodium chloride injection or 50 mg/mL (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.

Administration of Ronapreve by intravenous infusion

- 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 9 mg/mL (0.9%) sodium chloride injection or 50 mg/mL (5%) dextrose injection is not known.
- After infusion is complete, flush the tubing with 9 mg/mL (0.9%) sodium chloride injection or 50 mg/mL (5%) dextrose injection to ensure delivery of the required dose.
- Individuals should be monitored post intravenous infusion according to local medical practice.

Preparation of Ronapreve for subcutaneous injection

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 3). 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 3) 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.
4. This product is preservative-free and therefore, the prepared syringes should be administered immediately. If immediate administration is not possible, store the prepared casirivimab and imdevimab syringes at 2 ºC to 8 ºC for no more than 72 hours and at room temperature up to 25 ºC for no more than 24 hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 10-15 minutes prior to administration.

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 3) 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 3) 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).

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1601/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 November 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼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 adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Ronapreve 120 mg/mL+ 120 mg/mL solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Ronapreve is indicated for:

- Treatment of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.
- Treatment of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg and receiving supplemental oxygen, who have a negative SARS-CoV-2 antibody test result.
- Prevention of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg.

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.

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 patients who do not require supplemental oxygen is 600 mg of casirivimab and 600 mg of imdevimab administered as a single intravenous infusion or by subcutaneous injection (see Tables 1 and 3). See sections 4.4 and 5.1. For these patients only, casirivimab with imdevimab should be given within 7 days of the onset of symptoms of COVID-19.

The dosage in patients who require supplemental oxygen (including low flow and high flow oxygen devices, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)) is 4 000 mg of casirivimab and 4 000 mg of imdevimab administered as a single intravenous infusion (see Table 2 of Ronapreve SmPC 120 mg/mL + 120 mg/mL). See section 5.1.

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 3).

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 3). 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 and intravenous infusion instructions for 600 mg casirivimab and 600 mg imdevimab or 300 mg casirivimab and 300 mg imdevimab

Indication	**Size of prefilled 9 mg/mL (0.9%) sodium chloride or 50 mg/mL (5%) dextrose infusion bag**	**Ronapreve Dose**	**Total Volume for 1 Dose**	**Volume to be withdrawn from each respective vial and injected into a single prefilled 9 mg/mL (0.9%) sodium chloride or 50 mg/mL (5%) dextrose infusion bag of 50-250 mL for co-administration**	**Minimum Infusion Time**
Treatment (patients not on supplemental oxygen), Post-exposure prophylaxis (single dose), Pre-exposure prophylaxis (initial dose)	50 mL, 100 mL, 150 mL	600 mg casirivimab and 600 mg imdevimab	10 mL	5 mL from one 1 332 mg multidose vial of casirivimab 5 mL from one 1 332 mg multidose vial of imdevimab	20 minutes
	250 mL				30 minutes
Pre-exposure prophylaxis (repeat dose)	50 mL, 100 mL, 150 mL	300 mg casirivimab and 300 mg imdevimab	5 mL	2.5 mL from one 1 332 mg multidose vial of casirivimab 2.5 mL from one 1 332 mg multidose vial of imdevimab	20 minutes
	250 mL				30 minutes

Table 2: Recommended dilution and intravenous infusion instructions for 4 000 mg casirivimab and 4 000 mg imdevimab

Indication	Size of prefilled 9 mg/mL (0.9%) sodium chloride or 50 mg/mL (5%) dextrose infusion bag	Ronapreve Dose	Total Volume for 1 Dose	Volume to be withdrawn from each respective vial and injected into a single prefilled 9 mg/mL (0.9%) sodium chloride or 50 mg/mL (5%) dextrose infusion bag of 50-250 mL for co-administration	Minimum Infusion Time
Treatment (patients on supplemental oxygen)	250 mL*	4 000 mg casirivimab and 4 000 mg imdevimab	66.6 mL	11.1 mL from three 1 332 mg multidose vials of casirivimab 11.1 mL from three 1 332 mg multidose vials of imdevimab	60 minutes

*Withdraw and discard 66.6 mL of 9 mg/mL (0.9%) sodium chloride or 50 mg/mL (5%) dextrose from the infusion bag prior to adding casirivimab and imdevimab

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 3: Preparation of 600 mg casirivimab and 600 mg imdevimab or 300 mg casirivimab and 300 mg 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 (patients not on supplemental oxygen), Post-exposure prophylaxis (single dose), Pre-exposure prophylaxis (initial dose)	600 mg casirivimab and 600 mg imdevimab	10 mL	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
Indication	**Ronapreve Dose**	**Total Volume for 1 Dose**	**Volume to be withdrawn from each respective vial to prepare 2 syringes**
Pre-exposure prophylaxis (repeat dose)	300 mg casirivimab and 300 mg imdevimab	5 mL	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.

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.

Cases of convulsive syncope have been observed following intravenous and subcutaneous administration (see section 4.8). Convulsive syncope should be differentiated from seizures and managed as clinically indicated.

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, pruritus, tachypnoea 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.

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, 8 596 subjects (6 173 via intravenous administration and 2 423 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 4 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 4: Tabulated list of adverse reactions identified from clinical trials and post-marketing:

System organ class	Adverse reaction	Frequency category
Intravenous administration		
Immune system disorders	Anaphylaxis	Rare
	Hypersensitivity	Rare
Nervous system disorders	Dizziness* Convulsive syncope	Uncommon Unknown
Vascular disorders	Flushing*	Uncommon
Respiratory, thoracic and mediastinal disorders	Tachypnoea*	Uncommon
Gastrointestinal disorders	Nausea*	Uncommon
Skin and subcutaneous tissue disorders	Pruritus*	Uncommon
	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, urticaria, and convulsive syncope
* In some cases, symptoms of IRRs and ISRs have been reported as individual ADRs

Paediatric population

Intravenous administration
In the RECOVERY study, 4 adolescents ≥ 12 and < 18 years old received treatment with casirivimab and imdevimab. The safety profile observed in this limited population was similar to that in adult patients.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Doses up to 4 000 mg each of casirivimab and imdevimab have been administered in clinical trials. No data are available beyond this 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

Pharmacotherapeutic group: Immune sera and immunoglobulins, antiviral monoclonal antibodies.
ATC code: J06BD07

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 EC_{50} 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 5.

