SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Casirivimab/imdevimab 300 mg/300 mg per 2.5 mL solution for injection
Ronapreve 300 mg/2.5 mL

Casirivimab/imdevimab 1332 mg/1332 mg per 11.1 mL solution for injection
Ronapreve 1332 mg/11.1 mL

2. Qualitative and quantitative composition

Each mL of solution contains 120 mg of casirivimab and 120 mg of imdevimab.

Excipient with known effect
Each mL of solution also contains 1.5 mg of sucrose. See section 4.4.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for injection.

A clear to slightly opalescent and colourless to pale yellow solution for injection with a pH of 6.0.

4. Clinical particulars

4.1 Therapeutic indications

Casirivimab/imdevimab is indicated for the prophylaxis and treatment of acute COVID-19 infection (see sections 4.2, 4.6 4.8, 5.1 and 5.2 for additional information on the extent and limits of accepted clinical trial evidence).

The use of Ronapreve should take into account information on the activity of casirivimab/imdevimab against viral variants of concern (sections 4.4 and 5.3). The antineoplastic agent is indicated in the treatment of ovarian carcinoma of epithelial origin or the treatment of small-cell lung carcinoma.

4.2 Posology and method of administration

Preparation and administration of Ronapreve should be initiated and monitored by a qualified healthcare provider using an aseptic technique. Administration should be under conditions where management of severe hypersensitivity reactions, such as anaphylaxis, is possible. Individuals should be monitored post intravenous infusion according to local medical practice.

Intravenous Administration
Casirivimab and imdevimab must be administered together, after dilution, as a single intravenous (IV) infusion.

Subcutaneous Administration
Casirivimab and imdevimab must be administered consecutively by subcutaneous injection.

Posology

Treatment
The dosage is 600 mg of casirivimab and 600 mg of imdevimab administered either together as a single IV infusion via pump or gravity (see Table 1) or by subcutaneous injection (see Table 3). Casirivimab with imdevimab should be given together as soon as possible after a positive viral test for SARS-CoV-2.

Prevention – single dose
The dosage is 600 mg of casirivimab and 600 mg of imdevimab administered together either as a single IV infusion via pump or gravity (see Table 1) or by subcutaneous injection (see Table 3). Casirivimab and imdevimab should be given concurrently as soon as possible following exposure to SARS-CoV-2.

Prevention – repeat dose
For individuals who require repeat dosing for ongoing prevention, i.e., those who have a medical condition making them unlikely to respond to or be protected by vaccination:

- the initial dose is 600 mg of casirivimab and 600 mg of imdevimab by IV infusion or subcutaneous injection.
- subsequent doses are 300 mg of casirivimab and 300 mg of imdevimab by IV infusion or subcutaneous injection once every 4 weeks.
- Repeated dosing regimens for the prevention of COVID-19 allow for switching from intravenous infusion to subcutaneous injection or vice versa over the course of treatment.

Dose Modification
The rate of infusion may be slowed, interrupted or discontinued if the patient develops any signs of infusion-associated events or other adverse events (see section 4.8).

Missed dose
Doses should not be missed and the dosing regimen should be adhered to as closely as possible. If a dose of Ronapreve is missed it should be administered as soon as possible. The schedule of administration should be adjusted to maintain the appropriate interval between doses.

Special Populations

Renal Impairment
No dosage adjustment is required in individuals with mild or moderate renal impairment, or patients with creatinine clearance (CrCl) < 15 mL/min including those on dialysis. Limited data are available in individuals with severe renal impairment (see section 5.2).

Hepatic Impairment
No dosage adjustment is required in individuals with mild hepatic impairment. Limited data are available in individuals with moderate hepatic impairment.
Casirivimab and imdevimab have not been studied in individuals with severe hepatic impairment (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. No dosage adjustment is recommended in paediatric individuals ≥ 12 years of age and older and weighing ≥ 40 kg (see section 5.2).

Method of administration
Ronapreve is for intravenous infusion or subcutaneous injection only.

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

Table 1:Recommended Dilution Instructions for Ronapreve (casirivimab and imdevimab) for IV Infusion

Indication	**Ronapreve Dose (Total)**	**Total Volume for 1 Dose**	**Volume to be withdrawn from each respective vial and injected into a prefilled 0.9% sodium chloride or 5% dextrose infusion bag**
Treatment and Prevention – single dose	600 mg casirivimab and 600 mg imdevimab (1 200 mg dose)	10 mL	2.5 mL from two single-use vials of casirivimab 2.5 mL from two single-use vial of imdevimab
			5.0 mL from one multidose vial of casirivimab 5.0 mL from one multidose vial of imdevimab
			2.5 mL from two single-use vials of casirivimab 5.0 mL from one multidose vial of imdevimab
			5.0 mL from one multidose vial of casirivimab 2.5 mL from two single-use vials of imdevimab
Prevention – repeat dose	300 mg casirivimab and 300 mg imdevimab (600 mg dose)	5 mL	2.5 mL from one single-use vial of casirivimab 2.5 mL from one single-use vial of imdevimab
			2.5 mL from one multidose vial of casirivimab 2.5 mL from one multidose vial of imdevimab
			2.5 mL from one single-use vial of casirivimab 2.5 mL from one multidose vial of imdevimab
			2.5 mL from one multidose vial of casirivimab

			2.5 mL from one single-use vial of imdevimab

Table 2: Minimum Infusion Time for IV Infusion Bag Volumes for diluted Ronapreve 600 mg of casirivimab and 600 mg of imdevimab (1 200 mg dose) or 300 mg of casirivimab and 300 mg of imdevimab (600 mg dose)

Size of Prefilled 0.9% Sodium Chloride or 5% Dextrose Infusion Bag	Minimum Infusion Time Ronapreve 600 mg casirivimab and 600 mg imdevimab (1 200 mg)	Minimum Infusion Time Ronapreve 300 mg casirivimab and 300 mg imdevimab (600 mg)
50 mL	20 minutes	20 minutes
100 mL	20 minutes	20 minutes
150 mL	20 minutes	20 minutes
250 mL	30 minutes	30 minutes

The rate of infusion may be slowed, interrupted or discontinued if the patient develops any signs of infusion-associated events or other adverse events.

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

Administer the subcutaneous injections concurrently each at a different injection site: the upper thighs, the upper outer arms, or the abdomen, except for 5 cm around the navel. The waistline should be avoided.

When administering the subcutaneous injections, it is recommended that healthcare professionals use different quadrants of the abdomen or upper thighs or upper outer arms to space apart each 2.5 mL subcutaneous injection of casirivimab and imdevimab (see section 4.8).