Table 5: Pseudotyped virus-like particle neutralisation data for full sequence or key SARS-CoV-2 S-protein variant substitutions from variants of concern/interest* 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 (Colombia origin/Mu)	R346K, E484K, N501Y	no change[e]	23-fold	no change[e]
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: ≤ 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 concern/interest 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 6 for a comprehensive list of authentic SARS-CoV-2 Variants of Concern/Interest assessed for susceptibility to casirivimab and imdevimab alone and together.

Table 6: 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: ≤ 5-fold reduction in susceptibility.

Clinical efficacy

Treatment of COVID-19

COV-2067

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 and were at increased risk of progression to severe disease.

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 ≥ 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 ≥ 1 COVID-19-related hospitalisation or all-cause death through Day 29.

Table 7: 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 with ≥1 COVID-19-related hospitalisation 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 randomisation, 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).

RECOVERY

RECOVERY is an ongoing multi-centre, randomised, controlled, open-label platform study, evaluating the efficacy and safety of potential treatments in hospitalised subjects with COVID-19. RECOVERY enrolled hospitalised subjects on no oxygen, low or high flow oxygen therapy, non-invasive or invasive ventilation and ECMO. In this trial, 9 785 subjects in the United Kingdom (UK) were randomised to a single IV infusion of 4 000 mg of casirivimab and 4 000 mg of imdevimab plus usual care (n=4 839) or usual standard of care alone (n=4 946; herein after referred to as usual care alone). Subjects could receive between 0 and 4 treatments on top of usual standard of care.

Subjects had clinically suspected or laboratory-confirmed SARS-CoV-2 infection and were enrolled regardless of the respiratory support required. Baseline serology test results were used to define analysis populations.

At baseline, the mean age was 62 years (with 30% of subjects aged 70 years or older, 11 adolescents ≥ 12 and < 18 years old were included) and 63% of the subjects were male. Baseline demographics and disease characteristics were well balanced across the casirivimab and imdevimab, and usual care alone, treatment groups. Subjects were enrolled in the study when the B.1.1.7 (alpha) variant was the dominant variant in the UK. Respiratory support received by subjects included 7% on no supplemental oxygen, 61% on simple oxygen, 26% on non-invasive ventilation, and 6% on invasive ventilation (including 17 subjects on ECMO). In subjects who were seronegative at baseline, 10% were on no supplemental oxygen at baseline, 66% were on simple oxygen, 21% were on non-invasive ventilation, and 2% were on invasive ventilation (including one subject on ECMO). Approximately 94% of all randomised subjects received corticosteroids as part of background standard care.

The primary endpoint was 28-day all-cause mortality in all randomised subjects who were seronegative at baseline. The results are shown in Table 8.

Table 8: Summary of primary endpoint results from study RECOVERY

	4 000 mg of casirivimab and 4 000 mg of imdevimab (intravenously) plus usual care	Usual care alone
	n=1 633	n=1 520
28-Day all-cause mortality in seronegative subjects		
Number of subjects with all-cause mortality (%)	396 (24%)	452 (30%)
Rate Ratio (95% CI)	0.79 (0.69 – 0.91) (p=0.0009)	

In seropositive subjects, the 28-day all-cause mortality was 16% (410/2 636) in the casirivimab+imdevimab arm and 15% (384/2 636) in the usual care alone arm (rate ratio 1.09 [95% CI: 0.94, 1.25]).

In seronegative subjects aged ≥ 80 years, 28-day all-cause mortality was 54.5% (126/231) and 57.5% (134/233) in the casirivimab+imdevimab and usual care alone arms, respectively (rate ratio 0.97 [95% CI: 0.76, 1.25]).

Statistical testing of the secondary endpoint was performed outside of the hierarchy and is, therefore, considered descriptive.

The secondary endpoint of discharge alive from hospital within 28 days was more common in the all-randomised seronegative population treated with casirivimab and imdevimab compared with usual care alone (64% vs. 58%; rate ratio 1.19 [95% CI: 1.09, 1.31]), with a 4-day shorter median duration of hospital stay (13 days vs. 17 days).

Among the all-randomised seronegative population not on invasive mechanical ventilation at baseline, treatment with casirivimab and imdevimab was associated with a lower risk of progressing to the composite endpoint of invasive mechanical ventilation or death (31% vs. 37%, risk ratio 0.83, [95% CI: 0.75, 0.92]).

COV-2066

COV-2066 was a randomised, double-blinded, placebo-controlled clinical trial evaluating casirivimab and imdevimab for the treatment of hospitalised subjects with COVID-19 on low flow oxygen devices (e.g., by face mask or nasal cannula) or no supplemental oxygen. In this phase 2/3 trial, 1 197 subjects had a positive SARS-CoV-2 RT-qPCR result at baseline and were randomised 1:1:1 to a single intravenous infusion of 1 200 mg of casirivimab and 1 200 mg of imdevimab (n=406), 4 000 mg of casirivimab and 4 000 mg of imdevimab (n=398), or placebo (n=393), with all subjects receiving casirivimab and imdevimab, or placebo in addition to the usual standard of care for COVID-19. The overall sample size was smaller than anticipated due to the early study termination following several months of low recruitment rates. Overall, similar effects were observed in patients on no supplemental oxygen or on low flow oxygen devices for casirivimab and imdevimab 2 400 mg and casirivimab and imdevimab 8 000 mg doses, indicating an absence of a dose effect in this population. These dose groups were combined when compared to the placebo group for the efficacy analysis.