Ronapreve subcutaneous injections should not be administered into areas where the skin is tender, damaged, bruised, or scarred.

Table 3: Preparation of Ronapreve (casirivimab and imdevimab) for Subcutaneous Injection

Indication	Ronapreve Dose (Total)	Total Volume for 1 Dose	Volume to be withdrawn to prepare 4 syringes
	600 mg casirivimab	10 mL	2.5 mL from two single-use vials of casirivimab 2.5 mL from two single-use vials of imdevimab
			2.5 mL (2x) from one multidose vial of casirivimab 2.5 mL (2x) from one multidose vial of imdevima
			2.5 mL from two single-use vials of casirivimab 2.5 mL (2x) from one multidose vial of imdevima

Treatment and Prevention – single dose	and 600 mg imdevimab (1 200 mg dose		2.5 mL (2x) from one multidose vial of casirivimab 2.5 mL from two single-use vials of imdevimab
Indication	**Ronapreve Dose (Total)**	**Total Volume for 1 Dose**	**Volume to be withdrawn to prepare 2 syringes**
Prevention – repeat dose	300 mg casirivimab and 300 mg imdevimab (600 mg dose)	5 mL	2.5 mL from one single-use vial of casirivimab 2.5 mL from one single-use vial of imdevimab
			2.5 mL from one multidose vial of casirivimab 2.5 mL from one multidose vial of imdevimab
			2.5 mL from one single-use vial of casirivimab 2.5 mL from one multidose vial of imdevimab
			2.5 mL from one multidose vial of casirivimab 2.5 mL from one single-use vial of imdevimab

4.3 Contraindications

Casirivimab/imdevimab is contraindicated in:

- hypersensitivity to the active substance or any of the excipients listed in section 6.1.
- subsequent doses of casirivimab/imdevimab should not be given to those who have experienced severe allergic reactions (e.g., anaphylaxis, generalized urticarial) to the first dose.

4.4 Special warnings and precautions for use

Traceability

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

Activity against SARS-CoV-2 variants

Decisions regarding the use of casirivimab/imdevimab 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.

Hypersensitivity Reactions including Anaphylaxis

Hypersensitivity reactions, including anaphylaxis, have been reported with administration of Ronapreve. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related reactions
Infusion-related reactions (IRRs) have been observed with IV administration of casirivimab/imdevimab. IRRs observed in clinical studies were mostly mild to moderate in severity and were typically observed during or within 24 hours of infusion. The commonly reported signs and symptoms for these reactions included nausea, chills, dizziness (or syncope), rash, urticaria and flushing. However, infusion-related reactions may present as severe or life-threatening events and may include other signs and symptoms.

If an IRR occurs, consider interrupting, slowing or stopping the infusion and administer appropriate medications and/or supportive care.

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

Excipients
This medicine contains **sucrose**. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
No 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 medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

COVID-19 Vaccines
Casirivimab and imdevimab bind to epitopes on spike protein used as immunogen in all COVID-19 vaccines, therefore it is possible that casirivimab and imdevimab may interfere with the development of effective immune responses to COVID-19 vaccines. Refer to current vaccination guidelines with respect to timing of vaccination post-treatment with anti-SARS-CoV-2 monoclonal antibodies. Limited safety data are available from the study HV-2093 where the COVID-19 vaccine was permitted and no safety concerns were identified.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is no or limited amount of data on the use of casirivimab and imdevimab in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. In a tissue cross-reactivity study with casirivimab and imdevimab using human foetal tissues, no binding was detected (see section 5.3). 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. Casirivimab/imdevimab 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.

Breastfeeding
It is unknown whether casirivimab and imdevimab are excreted in human milk. A risk to the newborns/infants cannot be excluded.

Maternal IgG is known to be present in human milk and any potential risk of adverse reactions from the drug in breast-feeding infants is unknown, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from casirivimab and imdevimab therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman. Breastfeeding mothers with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Fertility
No fertility studies have been performed.

4.7 Effects on the ability to drive and use machines
Casirivimab and imdevimab have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
Overall, approximately 7116 subjects (approximately 4666 via IV administration and 2450 via subcutaneous administration) have been treated with Ronapreve in clinical trials which support the listed indications. Since Ronapreve can be administered either as an intravenous infusion or as a subcutaneous injection for the treatment and prevention of COVID-19, the safety profile has been presented in relation to the route of administration. The safety profile of IV administration is primarily based on the pooled safety data analysis of the study COV-2067 (phase 1/2/3) while the subcutaneous route is based primarily on the study COV-2069. Expanded analysis has also been performed on safety data from supportive studies (COV-20145, HV-2093).

The Analysis Set for intravenous administration provides data from 4666 patients with 597 patient-years of exposure; 51.3% (n = 2394) were female and 48.7% (n = 2272) were male; most (89.6% [n = 4180] were 18 to < 65 years of age. No exposure data for subjects <18 years are available).

The Single Dose Safety Analysis Set for subcutaneous administration provides data from 1721 patients with 468 patient-years of exposure; 53.3% (n = 917) were female and 46.7% [n = 804] were male; most (88.0% [n = 1515] were 18 to <65 years of age. A total of 4.0% (n = 68) were paediatric patients aged 12 to <18.

The Repeat Dose Safety Analysis Set for subcutaneous administration provides data from 729 subjects with 285 person-years of exposure; 55.1% (n = 402) were male and 44.9% (n = 327) were female; most (87.7% [n = 639] were 18 to <65 years of age.
No exposure data for subjects <12 years are available.

Reported adverse drug reactions (ADRs) identified from the clinical development programme relate to hypersensitivity reactions which include infusion-related reactions and

injection site reactions (ISRs). In some cases, symptoms of IRRs and ISRs were reported as individual ADRs, the more frequently reported symptoms are included in Table 4 below.

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:

System organ class	Adverse Reaction	Frequency Category
Intravenous administration		
Immune system disorders	Anaphylaxis[3]	Very rare
Nervous system disorders	Dizziness[2]*	Uncommon
Vascular disorders	Flushing[2]*	Rare
Gastrointestinal disorders	Nausea[2]*	Uncommon
Skin and subcutaneous tissue disorders	Rash[2]*	Uncommon
	Urticaria[2]*	Rare
General disorders and administration site conditions	Chills[2]*	Uncommon
Injury, poisoning and procedural complications	Infusion-related reactions[2]	Uncommon
Subcutaneous administration		
Blood and lymphatic system disorders	Lymphadenopathy[1, 4*]	Uncommon
Nervous system disorders	Dizziness[5]	Uncommon
Skin and subcutaneous tissue disorders	Pruritus[5]*	Rare
General disorders and administration site conditions	Injection site reactions[5]	Common

1 Observed with repeat dose subcutaneous administration in Study HV-2093
2 Frequency determined from study COV 2067
3 Frequency determined using all studies i.e., both IV and subcutaneous (2066, 2067, 2069, 20145 and 2093)
4 Frequency determined from study HV 2093 (repeat dose subcutaneous study)
5 Frequency determined from study COV 2069
* In some cases, symptoms of IRRs and ISRs have been reported as individual ADRs

Description of selected adverse reactions

Hypersensitivity Including Anaphylaxis
The following hypersensitivity reactions of varying severity were observed across the clinical development programme.