At baseline, the median age was 62 years (with 44% of subjects aged 65 years or older), and 54% of the subjects were male, 43% of the subjects were seronegative, 48% were seropositive and 9% had an unknown serostatus. Baseline respiratory support received by subjects included 44% on no supplemental oxygen and 56% on low flow oxygen devices. Prior to randomisation, approximately 33% of subjects received remdesivir and 50% received systemic corticosteroids as part of background usual care. Baseline demographics and disease characteristics were well balanced across the casirivimab and imdevimab and placebo treatment groups.

The primary virologic efficacy endpoint was time weighted average (TWA) daily change from baseline in viral load (log_{10} copies/mL) through day 7, measured by RT-qPCR in NP swab samples, in subjects who were seronegative and had a positive SARS-CoV-2 RT-qPCR result at baseline. Treatment with casirivimab and imdevimab for the combined doses group resulted in a statistically significant reduction in the LS mean viral load (log_{10} copies/mL) compared to placebo (-0.28 log_{10} copies/mL/day for casirivimab and imdevimab; p=0.0172).

The primary clinical endpoint was the proportion of subjects who died or went on mechanical ventilation in those with a positive SARS-CoV-2 RT-qPCR result.

Treatment with casirivimab and imdevimab for the combined doses group resulted in a reduced proportion of subjects with a high viral load who died or went on mechanical ventilation from day 6 to

day 29, but the endpoint did not achieve statistical significance (relative risk reduction [RRR] 25.5% [95% CI: -16.2%, 52.2%]; p=0.2048).

Treatment with casirivimab and imdevimab for the combined doses group resulted in a 47.1% RRR (95% CI: 10.2%, 68.8%) in the proportion of seronegative subjects who died or went on mechanical ventilation from day 6 to day 29.

In a post hoc analysis of all randomized seronegative subjects aged ≥ 80 years, all-cause mortality from day 1 to day 29 was 18.1% (19/105 subjects) and 30.0% (18/60 subjects) in the casirivimab+imdevimab (combined doses) and placebo arms, respectively (risk ratio 0.60 [95% CI: 0.34, 1.06]).

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 9: 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 10: 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 intravenous regimen of 8 000 mg (4 000 mg of each monoclonal antibody) in patients who require oxygen supplementation, the 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 1 046 mg/L, 9280 mg.day/L, 165.2 mg/L, respectively for casirivimab, and 1 132 mg/L, 8789 mg.day/L, 136.2 mg/L, respectively for imdevimab, after a single intravenous dose.

For the pre-exposure prophylaxis 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 results in peak serum concentrations at the end of infusion. The median (range) time to reach maximum serum concentration of casirivimab and imdevimab (T_{max}) 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 was 7.072 L and 7.183 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 (5^{th}, 95^{th} 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. The mean (5^{th}, 95^{th} percentile) clearances were 0.188 (0.11, 0.30) and 0.227 (0.15, 0.35), respectively, for casirivimab and imdevimab.

For patients who require supplemental oxygen, the mean (5^{th}, 95^{th} percentile) serum elimination half-lives after a 4 000 mg dose of each monoclonal antibody were 21.9 (12.4, 36.9) days and 18.8 (11.7, 29.4) days, respectively, for casirivimab and imdevimab. The mean (5^{th}, 95^{th} percentile) clearances were 0.303 (0.156, 0.514) and 0.347 (0.188, 0.566), 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.

The pharmacokinetics of casirivimab and imdevimab in children < 18 years of age who require supplemental oxygen 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. PHARMACEUTICAL 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: 2 years

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 20 mL clear Type 1 glass vials.

Ronapreve 120 mg/mL + 120 mg/mL 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 9 mg/mL (0.9%) sodium chloride injection or 50 mg/mL (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 9 mg/mL (0.9%) sodium chloride injection or 50 mg/mL (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.

Administration of Ronapreve by intravenous infusion

- 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 9 mg/mL (0.9%) sodium chloride injection or 50 mg/mL (5%) dextrose injection is not known.
- After infusion is complete, flush the tubing with 9 mg/mL (0.9%) sodium chloride injection or 50 mg/mL (5%) dextrose injection to ensure delivery of the required dose.
- Individuals should be monitored post intravenous infusion according to local medical practice.

Preparation of Ronapreve for subcutaneous injection

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 3). 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 3) 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.
4. This product is preservative-free and therefore, the prepared syringes should be administered immediately. If immediate administration is not possible, store the prepared casirivimab and imdevimab syringes at 2 ºC to 8 ºC for no more than 72 hours and at room temperature up to 25 ºC for no more than 24 hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 10-15 minutes prior to administration.

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 3) 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 3) 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).

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1601/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 November 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Regeneron Pharmaceuticals, Inc.
81 Columbia Turnpike
Rensselaer
NY 12144
United States

Genentech, Inc.
1000 New Horizons Way
Vacaville
CA 95688
United States

Name and address of the manufacturer(s) responsible for batch release

Roche Pharma AG
Emil Barrell Strasse 1
79639 Grenzach-Wyhlen
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – Single-Use

1. NAME OF THE MEDICINAL PRODUCT

Ronapreve 300 mg + 300 mg solution for injection/infusion
casirivimab/imdevimab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 300 mg/2.5 mL of casirivimab (120 mg/mL).
One vial contains 300 mg/2.5 mL of imdevimab (120 mg/mL).

3. LIST OF EXCIPIENTS

L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection/infusion
300 mg/2.5 mL
2 vials of 2.5 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
For intravenous or subcutaneous use
For IV, casirivimab and imdevimab must be administered together
For SC, casirivimab and imdevimab must be administered consecutively
For single-use only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. **Do not shake the vials.** Keep the vials in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1601/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CASIRIVIMAB VIAL LABEL – Single-Use Vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ronapreve 300 mg + 300 mg solution for injection/infusion
casirivimab
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

300 mg/2.5 mL

6. OTHER

Must administer with imdevimab

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

IMDEVIMAB VIAL LABEL – Single-Use Vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ronapreve 300 mg + 300 mg solution for injection/infusion
imdevimab
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

300 mg/2.5 mL

6. OTHER

Must administer with casirivimab

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – Multidose

1. NAME OF THE MEDICINAL PRODUCT

Ronapreve 120 mg/mL + 120 mg/mL solution for injection/infusion
casirivimab/imdevimab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One multidose vial contains 1 332 mg/11.1 mL of casirivimab (120 mg/mL).
One multidose vial contains 1 332 mg/11.1 mL of imdevimab (120 mg/mL).