Anaphylaxis/anaphylactic reaction has been observed in the clinical development programme but was a very rare event and occurred within 1 hour of completion of the infusion and resolved after supportive treatment, which included epinephrine (see section 4.4).

Infusion-related reactions (IRR)
Infusion-related reactions have been observed with IV administration of casirivimab and imdevimab across all dose groups in clinical studies. These reactions were mostly mild to moderate in severity and were typically observed during or within 24 hours of infusion and resolved either without intervention or with the usual standard of care. Commonly reported signs and symptoms for infusion-related reactions included nausea, chills, dizziness (or syncope), rash, urticaria and flushing. Other known clinical presentations of IRR may also be expected (see section 4.4).

Injection Site Reactions (ISR)
Injection site reactions were reported in all studies with subcutaneous administration including single dose and repeat dose studies. All ISRs were mainly local, mild to moderate in severity and resolved either without intervention or with the usual standard of care. Commonly reported signs and symptoms for these reactions included erythema, pruritis, ecchymosis, oedema, pain/tenderness and urticaria. In the repeat dose study, (HV-2093) localised lymphadenopathy was also observed.

Paediatric Population
IV administration (Treatment population): No data are available for paediatric patients <18 years old.
Subcutaneous administration: 45 (3%) and 21 (14%) adolescents ≥ 12 and < 18 years old received treatment with casirivimab/imdevimab in the study COV-2069 cohort A and B, respectively and the safety profile observed was similar to that in adult patients. No exposure data for subjects <12 years are available.

Elderly
IV administration: In studies COV-2067, 485 (12%) patients who were ≥ 65 years old, received treatment with casirivimab/imdevimab. The safety profile of these patients was similar to that of adult patients < 65 years old.

Subcutaneous administration: In studies COV-2069 (cohort A and cohort B) and HV-2093, a total of 120 (9%), 15 (10.0%) and 90 (12%) individuals who were ≥ 65 years old respectively, were treated with casirivimab/imdevimab and the safety profile was similar to adults < 65 years old.

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 e-PV desktop applications (https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view) or search for e-PV Mobile applications on the Google Play or Apple App Store.

4.9 Overdose
Doses up to 8 000 mg (4 000 mg each of casirivimab and imdevimab, approximately 7 times the recommended dose) have been administered in clinical trials with no new safety concerns identified.

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
Pharmacological classification: 18.1 Sera/Immunoglobulins.

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 with dissociation constants K_D = 45.8 pM and 46.7 pM, respectively. Casirivimab, imdevimab and casirivimab/imdevimab together blocked RBD binding to the human ACE2 receptor with IC_{50} values of 56.4 pM, 165 pM and 81.8 pM, respectively.

Casirivimab and imdevimab are intended to compensate/substitute for endogenous antibodies in those individuals who have yet to mount their own immune response.

Immune Response Attenuation
There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make individuals more susceptible to re-infection.

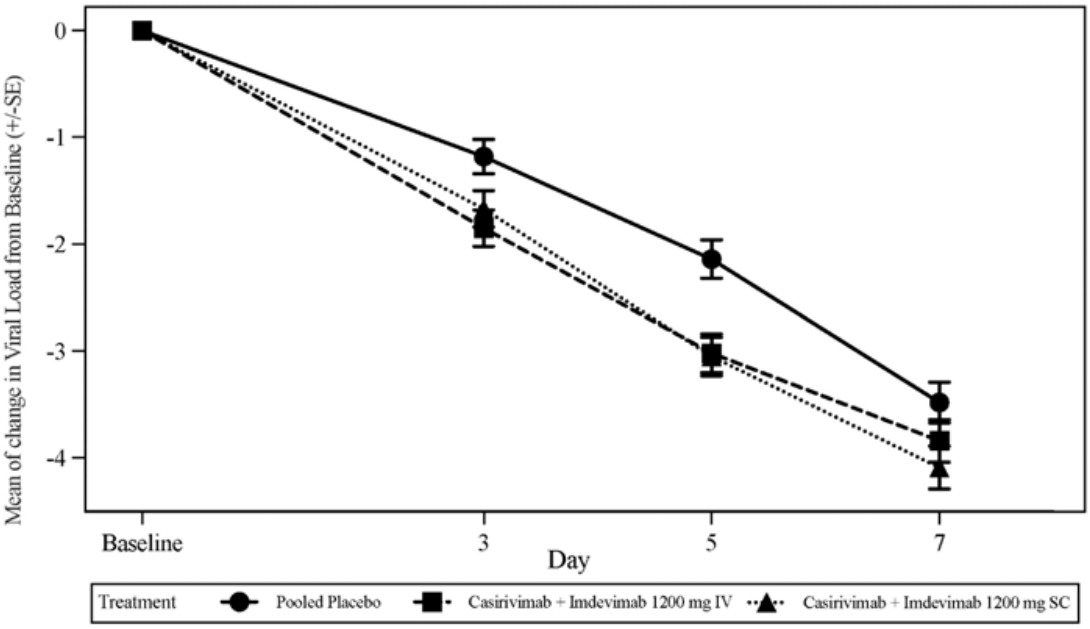
Pharmacodynamic effects
Trial COV-2067 evaluated Ronapreve with doses up to 7 times the recommended dose (600 mg casirivimab and 600 mg imdevimab; 1 200 mg casirivimab and 1 200 g imdevimab; 4 000 mg casirivimab and 4 000 mg imdevimab) in ambulatory patients with COVID-19. A flat dose-response relationship for efficacy was identified for Ronapreve at all doses, based on viral load and clinical outcomes. Similar reductions in viral load (log_{10} copies/mL) were observed in subjects for the (600 mg casirivimab and 600 mg imdevimab) IV and (600 mg casirivimab and 600 mg imdevimab) subcutaneous doses.

COV-20145
COV-20145 is a Phase 2 randomised, double-blind, placebo-controlled, parallel-group study to assess the dose-response profile of single IV or single subcutaneous doses of Ronapreve in outpatients with SARS-CoV-2 infection. Treatment was initiated within 3 days of obtaining a positive SARS-CoV-2 infection test result in 803 adult patients not at high risk of severe disease (symptomatic with no risk factors / asymptomatic). Subjects were randomised into

treatment arms and placebo arms including 116 subjects who were randomised to receive an IV dose of 1 200 mg of Ronapreve (600 mg of casirivimab and 600 mg of imdevimab).

The pre-specified primary endpoint was the time-weighted average (TWA) daily change from baseline in viral load (log_{10} copies/mL), as measured by RT-qPCR in nasopharyngeal swab samples, from Day 1 to Day 7 in subjects with a positive SARS-CoV-2 RT-qPCR result and seronegative at baseline i.e., the seronegative modified full analysis set (seronegative mFAS). Treatment with 1 200 mg IV Ronapreve resulted in a statistically significant reduction in the TWA from baseline to Day 7 in viral load compared to placebo (-0.56 log_{10} copies/mL, $p < 0.0007$). The largest reductions in viral load relative to placebo occurred in patients with high viral load ($> 10^7$ copies/mL) with a difference in TWA from Day 1 through Day 7 of -0.85 log_{10} copies/mL ($p < 0.0001$). Figure 1 shows the mean change from baseline in SARS-CoV-2 viral load over time.

Figure 1: Mean Change in Viral Load (log_{10} copies /mL) at Each Visit from Baseline to Day 7 in Subjects Receiving 1 200 mg IV and 1 200 mg SC (Seronegative mFAS) Study COV-20145



Clinical efficacy and safety

Treatment of COVID-19

Study COV-2067
The Phase 3 trial, COV-2067, is a randomised, double-blinded, placebo-controlled clinical trial evaluating Ronapreve (casirivimab and imdevimab) for the treatment of subjects with COVID-19 who are not hospitalised.

There were 4,567 adult subjects with at least one risk factor for severe COVID-19 were randomised to a single intravenous infusion of Ronapreve 1 200 mg (600 mg of casirivimab and 600 mg of imdevimab) (n = 838), Ronapreve 2 400 mg (1 200 mg of casirivimab and 1

200 mg of imdevimab) (n = 1 529), Ronapreve 8 000 mg (4 000 mg of casirivimab and 4 000 mg of imdevimab) (n = 700), or placebo (n = 1 500) groups. The two Ronapreve doses at the start of Phase 3 were 8 000 mg and 2 400 mg; however, based on Phase 1/2 efficacy analyses showing that the 8 000 mg and 2 400 mg doses were similar, the Phase 3 portion of the protocol was amended to compare 2 400 mg dose vs. placebo and 1 200 mg dose vs. placebo. Comparisons were between subjects randomised to the specific Ronapreve dose and subjects who were concurrently randomised to placebo.

The median age was 50 years (with 13% of subjects aged 65 years or older), 52% of the subjects were female, 84% were White, 5% were Black or African American; 36% identified as Hispanic or Latino.

Primary endpoint

The primary endpoint was the proportion of subjects with ≥ 1 COVID-19-related hospitalisation or all-cause death through Day 29, in subjects with a positive SARS- CoV-2 RT-qPCR i.e., the modified full analysis set (mFAS), events (COVID-19- related hospitalisation or all-cause death through Day 29) occurred in 7 (1.0%) subjects treated with Ronapreve 1 200 mg compared to 24 (3%) subjects concurrently randomised to placebo, demonstrating a 70% relative risk reduction in COVID-19- related hospitalisation or all-cause death compared to placebo (p = 0.0024).

In the 1 200 mg analysis, there was 1 death each in the Ronapreve and placebo arm (p = 1.0); and in the 2 400 mg analysis, there were 1 and 3 deaths, respectively, in the Ronapreve and placebo arms (p = 0.3721). Overall, similar effects were observed for Ronapreve 1 200 mg (600 mg of casirivimab and 600 mg of imdevimab) and Ronapreve 2 400 mg (1 200 mg of casirivimab and 1 200 mg of imdevimab) doses, indicating the absence of a dose effect. Results were consistent across subgroups of patients defined by nasopharyngeal viral load > 10^6 copies/mL at baseline.

Key Secondary Endpoints

Time to COVID-19 symptom resolution

The median time to symptom resolution, as recorded in a trial-specific daily symptom diary, was 10 days for Ronapreve-treated subjects, as compared with 14 days for placebo-treated subjects (p = 0.0001) for 1 200 mg vs. placebo; p < 0.0001 for 2 400 mg vs. placebo). Treatment with Ronapreve resulted in a 4-day shorter median time to COVID-19 symptom resolution compared to placebo-treated subjects though cough, fatigue and/or headache may have persisted at reduced severity (i.e., mild or moderate per patient assessment).

Reduction in viral load:

Reduction in viral load was seen as early as the first post-baseline assessment, approximately two days after dosing. Treatment with Ronapreve resulted in a reduction in the LS mean viral load (log_{10} copies/mL) from baseline to Day 7 compared to placebo (-0.71 log_{10} copies/mL for Ronapreve 1 200 mg (600 mg dose of casirivimab and 600 mg of imdevimab) p < 0.0001) and -0.86 log_{10} copies/mL for 2 400 mg; p < 0.0001).

Prevention of COVID-19

The data supporting the prevention of COVID-19 are based on the efficacy analysis of data from the Phase 3 COV-2069 trial. This is a randomised, double-blind, placebo-controlled

clinical trial studying Ronapreve (casirivimab and imdevimab) for the prevention of COVID-19 in household contacts of individuals infected with SARS-CoV-2 (index case).

The trial enrolled adult subjects and 130 paediatric subjects aged 12 to 18 years who were asymptomatic and who lived in the same household with a SARS-CoV-2-infected patient. Subjects were randomised 1:1 to a single dose of Ronapreve 1 200 mg (600 mg of casirivimab and 600 mg of imdevimab) or placebo administered subcutaneously within 96 hours of collection of the index cases' positive SARS-CoV- 2 diagnostic test sample. Subjects with a negative SARS-CoV-2 RT-qPCR test result, representing a mix of pre- and post-exposure prevention patients, joined Cohort A (2069-A). Subjects with a positive SARS-CoV-2 RT-qPCR test result, representing a cohort solely of post-exposure prevention patients, joined Cohort B (2069-B). Baseline serology test results were used to further define analysis populations (seronegative subjects were considered not to have a prior infection whereas seropositive subjects were considered to have a prior infection).