3. LIST OF EXCIPIENTS

L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, sucrose, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection/infusion
1 332 mg/11.1 mL
2 multidose vials of 11.1 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
For intravenous or subcutaneous use
For IV, casirivimab and imdevimab must be administered together
For SC, casirivimab and imdevimab must be administered consecutively

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze. **Do not shake the vials.** Keep the vials in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1601/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CASIRIVIMAB VIAL LABEL – Multidose Vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ronapreve 120 mg/mL + 120 mg/mL solution for injection/infusion
casirivimab
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 332 mg/11.1 mL

6. OTHER

Must administer with imdevimab

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

IMDEVIMAB VIAL LABEL – Multidose Vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ronapreve 120 mg/mL + 120 mg/mL solution for injection/infusion
imdevimab
IV/SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 332 mg/11.1 mL

6. OTHER

Must administer with casirivimab

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ronapreve 300 mg + 300 mg solution for injection/infusion
casirivimab and imdevimab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ronapreve is and what it is used for

What Ronapreve is

Ronapreve is made up of the active substances ‘casirivimab’ and ‘imdevimab’. Casirivimab and imdevimab are a type of protein called ‘monoclonal antibodies’.

What Ronapreve is used for

Ronapreve is used to treat adults and adolescents aged from 12 years weighing at least 40 kg with COVID-19 who do not require oxygen to treat COVID-19, and are at increased risk for the illness becoming severe based on the evaluation of your doctor.

Ronapreve is used to treat COVID-19 in adults and adolescents aged from 12 years weighing at least 40 kg who require oxygen to treat COVID-19, and who test negative for antibodies (proteins in the body’s defence system) against COVID-19.

Ronapreve is used to prevent COVID-19 in adults and adolescents aged from 12 years weighing at least 40 kg.

How Ronapreve works

Ronapreve attaches to a protein on the surface of the coronavirus called the ‘spike protein’. This stops the virus from getting into your cells and from spreading between cells.

2. What you need to know before you are given Ronapreve

You must not be given Ronapreve

- if you are allergic to casirivimab, imdevimab, or any of the other ingredients of this medicine (listed in section 6).

Talk to your doctor or nurse as soon as possible, if this applies to you.

Warnings and precautions

- This medicine can cause allergic reactions or reactions following the infusion or injection. The signs of these reactions are listed in Section 4. Tell your doctor straight away if you get any of these signs or symptoms.

Children and adolescents

Do not give this medicine to children under 12 years of age or adolescents that weigh less than 40 kg.

Other medicines and Ronapreve

Before you have Ronapreve, tell the doctor or nurse who is giving it to you about any other medicines you are taking, or have recently taken.
After you have had Ronapreve:

- tell the doctor, nurse or pharmacist that you have had this medicine to treat or prevent COVID-19
- tell the doctor, nurse or pharmacist you have had this medicine, if you are getting a COVID-19 vaccine.

Pregnancy and breast-feeding

Tell your doctor or nurse if you are pregnant, or if you might be pregnant.

- This is because there is not enough information to be sure that this medicine is safe for use in pregnancy.
- This medicine will only be given if the potential benefits of treatment outweigh the potential risks to the mother and the unborn child.

Tell your doctor or nurse if you are breast-feeding.

- This is because it is not yet known whether this medicine passes into human breast milk - or what the effects might be on the baby or milk production.
- Your doctor will help you decide whether to keep breast-feeding or to start treatment with this medicine.

Driving and using machines

This medicine is not expected to have any effect on your ability to drive.

3. How Ronapreve is given to you

How much is given?

The recommended dose for treatment of COVID-19 will depend on the severity of your illness.

The recommended dose for treatment of COVID-19 in adults and in adolescents 12 years of age and older weighing at least 40 kg, who do not need oxygen therapy, is 600 mg of casirivimab and 600 mg of imdevimab.

The recommended dose for treatment of COVID-19 in adults and adolescents 12 years of age and older weighing at least 40 kg, who need oxygen therapy, is 4 000 mg of casirivimab and 4 000 mg of imdevimab.

The recommended dose for prevention of COVID-19 in adults and in adolescents 12 years of age and older weighing at least 40 kg is 600 mg of casirivimab and 600 mg of imdevimab.

The recommended dose for continuous prevention of COVID-19 in adults and in adolescents 12 years of age and older weighing at least 40 kg is 600 mg of casirivimab and 600 mg of imdevimab as the initial dose, and the subsequent doses are 300 mg of casirivimab and 300 mg of imdevimab once every four weeks.

How is this medicine given?

Casirivimab and imdevimab may be given together as a single infusion (drip) into a vein over 20 to 60 minutes. In patients who do not need oxygen therapy, this medicine may also be given as injections, given immediately one after the other, under the skin made at separate body sites if an infusion would delay treatment. Your doctor or nurse will decide how long you will be monitored after you are given the medicine. This is in case you have any side effects.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects have been reported with Ronapreve.

Reactions following the infusion

Tell your doctor straight away if you get any of these signs of an allergic reaction or reaction listed below during or following the infusion. The infusion may need to be slowed down, interrupted or stopped and you may need other medicines to treat the symptoms. The signs or symptoms of allergic reaction or infusion-related reactions may include:

Uncommon: may affect up to 1 in 100 people
- feeling sick (nausea)
- chills
- dizziness
- flushing
- itching
- abnormally fast breathing
- rash

Rare: may affect up to 1 in 1 000 people
- severe allergic reaction (anaphylaxis)
- allergic reactions
- itchy rash

Other side effects that have been reported (frequency not known):
- fainting which may be accompanied by muscle spasm or twitching

Reactions following the subcutaneous (under the skin) injection

Tell your doctor straight away if you get any of these signs of a reaction following the injections.