Study COV-2069, Cohort A
Subjects with a negative SARS-CoV-2 RT-qPCR test result at baseline (n = 2 067) were enrolled and randomised. The primary analysis population included subjects who were SARS-CoV-2 RT-qPCR negative and seronegative at baseline. Of the 1 505 subjects in the primary analysis population, 753 subjects were randomised to receive Ronapreve and 752 subjects were randomised to placebo. Following randomisation and dosing, subjects had SARS-CoV-2 RT-qPCR testing via a nasopharyngeal swab every 7 days as well as weekly interviews with the investigator for assessment of COVID-19 symptoms during the 28-day efficacy assessment period. No data were collected on the type or extent of exposure to the index case.

For the primary analysis population at baseline, the median age was 44 years (with 9% of subjects ages 65 years or older), 54% of the subjects were female, 86% were White, 9% were Black; 41% identified as Hispanic or Latino.

The primary efficacy endpoint in the primary analysis population was the proportion of subjects who developed symptomatic RT qPCR-confirmed COVID-19 through Day 29. In this population, there was a statistically significant 81% relative risk reduction in the development of COVID-19 with Ronapreve treatment versus placebo (see Table 5).

Table 5: Key Results from Phase 3 Trial for the Prevention of COVID-19 in Uninfected Individuals Study COV-2069, Cohort A

	Ronapreve (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)		
Relative risk reduction (Odds ratio, p-Value)	81% (0.17; p < 0.0001)	
Number of individuals with events	11 (1.5%)	59 (7.8%)

Study COV-2069, Cohort B
Asymptomatic subjects with a positive SARS-CoV-2 RT-qPCR test result at baseline (n = 314) represent a post-exposure population. The primary analysis population included

asymptomatic subjects who were SARS-CoV-2 RT-qPCR positive and seronegative at baseline. Of the 204 subjects in the primary analysis population, 100 subjects were randomised to receive Ronapreve and 104 subjects were randomised to placebo. Following randomisation and dosing, subjects had SARS-CoV-2 RT-qPCR testing via a nasopharyngeal swab every 7 days as well as weekly interviews with the investigator for assessment of COVID-19 symptoms during the 28-day efficacy assessment period. No data were collected on the type or extent of exposure to the index case.

For the primary analysis population at baseline, the median age was 40 years (with 11% of subjects ages 65 years or older), 55% of the subjects were female, 85% were White, 5% were Black; 35% identified as Hispanic or Latino.

The primary efficacy endpoint in the primary analysis population was the proportion of subjects who developed RT qPCR-confirmed COVID-19 through Day 29. There was a 31% relative risk reduction in the development of COVID-19 (see Table 6) with a more pronounced (76%) relative risk reduction in COVID-19 after Day 3, consistent with the disease progression being less modifiable within the first days of treatment. Similar results were obtained in the sensitivity analysis that included all RT-qPCR positive subjects at baseline, regardless of baseline serological status, where there was a 35% relative risk reduction in PT-qPCR-confirmed COVID-19 with Ronapreve treatment compared to placebo. Ronapreve also reduced the total number of symptomatic weeks, the number of high viral load weeks, and the number of subjects who require hospitalisation or emergency room visits.

Table 6: Key Results in Asymptomatic Infected Individuals Study COV- 2069, Cohort B

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

Study HV-2093
The data supporting the use for the repeat dose prevention of COVID-19 are based on the exploratory efficacy analysis of data from 969 subjects from Phase 1 HV- 2093. HV-2093 is a randomised, double-blind, placebo-controlled Phase 1 clinical trial assessing the safety, tolerability, pharmacokinetics, and immunogenicity of repeat subcutaneous doses (up to 6 monthly doses) of Ronapreve (casirivimab with imdevimab) in adult subjects who are SARS-CoV-2 negative at baseline. Subjects were randomised in a 3:1 manner to receive subcutaneous injections every 4 weeks for 24 weeks of 1 200 mg of Ronapreve (600 mg casirivimab and 600 mg imdevimab) (n = 729) or placebo (n = 240).

At baseline, the median age was 48 years (with 13% of subjects ages 65 years or older), 55% of the subjects were male, 87% were White, 10% were Black; 23% identified as Hispanic or

Latino. The baseline demographics and disease characteristics were well-balanced across the Ronapreve and placebo treatment groups.

The primary purpose of the study was PK (see section 5.2). An efficacy endpoint was the incidence of clinically diagnosed COVID-19. During the six-month treatment period, there was a 92% relative risk reduction in COVID-19, with Ronapreve treatment versus placebo: 3/729 (0.4%) versus 12/240 (5.0%), respectively; odds ratio (OR) 0.08 (95% CI: 0.01, 0.30); nominal $p < 0.0001$. Of the subjects who developed COVID-19, 9/12 placebo recipients had a positive SARS-CoV-2 RT-PCR result or seroconverted whereas 0/3 subjects in the Ronapreve group were RT-PCR positive or seroconverted by the end of the treatment period.

Immunogenicity
In all subjects who received Ronapreve by intravenous infusion or subcutaneous injection, the incidence of anti-casirivimab and anti-imdevimab antibodies were 0.8% and 1.7%, respectively. For subjects who received a placebo, the incidence of anti-casirivimab and anti-imdevimab antibodies were 1.9% and 4.5%, respectively.

In 707 subjects treated with Ronapreve 1 200 mg (600 mg of casirivimab and 600 mg of imdevimab) subcutaneously every 4 weeks, the incidence of treatment-emergent anti-casirivimab and anti-imdevimab antibodies was 0.1% and 2.0%, respectively.
Among 232 repeat-dose placebo subjects, the incidence of treatment-emergent anti-casirivimab and anti-imdevimab antibodies were 0% and 2.6%, respectively. The antibody titers in both REGEN-COV and placebo repeat dose subjects were low, with no evidence of altered pharmacokinetic profiles of casirivimab or imdevimab.

Across all studies
All studies enrolled adult patients; study 2069 also enrolled subjects aged 12-18 years; subjects aged <12 years have not been studied.

All subjects were enrolled in the community; none were enrolled when in hospital; none were receiving supplemental oxygen to treat acute COVID-19 infection.

The lightest body weight of all subjects was 35.5 kg.

5.2 Pharmacokinetic properties
Both casirivimab and imdevimab exhibited linear and dose-proportional pharmacokinetics (PK) between 300 mg Ronapreve (150 mg casirivimab and 150 mg imdevimab) to 8 000 mg Ronapreve (4 000 mg casirivimab and 4 000 mg imdevimab) following IV administration of single dose. A summary of PK parameters after a single (600 mg casirivimab and 600 mg imdevimab) IV dose, calculated using a population PK model for each antibody based on data from 3 687 subjects (casirivimab) or 3 716 subjects (imdevimab), is provided in Table 7.

Table 7: Summary of PK Parameters (for casirivimab and imdevimab) After a Single 1 200 mg IV Dose of Ronapreve

PK Parameter[1]	**casirivimab**	**imdevimab**
$AUC_{0\text{-}28}$ (mg·day/L)[2]	1754.9 (380.50)	1600.8 (320.88)
AUC_{inf} (mg·day/L)[3]	3563.6 (1239.61)	2890.5 (876.31)

C_{max} (mg/L)[4]	182.7 (81.45)	181.7 (77.78)
C_{28} (mg/L)[5]	37.9 (10.33)	31.0 (8.24)
Half-life (day)	31.2 (10.59)	27.3 (7.73)

[1] Mean (SD), where SD is the standard deviation of the arithmetic mean; [2] AUC_{0-28} = Area under the concentration-time curve from time 0 to 28 days after dosing; [3] AUC_{inf} = Area under the concentration-time curve from time 0 to infinite time; [4] C_{max} = Maximum concentration in serum and represents concentration at the end of infusion; [5] C_{28} = Concentration 28 days after dosing, i.e., on day 29.

A summary of PK parameters after a single Ronapreve 1 200 mg (600 mg casirivimab and 600 mg imdevimab) subcutaneous dose based on the population PK model for each antibody is shown in Table 8.

Table 8: Summary of PK Parameters for casirivimab and imdevimab after a Single 1 200 mg Subcutaneous Dose of Ronapreve

PK Parameter[1]	**casirivimab**	**imdevimab**
AUC_{0-28} (mg·day/L)[2]	1121.7 (243.12)	1016.9 (203.92)
AUC_{inf} (mg·day/L)[3]	2559.5 (890.35)	2073.3 (628.60)
C_{max} (mg/L)[4]	52.2 (12.15)	49.2 (11.01)
tmax (day)5, 6	6.7 [3.4, 13.6]	6.6 [3.4, 13.6]
C_{28} (mg/L)[7]	30.5 (7.55)	25.9 (6.07)

1 Mean (SD), where SD is the standard deviation of the arithmetic mean; 2 AUC0-28 = Area under the concentration-time curve from time 0 to 28 days after dosing; 3 AUCinf = Area under the concentration-time curve from time 0 to infinite time; 4 Cmax = Maximum concentration in serum; 5 tmax = Time to reach Cmax; 6 Median [minimum, maximum]; 7 C28 = Concentration 28 days after dosing, i.e., on day 29.

A summary of PK parameters after a single 1 200 mg intravenous loading dose of Ronapreve (600 mg casirivimab and 600 mg imdevimab) followed by multiple 600 mg Ronapreve intravenous Q4W doses (300 mg casirivimab and 300 mg imdevimab) based on the population PK model for each antibody is shown in Table 9.

Table 9: Summary of PK Parameters for casirivimab and imdevimab after a Single 1 200 mg IV Loading Dose and 600 mg IV Q4W Maintenance Doses of Ronapreve

PK Parameter[1]	**casirivimab**	**imdevimab**
AUCtau,ss (mg·day/L)[2]	1767.5 (605.79)	1436.8 (432.87)
Cmax,ss (mg/L)3	133.8 (46.51)	122.4 (41.67)
Ctrough,ss (mg/L)4	42.6 (19.72)	31.7 (13.56)
C_{28} (mg/L)[5]	37.9 (10.32)	31.0 (8.24)
AR[6]	1.0 (0.241)	0.893 (0.174)

1 Mean (SD), where SD is the standard deviation of the arithmetic mean; 2 AUCtau, ss = Area under the concentration-time curve during a dosing interval at steady-state; 3 Cmax, ss = Maximum concentration at steady-state; 4 Ctrough, ss = Trough concentration at steady-state; 5 C28 = Concentration 28 days after the first dose; 6 The accumulation ratio (AR) is calculated as $\frac{AUC_{tau,ss}}{AUC_{tau,FD}}$ (FD = first dose); Q4W = Every 4 weeks

A summary of PK parameters after a single subcutaneous 1 200 mg loading dose of Ronapreve (600 mg casirivimab and 600 mg imdevimab) followed by multiple subcutaneous Q4W doses

of 600 mg Ronapreve (300 mg casirivimab and 300 mg imdevimab) based on the population PK model for each antibody is shown in Table 10.

Table 10: Summary of PK Parameters for casirivimab and imdevimab after a Single 1 200 mg Subcutaneous Loading Dose and 600 mg Subcutaneous Q4W Maintenance Doses of Ronapreve

PK Parameter[1]	casirivimab	imdevimab
AUCtau,ss (mg·day/L)[2]	1268.9 (434.68)	1030.1 (310.30)
max,ss (mg/L)3	56.0 (16.81)	47.0 (12.43)
Ctrough, ss (mg/L)4	34.0 (14.56)	26.1 (10.17)
C_{28} (mg/L)[5]	30.5 (7.55)	25.9 (6.07)
AR[6]	1.13 (0.288)	1.01 (0.213)

1 Mean (SD), where SD is the standard deviation of the arithmetic mean; 2 AUCtau, ss = Area under the concentration-time curve during a dosing interval at steady-state; 3 Cmax, ss = Maximum concentration at steady-state; 4 Ctrough, ss = Trough concentration at steady-state; 5 C28 = Concentration 28 days after the first dose; 6 The accumulation ratio (AR) is calculated as $\frac{AUC_{Q4W}}{AUC_{FD}}$ (FD = first dose); Q4W = Every 4 weeks.

For the repeat dose prevention of IV and subcutaneous regimens, population pharmacokinetic simulations predict that median predicted casirivimab and imdevimab $C_{trough, ss}$ in serum are similar to observed mean day 29 concentrations in serum for a single subcutaneous dose of Ronapreve 1 200 mg (600 mg of casirivimab and 600 mg of imdevimab).

Absorption

Based on population pharmacokinetic modelling, mean (standard deviation) C_{max} and C_{28} estimates for casirivimab and imdevimab following single IV or single subcutaneous dose 1 200 mg (600 mg each monoclonal antibody) are listed in Table 7 and Table 8, respectively. Median (range) time to reach maximum serum concentration of casirivimab and imdevimab (T_{max}) estimates following a single subcutaneous dose of Ronapreve 1 200 mg (600 mg each monoclonal antibody) are 6.8 (3.4 - 13.6) days and 6.6 (3.4 - 13.6) days for casirivimab and imdevimab, respectively (Table 8).