Common: may affect up to 1 in 10 people
- redness, bruising, swelling, pain or itchy rash at the injection site

Uncommon: may affect up to 1 in 100 people
- dizziness
- swollen lymph nodes close to injection site

Rare: may affect up to 1 in 1 000 people
- itching

Other side effects that have been reported (frequency not known):
- fainting which may be accompanied by muscle spasm or twitching

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ronapreve

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial label after EXP. The expiry date refers to the last day of that month.

Ronapreve will be stored by the healthcare professionals at the hospital or clinic under the following conditions:
- **Before use,** store unopened Ronapreve concentrated solution in a refrigerator until the day it is needed. Before diluting it, allow the concentrated solution to come up to room temperature.
- **Once diluted,** Ronapreve should be used immediately. If necessary, bags of diluted solution can be stored at 2 °C to 8 °C for no more than 72 hours and at room temperature up to 25 °C for no more than 20 hours. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.
- Prepared syringes should be used immediately. If necessary, store the prepared syringes at 2 ºC to 8 ºC for no more than 72 hours and at room temperature up to 25 ºC for no more than 24 hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 10-15 minutes prior to administration.

Do not use this medicine if you notice particulate matter or discolouration.

6. Contents of the pack and other information

What Ronapreve contains

- The active substances are casirivimab and imdevimab. Each 6 mL single-use vial contains 300 mg of casirivimab or 300 mg of imdevimab.
- The other ingredients are L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, sucrose, and water for injections.

What Ronapreve looks like and contents of the pack

Ronapreve is a solution for injection/infusion. It is a clear to slightly opalescent and colourless to pale yellow solution and is available in cartons that contain 2 vials per package, one vial for each active substance.

Marketing Authorisation Holder

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

Manufacturer

Roche Pharma AG
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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N.V. Roche S.A.
Tél/Tel: +32 (0) 2 525 82 11

Lietuva
UAB "Roche Lietuva"
Tel: +370 5 2546799

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Roche (Magyarország) Kft.
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Malta
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România
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Slovenija
Roche farmacevtska družba d.o.o.
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Slovenská republika
Roche Slovensko, s.r.o.
Tel: +421 - 2 52638201

Suomi/Finland
Roche Oy
Puh/Tel: +358 (0) 10 554 500

Sverige
Roche AB
Tel: +46 (0) 8 726 1200

United Kingdom (Northern Ireland)
Roche Products (Ireland) Ltd.
Tel: +44 (0) 1707 366000

This leaflet was last revised in.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://ema.europa.eu

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only. Please refer to the Summary of Product Characteristics for further information.

Instructions for healthcare professionals

Ronapreve 300 mg + 300 mg solution for injection/infusion

Casirivimab and imdevimab must be administered together by intravenous infusion (after dilution) or consecutively for subcutaneous injection

Casirivimab:
Each single-use vial contains 300 mg of casirivimab per 2.5 mL (120 mg/mL) as a clear to slightly opalescent and colourless to pale yellow solution.

Imdevimab:
Each single-use vial contains 300 mg of imdevimab per 2.5 mL (120 mg/mL) as a clear to slightly opalescent and colourless to pale yellow solution.

Summary of Treatment and Prevention

Ronapreve is indicated for:
- Treatment of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.
- Treatment of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg and receiving supplemental oxygen, who have a negative SARS-CoV-2 antibody test result.
- Prevention of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg.

Depending on the clinical indication, the recommended dose is:
- 600 mg of casirivimab and 600 mg of imdevimab, or
- 4 000 mg of casirivimab and 4 000 mg of imdevimab, or
- 300 mg of casirivimab and 300 mg of imdevimab

Preparation for Intravenous Infusion Administration

Ronapreve concentrated solution must be diluted with sodium chloride 9 mg/mL (0.9%) solution or 50 mg/mL (5%) dextrose injection for infusion under aseptic conditions. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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 9 mg/mL (0.9%) sodium chloride injection or 50 mg/mL (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 9 mg/mL (0.9%) sodium chloride injection or 50 mg/mL (5%) dextrose injection (see Tables 1 and 2).
5. Gently mix infusion bag by inversion. Do not shake.
6. This product is preservative-free and therefore, the diluted infusion solution should be administered immediately.
    - If immediate administration is not possible, store the diluted casirivimab and imdevimab infusion solution at 2 °C to 8 °C for no more than 72 hours and at room temperature up to 25 °C for no more than 20 hours. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.

Table 1: Recommended dilution and intravenous infusion instructions for 600 mg casirivimab and 600 mg imdevimab or 300 mg casirivimab and 300 mg imdevimab

Indication	**Size of prefilled 9 mg/mL (0.9%) sodium chloride or 50 mg/mL (5%) dextrose infusion bag**	**Ronapreve Dose**	**Total Volume for 1 Dose**	**Volume to be withdrawn from each respective vial and injected into a single prefilled 9 mg/mL (0.9%) sodium chloride or 50 mg/mL (5%) dextrose infusion bag of 50-250 mL for co-administration**	**Minimum Infusion Time**
Treatment (patients not on supplemental oxygen), Post-exposure prophylaxis (single dose), Pre-exposure prophylaxis (initial dose)	50 mL, 100 mL, 150 mL	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	20 minutes
	250 mL				30 minutes
Pre-exposure prophylaxis (repeat dose)	50 mL, 100 mL, 150 mL	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	20 minutes
	250 mL				30 minutes

Table 2: Recommended dilution and intravenous infusion instructions for 4 000 mg casirivimab and 4 000 mg imdevimab

Indication	Size of prefilled 9 mg/mL (0.9%) sodium chloride or 50 mg/mL (5%) dextrose infusion bag	Ronapreve Dose	Total Volume for 1 Dose	Volume to be withdrawn from each respective vial and injected into a single prefilled 9 mg/mL (0.9%) sodium chloride or 50 mg/mL (5%) dextrose infusion bag of 50-250 mL for co-administration	Minimum Infusion Time
Treatment (patients on supplemental oxygen)	250 mL*	4 000 mg casirivimab and 4 000 mg imdevimab	66.6 mL	33.3 mL total of casirivimab from the 300 mg single-use vials 33.3 mL total of imdevimab from the 300 mg single-use vials	60 minutes

*Withdraw and discard 66.6 mL of 9 mg/mL (0.9%) sodium chloride or 50 mg/mL (5%) dextrose from the infusion bag prior to adding casirivimab and imdevimab

Administration by Intravenous Infusion

Ronapreve infusion solution should be administered by a qualified healthcare professional using aseptic technique.