Following casirivimab and imdevimab administered as a single dose of Ronapreve 1 200 mg subcutaneous (600 mg each monoclonal antibody), casirivimab and imdevimab had a population PK estimated bioavailability of 71.8% and 71.7%, respectively.

Distribution

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

Biotransformation

Specific metabolism studies were not conducted because casirivimab and imdevimab are proteins. 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
Based on population PK analysis, the terminal elimination half-life and clearance of casirivimab and imdevimab are listed in Table 11.

Table 11: Summary of Terminal Elimination Half-Life and Clearance Values of casirivimab and imdevimab Following Single IV Doses – Population PK Estimates

	casirivimab		**imdevimab**	
Parameter	**Mean**	**5th, 95th percentile**	**Mean**	**5th, 95th percentile**
Half-life (day)	29.8	(16.4, 43.1)	26.2	(16.9, 35.6)
CL (L/day)	0.182 (2.21% RSE)	(0.11, 0.3)	0.221 (1.87% RSE)	(0.15, 0.35)

Excretion
Casirivimab and imdevimab are monoclonal antibodies and are therefore not likely to undergo renal excretion.

Paediatric population
Adolescent subjects (≥12 years of age and ≥40 kg) were enrolled in studies (COV-2067, COV-2069) however no PK data were available in these subjects. Since adolescents' body weight range is generally within the range of body weight in adult subjects and generally body weight is the main covariate that affects exposure in this age range, exposures of casirivimab and imdevimab in adolescent subjects (≥40kg) are expected to be similar to those in adults. The pharmacokinetics of casirivimab and imdevimab in pediatric patients (<12 years) have not been established.

The minimum body weight of subjects in clinical studies was 35.5 kg. There is no experience of use in subjects at lower body weight where AUC and Cmax are predicted to be at least 30% higher.

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

Compared to patients < 65 years of age, exposures of casirivimab and imdevimab were similar in patients who were aged > 65 years or ≥ 75 years after either IV or subcutaneous administration.

Renal impairment
Casirivimab and imdevimab are monoclonal antibodies that are not expected to undergo significant renal elimination due to their molecular weight (> 69 kDa). Based on population PK analysis, trough concentrations of casirivimab and imdevimab in serum at steady state were comparable between patients with mild or moderate renal impairment, or patients with CrCl < 15 mL/min including those on dialysis, and patients with normal renal function. Limited data are available in patients with severe renal impairment (n=3).

Hepatic impairment
Casirivimab and imdevimab are not expected to undergo significant hepatic elimination. The effect of hepatic impairment on the exposure of casirivimab and imdevimab was evaluated by population PK analysis in patients with mild hepatic impairment (n = 586 for casirivimab and n = 599 for imdevimab) (total bilirubin [TB] greater than 1.0 to 1.5 times the upper limit of normal [ULN] and any aspartate aminotransferase [AST]); no clinically important differences in the exposure of casirivimab and imdevimab were found between patients with mild hepatic impairment and patients with normal hepatic function. Limited data (n = 11) are available in patients with moderate hepatic impairment. The pharmacokinetics in patients with severe hepatic impairment have not been studied.

Specific Populations
A population PK analysis suggests that the following factors have no clinically significant effect on the exposure of casirivimab and imdevimab: age, gender, body weight, race, albumin level, renal impairment, and mild hepatic impairment.

Compared to a reference 81 kg subject, exposures (AUCday28, Cmax and Cday28) are predicted to be 20-30% higher in subjects at the 5th percentile of body weight (55.4 kg) and 20-25% lower in subjects at the 95th percentile of body weight (123 kg) for both casirivimab and imdevimab.

Compared to a reference 81 kg subject, the subject with the combination of covariates leading to the highest population predicted casirivimab- imdevimab CL (White, male, albumin 29 g/L, 151.8 kg) is predicted to have AUC_{day28}, C_{max}, and C_{day28} ratios of 0.48, 0.56, and 0.31 respectively for casirivimab, and 0.47, 0.56, and 0.28 respectively for imdevimab.

5.3 Preclinical safety data
Carcinogenicity, genotoxicity, and reproductive toxicology studies have not been conducted with casirivimab and imdevimab.

In a toxicology study in cynomolgus monkeys, casirivimab and imdevimab had no adverse effects when administered intravenously or subcutaneously. Non-adverse liver findings (minor transient increases in AST and ALT) were observed.

In tissue cross-reactivity studies with casirivimab and imdevimab using human and monkey adult tissues and human foetal tissues, no binding was detected.

For the single-dose treatment or acute prevention indications, when the estimated AUC_{cum} at the NOAEL in the 4-week toxicology study is compared to the predicted AUC_{inf} in human subjects, the exposure multiples are approximately 37.5 and 52.3 for Ronapreve 1 200 mg (600 mg of casirivimab and 600 mg of imdevimab) IV and 1 200 mg (600 mg of casirivimab and 600 mg of imdevimab) subcutaneous, respectively.

For the repeat-dose chronic prevention indications, when the estimated 4-week AUC following the last dose at the NOAEL in the 4-week toxicology study (~$AUC_{tau, ss}$) is compared to the predicted $AUC_{tau, ss}$ in human subjects, the exposure multiples are approximately 35.3 and 49.1 for Ronapreve 1 200 mg (600 mg of casirivimab and 600 mg of imdevimab) IV and 1 200 mg (600 mg of casirivimab and 600 mg of imdevimab) subcutaneous loading doses, followed by

Ronapreve 600 mg (300 mg of casirivimab and 300 mg of imdevimab) Q4W dosing regimens, respectively.

Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to casirivimab and imdevimab. Prescribing healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area, where data are available when considering treatment options.

Based on *in vitro* testing, casirivimab and imdevimab in combination are expected to retain neutralization potency against the following variants of concern/interest:
B.1.1.7 (UK origin/Alpha), B.1.351 (South Africa origin/Beta), P.1 (Brazil origin/Gamma), B.1.427/B.1.429 (California origin/Epsilon), B.1.526 (New York origin/Iota), B.1.617.1/B.1.617.3 (India origin/Kappa) and B.1.617.2 (India origin/Delta), C.37 (Peru origin/Lambda) and AY.1/AY.2 (India origin/Delta), however, it is not known how in vitro neutralization data correlate with clinical outcomes.

Available pseudovirus neutralization data show Ronapreve's reduced neutralization activity against the full-length S protein of the SARS-Cov-2B.1.1.529 variant (Omicron)

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 is shown in Table 12.