- 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 infusion should be administered over 20-60 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.
- 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 9 mg/mL (0.9%) sodium chloride injection or 50 mg/mL (5%) dextrose injection is not known.
- After infusion is complete, flush the tubing with 9 mg/mL (0.9%) sodium chloride injection or 50 mg/mL (5%) dextrose injection to ensure delivery of the required dose.

Preparation for Subcutaneous Injection

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 Table 3). Obtain 3 mL or 5 mL polypropylene syringes with luer connection and 21-gauge transfer needles.
2. Using a sterile syringe and needle, withdraw the appropriate volume of casirivimab and imdevimab from each respective vial into each syringe (see Table 3) 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.
3. Replace the 21-gauge transfer needle with a 25-gauge or 27-gauge needle for subcutaneous injection.
4. This product is preservative-free and therefore, the prepared syringes should be administered immediately. If immediate administration is not possible, store the prepared casirivimab and imdevimab syringes at 2ºC to 8ºC for no more than 72 hours and at room temperature up to 25ºC for no more than 24 hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 10-15 minutes prior to administration.

Table 3 Preparation of 600 mg casirivimab and 600 mg imdevimab or 300 mg casirivimab and 300 mg 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 (patients not on supplemental oxygen), 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
Indication	**Ronapreve Dose**	**Total Volume for 1 Dose**	**Volume to be withdrawn from each respective vial to prepare 2 syringes**
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

Administration for Subcutaneous Injection

- For the administration of Ronapreve 1 200 mg dose (600 mg of casirivimab and 600 mg of imdevimab), gather 4 syringes (Table 3) 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 (Table 3) and prepare for subcutaneous injections.
- Due to the volume, 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).

Monitor and report side effects

- Monitor the patient for side effects during and after the infusion or injection according to current medical practice. The rate of infusion may be slowed or interrupted if the patient develops any signs of infusion-associated events or other adverse events. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.
- Report side effects via the national reporting system listed in Appendix V.

Storage

- **Before use,** store casirivimab and imdevimab vials in a fridge between 2 °C to 8 °C until they are required. Do not use after expiry date, marked on the vials/cartons after the letters EXP.
- Casirivimab and imdevimab concentrates are clear to slightly opalescent and colourless to pale yellow solutions.
- **Before dilution,** allow casirivimab and imdevimab vials to warm up to room temperature (up to 25 °C).
- **After initial puncture of the 6 mL vial,** the medicinal product should be used immediately, and any remaining product should be discarded.
- **Once diluted,** Ronapreve should be administered immediately. If necessary, bags of diluted solution can be stored for up to 20 hours at room temperature (up to 25 °C) and 2 °C to 8 °C for no more than 72 hours. 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.

Package leaflet: Information for the patient

Ronapreve 120 mg/mL + 120 mg/mL solution for injection/infusion
casirivimab and imdevimab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ronapreve is and what it is used for

What Ronapreve is

Ronapreve is made up of the active substances ‘casirivimab’ and ‘imdevimab’. Casirivimab and imdevimab are a type of protein called ‘monoclonal antibodies’.

What Ronapreve is used for

Ronapreve is used to treat adults and adolescents aged from 12 years weighing at least 40 kg with COVID-19 who do not require oxygen to treat COVID-19, and are at increased risk for the illness becoming severe based on the evaluation of your doctor.

Ronapreve is used to treat COVID-19 in adults and adolescents aged from 12 years weighing at least 40 kg who require oxygen to treat COVID-19, and who test negative for antibodies (proteins in the body’s defence system) against COVID-19.

Ronapreve is used to prevent COVID-19 in adults and adolescents aged from 12 years weighing at least 40 kg.

How Ronapreve works

Ronapreve attaches to a protein on the surface of the coronavirus called the ‘spike protein’. This stops the virus from getting into your cells and from spreading between cells.

2. What you need to know before you are given Ronapreve

You must not be given Ronapreve

- if you are allergic to casirivimab, imdevimab, or any of the other ingredients of this medicine (listed in section 6).

Talk to your doctor or nurse as soon as possible, if this applies to you.

Warnings and precautions

- This medicine can cause allergic reactions or reactions following the infusion or injection. The signs of these reactions are listed in Section 4. Tell your doctor straight away if you get any of these signs or symptoms.

Children and adolescents

Do not give this medicine to children under 12 years of age or adolescents that weigh less than 40 kg.

Other medicines and Ronapreve

Before you have Ronapreve, tell the doctor or nurse who is giving it to you about any other medicines you are taking, or have recently taken.
After you have had Ronapreve:

- tell the doctor, nurse or pharmacist that you have had this medicine to treat or prevent COVID-19
- tell the doctor, nurse or pharmacist you have had this medicine, if you are getting a COVID-19 vaccine.

Pregnancy and breast-feeding

Tell your doctor or nurse if you are pregnant, or if you might be pregnant.

- This is because there is not enough information to be sure that this medicine is safe for use in pregnancy.
- This medicine will only be given if the potential benefits of treatment outweigh the potential risks to the mother and the unborn child.

Tell your doctor or nurse if you are breast-feeding.

- This is because it is not yet known whether this medicine passes into human breast milk - or what the effects might be on the baby or milk production.
- Your doctor will help you decide whether to keep breast-feeding or to start treatment with this medicine.

Driving and using machines

This medicine is not expected to have any effect on your ability to drive.

3. How Ronapreve is given to you

How much is given?

The recommended dose for treatment of COVID-19 will depend on the severity of your illness.

The recommended dose for treatment of COVID-19 in adults and in adolescents 12 years of age and older weighing at least 40 kg, who do not need oxygen therapy, is 600 mg of casirivimab and 600 mg of imdevimab.

The recommended dose for treatment of COVID-19 in adults and adolescents 12 years of age and older weighing at least 40 kg, who need oxygen therapy, is 4 000 mg of casirivimab and 4 000 mg of imdevimab.

The recommended dose for prevention of COVID-19 in adults and in adolescents 12 years of age and older weighing at least 40 kg is 600 mg of casirivimab and 600 mg of imdevimab.

The recommended dose for continuous prevention of COVID-19 in adults and in adolescents 12 years of age and older weighing at least 40 kg is 600 mg of casirivimab and 600 mg of imdevimab as the initial dose, and the subsequent doses are 300 mg of casirivimab and 300 mg of imdevimab once every four weeks.

How is this medicine given?

Casirivimab and imdevimab may be given together as a single infusion (drip) into a vein over 20 to 60 minutes. In patients who do not need oxygen therapy, this medicine may also be given as injections, given immediately one after the other, under the skin made at separate body sites if an infusion would delay treatment. Your doctor or nurse will decide how long you will be monitored after you are given the medicine. This is in case you have any side effects.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects have been reported with Ronapreve.

Reactions following the infusion

Tell your doctor straight away if you get any of these signs of an allergic reaction or reaction listed below during or following the infusion. The infusion may need to be slowed down, interrupted or stopped and you may need other medicines to treat the symptoms. The signs or symptoms of allergic reaction or infusion-related reactions may include:

Uncommon: may affect up to 1 in 100 people
- feeling sick (nausea)
- chills
- dizziness
- flushing
- itching
- abnormally fast breathing
- rash

Rare: may affect up to 1 in 1 000 people
- severe allergic reaction (anaphylaxis)
- allergic reactions
- itchy rash

Other side effects that have been reported (frequency not known):
- fainting which may be accompanied by muscle spasm or twitching

Reactions following the subcutaneous (under the skin) injection

Tell your doctor straight away if you get any of these signs of a reaction following the injections.

Common: may affect up to 1 in 10 people
- redness, bruising, swelling, pain or itchy rash at the injection site

Uncommon: may affect up to 1 in 100 people
- dizziness
- swollen lymph nodes close to injection site

Rare: may affect up to 1 in 1 000 people
- itching

Other side effects that have been reported (frequency not known):
- fainting which may be accompanied by muscle spasm or twitching

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Ronapreve

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial label after EXP. The expiry date refers to the last day of that month.

Ronapreve will be stored by the healthcare professionals at the hospital or clinic under the following conditions:
- **Before use,** store unopened Ronapreve concentrated solution in a refrigerator until the day it is needed. Before diluting it, allow the concentrated solution to come up to room temperature.
- **Once diluted,** Ronapreve should be used immediately. If necessary, bags of diluted solution can be stored at 2 °C to 8 °C for no more than 72 hours and at room temperature up to 25 °C for no more than 20 hours. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.
- Prepared syringes should be used immediately. If necessary, store the prepared syringes at 2 ºC to 8 ºC for no more than 72 hours and at room temperature up to 25 ºC for no more than 24 hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 10-15 minutes prior to administration.

Do not use this medicine if you notice particulate matter or discolouration.

6. Contents of the pack and other information

What Ronapreve contains

- The active substances are casirivimab and imdevimab. Each 20 mL multidose vial contains 1 332 mg of casirivimab or 1 332 mg of imdevimab.
- The other ingredients are L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, sucrose, and water for injections.

What Ronapreve looks like and contents of the pack

Ronapreve is a solution for injection/infusion. It is a clear to slightly opalescent and colourless to pale yellow solution and is available in cartons that contain 2 vials per package, one vial for each active substance.

Marketing Authorisation Holder

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Manufacturer

Roche Pharma AG
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://ema.europa.eu

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only. Please refer to the Summary of Product Characteristics for further information.

Instructions for healthcare professionals

Ronapreve 120 mg/mL + 120 mg/mL solution for injection/infusion

Casirivimab and imdevimab must be administered together by intravenous infusion (after dilution) or consecutively for subcutaneous injection

Casirivimab:
Each multidose vial contains 1 332 mg of casirivimab per 11.1 mL (120 mg/mL) as a clear to slightly opalescent and colourless to pale yellow solution.

Imdevimab:
Each multidose vial contains 1 332 mg of imdevimab per 11.1 mL (120 mg/mL) as a clear to slightly opalescent and colourless to pale yellow solution.

Summary of Treatment and Prevention

Ronapreve is indicated for:
- Treatment of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.
- Treatment of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg and receiving supplemental oxygen, who have a negative SARS-CoV-2 antibody test result.
- Prevention of COVID-19 in adults and adolescents aged 12 years and older weighing at least 40 kg.

Depending on the clinical indication, the recommended dose is:
- 600 mg of casirivimab and 600 mg of imdevimab, or
- 4 000 mg of casirivimab and 4 000 mg of imdevimab, or
- 300 mg of casirivimab and 300 mg of imdevimab

Preparation for Intravenous Infusion Administration

Ronapreve concentrated solution must be diluted with sodium chloride 9 mg/mL (0.9%) solution or 50 mg/mL (5%) dextrose injection for infusion under aseptic conditions. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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 9 mg/mL (0.9%) sodium chloride injection or 50 mg/mL (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 9 mg/mL (0.9%) sodium chloride injection or 50 mg/mL (5%) dextrose injection (see Tables 1 and 2).
5. Gently mix infusion bag by inversion. Do not shake.
6. This product is preservative-free and therefore, the diluted infusion solution should be administered immediately.
    - If immediate administration is not possible, store the diluted casirivimab and imdevimab infusion solution at 2 °C to 8 °C for no more than 72 hours and at room temperature up to 25 °C for no more than 20 hours. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.