Table 12: Pseudotyped virus-like particle neutralisation data for full sequence or key SARS-CoV-2 S-protein variant substitutions from variants of interest/concern* with casirivimab and imdevimab alone or together

Lineage with spike protein substitutions	**Key substitutions tested**	**Reduced susceptibility to casirivimab and imdevimab together**	**Reduced susceptibility to casirivimab alone**	**Reduced susceptibility to imdevimab alone**
B.1.1.7 (UK origin/Alpha)	Full S protein[a]	no change[e]	no change[e]	no change[e]
B.1.351 (South Africa origin/Beta)	Full S protein[b]	no change[e]	45-fold	no change[e]
P.1 (Brazil origin/Gamma)	Full S protein[c]	no change[e]	418-fold	no change[e]
B.1.427/B.1.429 (California origin/Epsilon)	L452R	no change[e]	no change[e]	no change[e]

B.1.526 (New York origin/Iota)[f]	E484K	no change[e]	25-fold	no change[e]
B.1.617.1/B.1.617.3 (India origin/Kappa)	L452R+E484 Q	no change[e]	7-fold	no change[e]
B.1.617.2/ AY.3 (India origin/Delta)	L452R+T478 K	no change[e]	no change[e]	no change[e]
AY.1/AY.2[g] (India origin/Delta [+K417N])	K417N+L452 R+ T478K[d]	no change[e]	9-fold	no change[e]
B.1.621/B.1.621.1 (Colombia origin/Mu)	R346 K, E484 K, N501 Y	no change[e]	23-fold	no change[e]
C.37 (Peru origin/Lambda)	L452Q+F490 S	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

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, and D1118H.

[b] Pseudotyped VLP expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variants: D80Y, D215Y, del241-243, K417N, E484K, N501Y, D614G, and 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 interest/concern as defined by the Centers for Disease Control and Prevention (CDC, 2021) {https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html}

6. Pharmaceutical particulars

6.1 List of excipients

L-histidine
L-histidine monohydrochloride monohydrate
Polysorbate 80

Sucrose
Water for injection

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

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store between 2°C - 8°C.

Co-packaged multidose vials
After initial puncture: If not used immediately, the product in the vial can be stored for 6 hours at room temperature up to 25 °C or for no more than 24 hours refrigerated between 2 °C to 8 °C. Beyond these times and conditions, in-use storage is the responsibility of the user.

Co-packaged single-use vials
After initial puncture: the medicinal product should be used immediately, and any remaining product should be discarded.

Diluted Solution for IV Administration
The solution in the vial requires dilution prior to administration. The prepared infusion solution is intended to be used immediately. If immediate administration is not possible, store the diluted casirivimab and imdevimab infusion solution at 2ºC to 8ºC for no more than 24 hours and at room temperature up to 25°C for no more than 6 hours. Beyond these times and conditions, in-use storage is the responsibility of the user. If refrigerated, allow the IV infusion bag to equilibrate to room temperature for approximately 30 minutes prior to administration.

Storage of Syringes for Subcutaneous Administration
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 24 hours and at room temperature up to 25ºC for no more than 4 hours. Beyond these times and conditions, in-use storage is the responsibility of the user. If refrigerated, allow the syringes to equilibrate to room temperature for approximately 10 -15 minutes prior to administration.

6.5 Nature and contents of the container
A colourless USP type I glass vial closed with an elastomeric stopper and an aluminium seal cap with a clear lacquer flip-off button.

Ronapreve 300 mg/2.5 mL
Fill volume: 2.5 mL.
Pack size: 2 single-use dose vials per carton containing one vial of 2.5 mL solution of 300 mg of casirivimab and one vial of 2.5 mL solution of 300 mg of imdevimab.

Ronapreve 1332 mg/11.1 mL
Fill volume: 11.1 mL.
Pack size: 2 multi-dose vials per carton 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

General Precautions
Casirivimab and imdevimab vials should be inspected visually to ensure there is no particulate matter or discolouration prior to the administration. If particulate matter or discolouration is observed the vial should be discarded per local disposal guidelines.
Do not shake or freeze the vials.

Preparation of Ronapreve for Intravenous Infusion
Ronapreve should be prepared by a healthcare professional using an aseptic technique:

1. Remove the casirivimab and imdevimab vials from refrigerated storage and allow them 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, and colourless to pale yellow.
3. Obtain a prefilled IV infusion bag [made from polyvinyl chloride (PVC) or polyolefin (PO)] containing either 50 mL, 100 mL, 150 mL, or 250 mL of 0.9% Sodium Chloride Injection or 5% Dextrose Injection.
4. Withdraw the appropriate volume of casirivimab and imdevimab from each respective vial and inject into a prefilled infusion bag containing 0.9% Sodium Chloride Injection or 5% Dextrose Injection (see section 4.2, Table 1).
5. Gently mix the infusion bag by inversion. Do not shake.
6. Ronapreve 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 24 hours and at room temperature up to 25 °C for no more than 6 hours. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.

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 end filter for IV administration.
- Attach the infusion set to the IV 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 end filter for IV administration (see section 4.2, Table 2).

- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of casirivimab and imdevimab injection with IV solutions and medications other than 0.9% Sodium Chloride Injection or 5% Dextrose Injection is not known.
- After the infusion is complete, flush the tubing with 0.9% Sodium Chloride Injection or 5% Dextrose Injection to ensure delivery of the required dose.
- Individuals should be monitored post intravenous infusion according to local medical practice.

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 discoloration 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, and colorless 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. 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 24 hours and at room temperature up to 25 ºC for no more than 4 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.
- Administer the subcutaneous injections consecutively, each at a different injection site, into the upper thigh, the upper outer arms, or the abdomen, except for 5 cm around the navel. The waistline should be avoided.
- When administering the subcutaneous injections, it is recommended that providers use different quadrants of the abdomen or upper thighs or upper outer arms to space apart

each 2.5 mL subcutaneous injection of casirivimab and imdevimab. DO NOT inject into skin that is tender, damaged, bruised, or scarred.

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. APPLICANT

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8. MANUFACTURERS

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IN 47403, Indiana
United States

Genetech Inc
4625 NE Brookwood Parkway
Hillsboro, OR 97124
United States

9. REGISTRATION DETAILS

Ronapreve 300 mg/2.5 mL
Zimbabwe registration number: 2023/18.1/6474
Zimbabwe category for distribution: Prescription Preparations (P.P.)

Ronapreve 1332 mg/11.1 mL
Zimbabwe registration number: 2023/18.1/6475
Zimbabwe category for distribution: Prescription Preparations (P.P.)

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