Table 1: Recommended dilution and intravenous infusion instructions for 600 mg casirivimab and 600 mg imdevimab or 300 mg casirivimab and 300 mg imdevimab

Indication	**Size of prefilled 9 mg/mL (0.9%) sodium chloride or 50 mg/mL (5%) dextrose infusion bag**	**Ronapreve Dose**	**Total Volume for 1 Dose**	**Volume to be withdrawn from each respective vial and injected into a single prefilled 9 mg/mL (0.9%) sodium chloride or 50 mg/mL (5%) dextrose infusion bag of 50-250 mL for co-administration**	**Minimum Infusion Time**
Treatment (patients not on supplemental oxygen), Post-exposure prophylaxis (single dose), Pre-exposure prophylaxis (initial dose)	50 mL, 100 mL, 150 mL	600 mg casirivimab and 600 mg imdevimab	10 mL	5 mL from one 1 332 mg multidose vial of casirivimab 5 mL from one 1 332 mg multidose vial of imdevimab	20 minutes
	250 mL				30 minutes
Pre-exposure prophylaxis (repeat dose)	50 mL, 100 mL, 150 mL	300 mg casirivimab and 300 mg imdevimab	5 mL	2.5 mL from one 1 332 mg multidose vial of casirivimab 2.5 mL from one 1 332 mg multidose vial of imdevimab	20 minutes
	250 mL				30 minutes

Table 2: Recommended dilution and intravenous infusion instructions for 4 000 mg casirivimab and 4 000 mg imdevimab

Indication	Size of prefilled 9 mg/mL (0.9%) sodium chloride or 50 mg/mL (5%) dextrose infusion bag	Ronapreve Dose	Total Volume for 1 Dose	Volume to be withdrawn from each respective vial and injected into a single prefilled 9 mg/mL (0.9%) sodium chloride or 50 mg/mL (5%) dextrose infusion bag of 50-250 mL for co-administration	Minimum Infusion Time
Treatment (patients on supplemental oxygen)	250 mL*	4 000 mg casirivimab and 4 000 mg imdevimab	66.6 mL	11.1 mL from three 1 332 mg multidose vials of casirivimab 11.1 mL from three 1 332 mg multidose vials of imdevimab	60 minutes

*Withdraw and discard 66.6 mL of 9 mg/mL (0.9%) sodium chloride or 50 mg/mL (5%) dextrose from the infusion bag prior to adding casirivimab and imdevimab

Administration by Intravenous Infusion

Ronapreve infusion solution should be administered by a qualified healthcare professional using aseptic technique.

- 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 infusion should be administered over 20-60 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.
- 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 9 mg/mL (0.9%) sodium chloride injection or 50 mg/mL (5%) dextrose injection is not known.
- After infusion is complete, flush the tubing with 9 mg/mL (0.9%) sodium chloride injection or 50 mg/mL (5%) dextrose injection to ensure delivery of the required dose.

Preparation for Subcutaneous Injection

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 Table 3). Obtain 3 mL or 5 mL polypropylene syringes with luer connection and 21-gauge transfer needles.
2. Using a sterile syringe and needle, withdraw the appropriate volume of casirivimab and imdevimab from each respective vial into each syringe (see Table 3) 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.
3. Replace the 21-gauge transfer needle with a 25-gauge or 27-gauge needle for subcutaneous injection.
4. This product is preservative-free and therefore, the prepared syringes should be administered immediately. If immediate administration is not possible, store the prepared casirivimab and imdevimab syringes at 2ºC to 8ºC for no more than 72 hours and at room temperature up to 25ºC for no more than 24 hours. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 10-15 minutes prior to administration.

Table 3: Preparation of 600 mg casirivimab and 600 mg imdevimab or 300 mg casirivimab and 300 mg 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 (patients not on supplemental oxygen), Post-exposure prophylaxis (single dose), Pre-exposure prophylaxis (initial dose)	600 mg casirivimab and 600 mg imdevimab	10 mL	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
Indication	**Ronapreve Dose**	**Total Volume for 1 Dose**	**Volume to be withdrawn from each respective vial to prepare 2 syringes**
Pre-exposure prophylaxis (repeat dose)	300 mg casirivimab and 300 mg imdevimab	5 mL	2.5 mL from one 1 332 mg multidose vial of casirivimab 2.5 mL from one 1 332 mg multidose vial of imdevimab

Administration for Subcutaneous Injection

- For the administration of Ronapreve 1 200 mg dose (600 mg of casirivimab and 600 mg of imdevimab), gather 4 syringes (Table 3) 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 (Table 3) and prepare for subcutaneous injections.
- Due to the volume, 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).

Monitor and report side effects

- Monitor the patient for side effects during and after the infusion or injection according to current medical practice. The rate of infusion may be slowed or interrupted if the patient develops any signs of infusion-associated events or other adverse events. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.
- Report side effects via the national reporting system listed in Appendix V.

Storage

- **Before use,** store casirivimab and imdevimab vials in a fridge between 2 °C to 8 °C until they are required. Do not use after expiry date, marked on the vials/cartons after the letters EXP.
- Casirivimab and imdevimab concentrates are clear to slightly opalescent and colourless to pale yellow solutions.
- **Before dilution,** allow casirivimab and imdevimab vials to warm up to room temperature (up to 25 °C).
- **After initial puncture of the 20 mL vial**, if not used immediately, the medicinal product in the vial can be stored for 16 hours at room temperature up to 25 °C or for 48 hours in a refrigerator (2 °C to 8 °C). Other in-use storage times and conditions are the responsibility of the user.
- **Once diluted,** Ronapreve should be administered immediately. If necessary, bags of diluted solution can be stored for up to 20 hours at room temperature (up to 25 °C) and 2 °C to 8 °C for no more than 72 hours. 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.